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Emicizumab Prophylaxis in Hemophilia A with Inhibitors

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ABSTRACT

BACKGROUND

Emicizumab (ACE910) bridges activated factor IX and factor X to restore the function of activated factor VIII, which is deficient in persons with hemophilia A. This phase 3, multicenter trial assessed once-weekly subcutaneous emicizumab prophylaxis in persons with hemophilia A with factor VIII inhibitors.

METHODS

We enrolled participants who were 12 years of age or older. Those who had previously received episodic treatment with bypassing agents were randomly assigned in a 2:1 ratio to emicizumab prophylaxis (group A) or no prophylaxis (group B). The primary end point was the difference in bleeding rates between group A and group B. Participants who had previously received prophylactic treatment with bypassing agents received emicizumab prophylaxis in group C.

RESULTS

A total of 109 male participants with hemophilia A with inhibitors were enrolled. The annualized bleeding rate was 2.9 events (95% confidence interval [CI], 1.7 to 5.0) among participants who were randomly assigned to emicizumab prophylaxis (group A, 35 participants) versus 23.3 events (95% CI, 12.3 to 43.9) among those assigned to no prophylaxis (group B, 18 participants), representing a significant difference of 87% in favor of emicizumab prophylaxis (P<0.001). A total of 22 participants in group A (63%) had zero bleeding events, as compared with 1 participant (6%) in group B. Among 24 participants in group C who had participated in a noninterventional study, emicizumab prophylaxis resulted in a bleeding rate that was significantly lower by 79% than the rate with previous bypassing-agent prophylaxis (P<0.001). Overall, 198 adverse events were reported in 103 participants receiving emicizumab prophylaxis; the most frequent events were injection-site reactions (in 15% of participants). Thrombotic microangiopathy and thrombosis were reported in 2 participants each (in the primary analysis) who had received multiple infusions of activated prothrombin complex concentrate for breakthrough bleeding. No antidrug antibodies were detected.

CONCLUSIONS

Emicizumab prophylaxis was associated with a significantly lower rate of bleeding events than no prophylaxis among participants with hemophilia A with inhibitors. (Funded by F. Hoffmann–La Roche and Chugai Pharmaceutical; HAVEN 1 ClinicalTrials.gov number, NCT02622321.)

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Hemophilia A is characterized by spontaneous or traumatic bleeding caused by deficient coagulation factor VIII activity.[1] The current standard of care for persons with hemophilia A with a severe bleeding phenotype is prophylactic intravenous infusions of factor VIII two to three times weekly; however, exposure to factor VIII concentrates is associated with the development of neutralizing anti–factor VIII alloantibodies (inhibitors), which render replacement factor VIII ineffective, in approximately 30% of patients with hemophilia A.[2] Inhibitors result in substantial medical complications and decreased health-related quality of life.[3-5] Treatments for hemophilia A in patients with a high titer of inhibitors (≥5 Bethesda units per milliliter) include eradication with induction of immune tolerance and episodic or prophylactic treatment with bypassing agents (recombinant activated factor VII [factor VIIa] or activated prothrombin complex concentrate).[2] The efficacy of bypassing agents remains suboptimal, and both options involve frequent intravenous infusions that depend on adequate venous access; thus, more effective and less burdensome treatments are needed.

Emicizumab (ACE910) is a recombinant, humanized, bispecific monoclonal antibody[6,7] that bridges activated factor IX and factor X to restore the function of missing activated factor VIII, which is needed for effective hemostasis. Owing to its unique structure, emicizumab is not expected to be affected by existing factor VIII inhibitors or to induce new development of such inhibitors. In a small phase 1 study, there were no dose-limiting toxic effects with once-weekly subcutaneous administration of emicizumab; this treatment markedly reduced the rate of bleeding episodes among participants with hemophilia A with or without inhibitors.[8]

The phase 3 HAVEN 1 trial assessed the efficacy, safety, and pharmacokinetics of once-weekly subcutaneous emicizumab prophylaxis in patients with hemophilia A with inhibitors. The primary objective was to compare bleeding rates among participants previously given episodic treatment with bypassing agents who received emicizumab prophylaxis versus no prophylaxis. In addition, to enable direct and accurate intraindividual comparisons of previous outcomes with bypassing agents with outcomes with emicizumab prophylaxis, a prospective, noninterventional study (ClinicalTrials.gov number, NCT02476942) was designed and conducted as part of the clinical development of emicizumab. The noninterventional study collected detailed, real-world data on bleeding events and safety outcomes from a cohort of patients with hemophilia A who received episodic or prophylactic treatment with bypassing agents according to local, routine clinical practice.[9] Participants in the noninterventional study were eligible to subsequently participate in the HAVEN 1 trial, provided that they met the eligibility criteria.

METHODS

TRIAL OVERSIGHT

This phase 3, open-label, multicenter, randomized trial was initiated on November 17, 2015. A delay in trial registration (December 2, 2015) occurred owing to an unexpected issue in the internal tracking systems of the sponsor (F. Hoffmann–La Roche), which prevented an accurate assessment of the estimated timing of the enrollment of the first participant; one participant was enrolled before trial registration. The trial was designed by the sponsor, and data were collected by the participants and site investigators. Data analysis was conducted by the trial statistician and pharmacologist (both employed by the sponsor), who vouch for the completeness and accuracy of the data and analyses. Specific direction from the authors informed the development of the first draft of the manuscript by Envision Pharma Group (funded by F. Hoffmann–La Roche), and that draft was subsequently critically reviewed by the authors. All the authors had access to the data and confirm adherence to the protocol and statistical analysis plan, which are available with the full text of this article at NEJM.org.

The trial was conducted at 43 centers (in 14 countries) in compliance with the International Conference on Harmonisation Guidelines for Good Clinical Practice[10] and the principles of the Declaration of Helsinki.[11] The trial protocol was approved by the institutional review board or ethics committee at each participating center. All adult participants or legally authorized representatives provided written informed consent before trial participation, and adolescents (12 to 17 years of age) also provided written informed assent. The data cutoff date for the primary analysis and all the data points included in this article was October 25, 2016.

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TRIAL PARTICIPANTS

Eligible participants, including participants from the noninterventional study, were 12 years of age or older with congenital hemophilia A (of any severity), had a history of a high titer of factor VIII inhibitor (≥5 Bethesda units per milliliter), and were receiving episodic or prophylactic treatment with bypassing agents. Additional eligibility criteria are provided in the Methods section in the Supplementary Appendix, available at NEJM.org.

TRIAL DESIGN

Participants receiving episodic treatment with bypassing agents before trial entry were randomly assigned in a 2:1 ratio to receive subcutaneous emicizumab prophylaxis at a dose of 3.0 mg per kilogram of body weight weekly for 4 weeks, followed by 1.5 mg per kilogram weekly thereafter (group A), or to the control group (no emicizumab prophylaxis and, because the trial was open-label, no subcutaneous control injections; group B) (Figs. S1 and S2 in the Supplementary Appendix). Participants who had previously received prophylactic treatment with bypassing agents were assigned to emicizumab prophylaxis in group C. Group D (also receiving emicizumab prophylaxis) comprised participants who were unable to enroll in HAVEN 1 groups A, B, or C before they were closed to enrollment. Participants who were randomly assigned to group B could receive emicizumab prophylaxis after completing at least 24 weeks in the trial (and remained in group B). All the participants receiving emicizumab were administered the same dose according to the same schedule and could receive episodic treatment with bypassing agents for breakthrough bleeding, as needed.

After at least 24 weeks of emicizumab prophylaxis, participants could continue taking maintenance therapy with 1.5 mg per kilogram weekly or, if they had had at least two spontaneous and clinically significant treated bleeding events in the past 24 weeks of emicizumab administration, both occurring after the end of the loading-dose period (termed "suboptimal control of bleeding"), start taking an increased dose of 3.0 mg per kilogram weekly. (For details on suboptimal control of bleeding, see the Methods section in the Supplementary Appendix.)

Definitions of bleeding events were adapted from the criteria of the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee.[12] A bleeding event was considered to be treated if it was directly followed by the administration of a hemophilia medication that was reported to be a treatment for bleeding. (For details on definitions, see the Methods section in the Supplementary Appendix.) Information on bleeding and medications was documented at the time of a bleeding event or medication use or at least once every 8 days. Assessment of health-related quality of life occurred every 4 weeks, and assessment of health status occurred at the time of a bleeding event and every 4 weeks.

END POINTS

The primary end point was the difference in the rate of treated bleeding events (hereafter referred to as the bleeding rate) over a period of at least 24 weeks between participants receiving emicizumab prophylaxis (group A) and those receiving no prophylaxis (group B) after the last randomly assigned participant had completed 24 weeks in the trial or had discontinued participation, whichever occurred first. Secondary end points for the randomized comparison (group A vs. group B) included additional bleeding-related end points (all bleeding events [both treated and not treated with bypassing agents] and events of spontaneous bleeding, joint bleeding, and target-joint bleeding), health-related quality of life (Haemophilia Quality of Life Questionnaire for Adults [Haem-A-QoL] physical health subscale and total score at week 25), and health status (the five-level version of the EuroQol Group 5-Dimension Self-Report Questionnaire [EQ-5D-5L] visual-analogue scale and index utility score at week 25). The Haem-A-QoL scales range from 0 to 100, with lower scores reflecting better health-related quality of life. Clinically meaningful differences are 10 points for the score on the physical health subscale and 7 points for the total score.[13] Scores on the EQ-5D-5L visual-analogue scale range from 0 to 100, and index utility scores range from −0.4 to 1.0; higher scores indicate better health status. Clinically meaningful differences are 7 and 0.07 points, respectively.[14,15] Additional bleeding-related end points included intraindividual comparisons of the bleeding rate and the rate of all bleeding events among participants in groups A and C who had participated in the noninterventional study.

Safety end points were adverse events, injection-site reactions, serious adverse events, thromboembolic events, abnormal laboratory values,

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and antidrug antibodies. The pharmacokinetic objective was to characterize emicizumab exposure over time. Exploratory biomarkers included those related to thrombosis (time profiles of D-dimer and prothrombin fragment 1.2).

STATISTICAL ANALYSIS

Calculation of the sample size (with the use of the Wald test) was based on the primary efficacy end point and clinical considerations. We estimated that a sample of 51 participants with a withdrawal rate of 10% in the control group would provide a power of more than 95% at a two-sided significance level of 0.05 to detect an effect size of 4/18=0.22 (null hypothesis: rate ratio=1). For all bleeding-related end points, comparisons of the bleeding rate in group A versus group B and the intraindividual comparisons were performed with the use of a negative binomial-regression model to determine the bleeding rate per day, which was converted to an annualized bleeding rate. End points with respect to health-related quality of life and health status were analyzed with the use of analysis of covariance. Type I error for secondary end points was controlled through the hierarchical testing framework. For all efficacy end points and corresponding safety analyses, only the no-prophylaxis period was included from group B. For end points with respect to intraindividual comparisons, only those who participated in the noninterventional study were included, to allow for analyses that used prospective data collection with the same detail for bleeding and medication data before and during emicizumab treatment. Additional analyses to allow for a comprehensive assessment of emicizumab efficacy and safety were conducted with the use of all the data collected during emicizumab prophylaxis.

RESULTS

TRIAL POPULATION

All 109 participants enrolled were male patients with hemophilia A with inhibitors, with a median age of 28 years (range, 12 to 75) (Table 1, and Table S1 in the Supplementary Appendix). Most had severe hemophilia; 7 of 109 participants previously had mild or moderate disease. Although participants who had previously received episodic or prophylactic treatment with bypassing agents could enroll in group D, at the time of data cutoff all 7 participants in group D had received episodic treatment with bypassing agents. The percentage of participants who had previously undergone induction of immune tolerance was as follows: 40% in group A, 39% in group B, 67% in group C, and 43% in group D. Most participants (70%) had target joints; 49% had more than one target joint. The median exposure to emicizumab treatment was 24.0 weeks (range, 3.0 to 47.9) overall and 29.5 weeks (range, 3.3 to 47.9) in group A (see the Results section in the Supplementary Appendix).

EFFICACY

The annualized bleeding rate was 2.9 events (95% confidence interval [CI], 1.7 to 5.0) with emicizumab prophylaxis (group A) versus 23.3 events (95% CI, 12.3 to 43.9) with no prophylaxis (group B), representing a significant difference of 87% in favor of emicizumab prophylaxis (P<0.001) (Fig. 1, and Table S2 in the Supplementary Appendix). Results were consistent across subgroups (Fig. S3 in the Supplementary Appendix). Significant differences in favor of emicizumab prophylaxis were also observed in all secondary bleeding-related end points, including events of spontaneous bleeding, joint bleeding, and target-joint bleeding as well as all bleeding events (Table S2 in the Supplementary Appendix). Of the 35 participants who were randomly assigned to emicizumab prophylaxis, 22 (63%) had zero bleeding events (median annualized bleeding rate, 0.0 events; interquartile range, 0.0 to 3.7) (Table S2 in the Supplementary Appendix). Only 1 of the 18 participants (6%) who were assigned to no prophylaxis had zero bleeding events.

Among 24 participants in group C who had participated in the noninterventional study, intraindividual comparisons showed a significantly lower bleeding rate with emicizumab prophylaxis than with previous bypassing-agent prophylaxis (annualized bleeding rate, 3.3 events [95% CI, 1.3 to 8.1] vs. 15.7 events [95% CI, 11.1 to 22.3]), representing a difference of 79% (P<0.001) (Fig. 2). Among 24 participants in group A who had participated in the noninterventional study, the bleeding rate was also significantly lower with emicizumab prophylaxis than with previous episodic treatment with bypassing agents (annualized bleeding rate, 1.7 events [95% CI, 0.7 to 4.1] vs. 21.6 events [95% CI, 15.4 to 30.2]), representing a difference of 92% (P<0.001) (Fig. S3 in the Supplementary Appendix).

For emicizumab prophylaxis as compared with

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Table 1. Demographic and Clinical Characteristics of the Participants.*

Characteristic	Group A: Emicizumab Prophylaxis (N=35)	Group B: No Prophylaxis (N=18)	Group C: Emicizumab Prophylaxis (N=49)	Group D: Emicizumab Prophylaxis (N=7)	Total (N=109)
Age					
Median — yr	38.0	35.5	17.0	26.0	28.0
Range — yr	12–68	13–65	12–75	19–49	12–75
<18 yr — no. (%)	4 (11)	2 (11)	26 (53)	0	32 (29)
Hemophilia severity at baseline — no. (%)					
Mild	2 (6)	0	1 (2)	0	3 (3)
Moderate	2 (6)	0	1 (2)	1 (14)	4 (4)
Severe	31 (89)	18 (100)	47 (96)	6 (86)	102 (94)
≥9 Bleeding events in 24 wk before trial entry — no. (%)	24 (69)	13 (72)	26 (53)	3 (43)	66 (61)
Target joints†					
Yes — no. (%)	25 (71)	13 (72)	34 (69)	4 (57)	76 (70)
>1 — no./total no. (%)	18/25 (72)	10/13 (77)	24/34 (71)	1/4 (25)	53/76 (70)
Highest historical titer of factor VIII inhibitor					
No. of participants with available data‡	32	16	47	6	101
Median — Bethesda units/ml	84.5	102.0	309.0	240.0	180.0
Range — Bethesda units/ml	5–1570	18–4500	11–5000	28–2125	5–5000
Previous induction of immune tolerance — no. (%)	14 (40)	7 (39)	33 (67)	3 (43)	57 (52)

* Participants who had received episodic treatment with bypassing agents before trial entry were randomly assigned in a 2:1 ratio to receive subcutaneous emicizumab prophylaxis (group A) or no emicizumab prophylaxis (group B). Participants who had previously received prophylactic treatment with bypassing agents were assigned to emicizumab prophylaxis in group C. Group D (also receiving emicizumab prophylaxis) comprised participants who were unable to enroll in groups A, B, or C before they were closed to enrollment. Participants who were randomly assigned to group B had the opportunity to receive emicizumab prophylaxis once they had completed at least 24 weeks in the trial (and remained in group B) (Figs. S1 and S2 in the Supplementary Appendix). Participants receiving emicizumab continued to receive episodic treatment with bypassing agents for breakthrough bleeding, as needed. Information on previous use of episodic and prophylactic coagulation products is available in Table S1 in the Supplementary Appendix.
† All values are based on electronic case-report forms and not on data from the noninterventional study.
‡ All participants with available data had a factor VIII inhibitor titer of at least 5 Bethesda units per milliliter.

no prophylaxis (group A vs. group B), the adjusted means of observed differences at week 25 and clinically meaningful differences as determined from published literature, respectively, were as follows: score on the Haem-A-QoL physical health subscale, 21.6 points (95% CI, 7.9 to 35.2; P=0.003) and 10 points; total score on the Haem-A-QoL, 14.0 points (95% CI, 5.6 to 22.4; P=0.002) and 7 points; score on the EQ-5D-5L visual-analogue scale, –9.7 points (95% CI, –17.6 to –1.8; P=0.02) and 7 points; and EQ-5D-5L index utility score, –0.16 points (95% CI, –0.25 to –0.07; P=0.001) and 0.07 points. The observed differences between the two groups indicate that emicizumab prophylaxis had significant benefits with respect to health-related quality of life and health status.

SAFETY

Overall, 198 adverse events were reported in 103 participants receiving emicizumab prophylaxis. The most frequently reported adverse events were injection-site reactions, with 28 events in 15 participants (15%) (Table 2). All were mild in intensity and resolved, except for 1 moderate event of injection-site hematoma, which occurred on trial day 2 and resolved on day 28. Proportionally fewer participants had adverse events in groups B and D than in groups A and C; however, observation periods were also shorter. Overall, 12 serious adverse events were reported in 9 participants (9%) (Table S3 in the Supplementary Appendix). Thrombotic microangiopathy (in 2 participants) and cavernous sinus thrombosis and skin necrosis–superficial throm-

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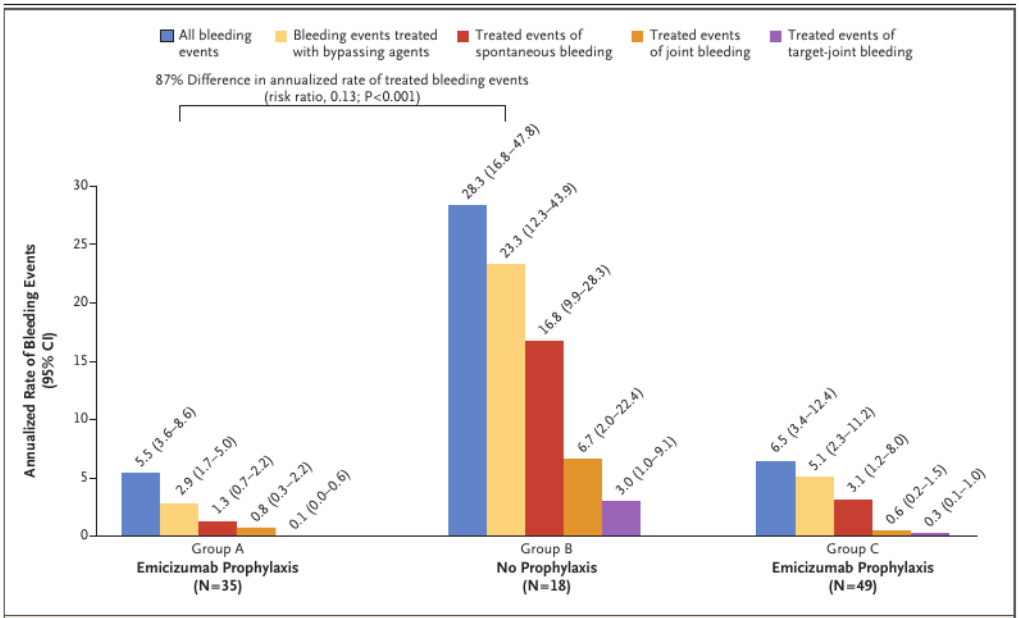

Figure 1. Annualized Bleeding Rate in Trial Groups A, B, and C.

The annualized bleeding rate was calculated with the use of a negative binomial-regression model. Participants in groups A and B had previously received episodic treatment with bypassing agents; participants in group C had previously received prophylaxis with bypassing agents. Group D was not included in the current analysis owing to the short follow-up at the time of data cutoff.

bophlebitis (in 1 participant each) were reported in participants who had received multiple infusions of activated prothrombin complex concentrate while receiving emicizumab prophylaxis before event onset. (Case details are provided in the Results section in the Supplementary Appendix.) Both events of thrombotic microangiopathy resolved after treatment with activated prothrombin complex concentrate was stopped, and neither thrombotic event required anticoagulation. Two participants (1 with thrombotic microangiopathy and 1 with thrombosis) restarted emicizumab treatment.

After the data cutoff for the primary analysis, thrombotic microangiopathy developed in 1 additional participant 5 days after his previous emicizumab dose and after 4 consecutive days of treatment with activated prothrombin complex concentrate for rectal hemorrhage; the rectal bleeding was recurrent and eventually fatal. As assessed by the investigator, thrombotic microangiopathy was resolving at the time of death.

Of 104 participants who received emicizumab prophylaxis, 28 (27%) used activated prothrombin complex concentrate, 34 (33%) used recombinant factor VIIa, and 13 (12%) used both bypassing agents (Table S4 in the Supplementary Appendix). A range of doses of recombinant factor VIIa was used, although treatment episodes generally lasted for 1 day. Most use of activated prothrombin complex concentrate was less than 100 U per kilogram for 1 day, but a small number of treatment episodes averaged more than 100 U per kilogram daily and lasted more than 1 day (19 treatment events) (Table S5 in the Supplementary Appendix). The 5 participants who had thrombotic microangiopathy or thrombosis did so after treatment with activated prothrombin complex concentrate that averaged more than 100 U per kilogram daily for more

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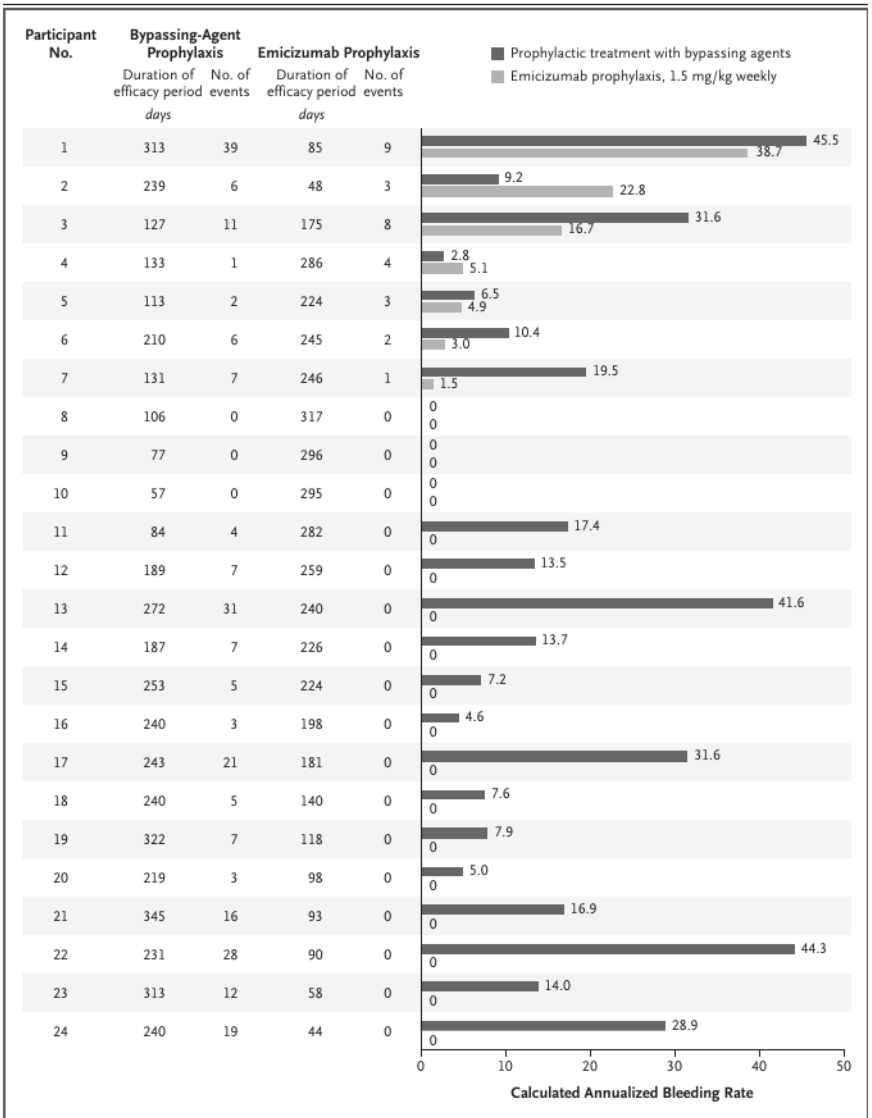

Figure 2. Intraindividual Comparison of Treated Bleeding Events in Participants Receiving Emicizumab Prophylaxis (Group C) versus Previous Prophylactic Treatment with Bypassing Agents before Trial Entry.

Shown are data for the 24 participants in group C who had participated in the noninterventional study. Data are sorted according to the annualized bleeding rate with emicizumab prophylaxis in descending order and then according to descending duration of efficacy period with regard to emicizumab prophylaxis.

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Table 2. Adverse Events in Participants Receiving Emicizumab Prophylaxis, According to Trial Group.*

Event	Group A (N=34)	Group B (N=13)†	Group C (N=49)	Group D (N=7)	Total (N=103)
	number of participants (percent)				
Injection-site reaction	8 (24)	1 (8)	5 (10)	1 (14)	15 (15)
Headache	3 (9)	1 (8)	6 (12)	2 (29)	12 (12)
Fatigue	3 (9)	1 (8)	2 (4)	0	6 (6)
Upper respiratory tract infection	7 (21)	0	2 (4)	0	9 (9)
Arthralgia	2 (6)	1 (8)	3 (6)	0	6 (6)

* Shown are events that occurred in at least 5% of all the participants who received emicizumab prophylaxis.
† Data are for the period of emicizumab prophylaxis only.

than 1 day (see the Results section in the Supplementary Appendix). No events occurred after the use of activated prothrombin complex for 1 day, after treatment with recombinant factor VIIa alone (even at high doses), or with emicizumab prophylaxis alone. Levels of D-dimer and prothrombin fragment 1.2 were not affected by emicizumab treatment over time.

PHARMACOKINETIC AND IMMUNOGENICITY VARIABLES

Mean trough plasma concentrations of emicizumab of more than 50 μg per milliliter were observed after four loading doses of 3.0 mg per kilogram weekly and sustained throughout the trial with maintenance doses of 1.5 mg per kilogram weekly (Fig. 3). No participants tested positive for antidrug antibodies; however, two participants had pharmacokinetic profiles with declining exposure to emicizumab that were potentially indicative of antidrug antibodies (Fig. S7 in the Supplementary Appendix). After 24 weeks of emicizumab treatment, factor VIII inhibitor titers remained stable or tended to decline over time in the majority of participants.

DISCUSSION

In the HAVEN 1 trial, once-weekly emicizumab prophylaxis that was administered subcutaneously in patients with hemophilia A with inhibitors was associated with a bleeding rate that was 87% lower than the rate with no prophylaxis. These findings were supported by substantially lower rates of other bleeding-related end points (events of spontaneous bleeding, joint bleeding, and target-joint bleeding as well as all bleeding events) with emicizumab prophylaxis than with no prophylaxis. A total of 63% of the participants who were randomly assigned to receive emicizumab prophylaxis had zero bleeding events during the trial. These positive outcomes confirm previously reported results of a phase 1 study.[8] The events of thrombotic microangiopathy and thrombosis that developed in five participants during the trial were associated with the use of high cumulative doses of activated prothrombin complex concentrate for breakthrough bleeding during the receipt of emicizumab prophylaxis.

A prospective intraindividual comparison showed that emicizumab prophylaxis resulted in a bleeding rate that was 79% lower than the rate observed with previous bypassing-agent prophylaxis. The markedly lower rate of bleeding events with emicizumab prophylaxis than with no prophylaxis translated into significant benefits in participants' health-related quality of life and health status.[13-15]

The events of thrombotic microangiopathy and thrombosis that were observed developed after treatment with activated prothrombin complex concentrate at doses averaging more than 100 U per kilogram daily for more than 1 day during the administration of emicizumab prophylaxis; no events were reported with emicizumab prophylaxis either alone or with activated prothrombin complex concentrate administered for only 1 day or with recombinant factor VIIa (administered without activated prothrombin complex concentrate). In addition, no elevations in the level of D-dimer or prothrombin fragment 1.2 over time were observed, which suggests no significantly increased risk of thromboembolism

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in association with emicizumab prophylaxis alone. Two events of thrombotic microangiopathy resolved completely (the third participant died from rectal hemorrhage after the primary analysis), and the thrombotic events did not require anticoagulation. Recovery from these events occurred in the continued presence of emicizumab in plasma owing to its long half-life,[16] and no recurrence of thrombotic microangiopathy or thrombosis was seen in the two participants who restarted emicizumab.

Synergistic thrombin generation has previously been shown with activated prothrombin complex concentrate in combination with emicizumab in vitro and in vivo.[17] Substrates for emicizumab to form the intrinsic tenase complex are supplied by activated prothrombin complex concentrate, along with other activated and nonactivated coagulation factors that have half-lives of up to 60 hours and can accumulate with multiple doses.[18] Although the data are scant, the combined use of activated prothrombin complex concentrate and emicizumab prophylaxis appears to be associated with a substantial risk of toxic effects, which may limit the usefulness of this bypassing agent in patients who bleed while receiving emicizumab prophylaxis.

No antidrug antibodies were detected; however, two participants had pharmacokinetic profiles with declining emicizumab concentrations over time that were potentially indicative of antidrug antibodies. One participant had no bleeding events while receiving emicizumab prophylaxis, and the other is being monitored after an increase in the dose of emicizumab, which occurred shortly before the primary analysis. Both participants remained in the trial; longer follow-up will provide further insight into the efficacy and pharmacokinetic outcomes of these participants.

Stable trough plasma concentrations of emicizumab were observed after 4 weeks of loading doses and were sustained with weekly maintenance doses throughout the trial. With this previously untested dosing regimen, which was determined by means of pharmacokinetic and pharmacodynamic modeling, the trough concentrations that were observed (>50 μg per milliliter) are expected to result in a bleeding rate of zero among at least 50% of the participants.[19]

Limitations of the trial include its open-label nature, which may have affected the results for end points with respect to health-related quality of life and health status; however, because all results for primary and secondary end points were positive, these consistent results probably reflect true differences between the randomly assigned groups. Selection bias for groups C and D should also be considered. At the time of enrollment, participants had had at least six and two bleeding events during the previous 24 weeks of prophylactic and episodic treatment with bypassing agents, respectively. Thus, these participants could potentially show a more substantial decrease in bleeding events over the course of the trial than participants with lower pretrial bleeding rates, had they been eligible. Finally, follow-up for some participants (in groups C and D) was less than 24 weeks; however, all randomly assigned participants had at least 24 weeks of follow-up for the primary and secondary end points, and durable efficacy has been shown for up to 2 years in the phase 1 study.[20]

In conclusion, emicizumab prophylaxis was associated with a significantly lower rate of bleeding events than no prophylaxis or previous prophylactic treatment with bypassing agents among patients with hemophilia A with inhibitors, and it improved health-related quality of life. Emicizumab was safe when administered alone or in conjunction with recombinant factor VIIa

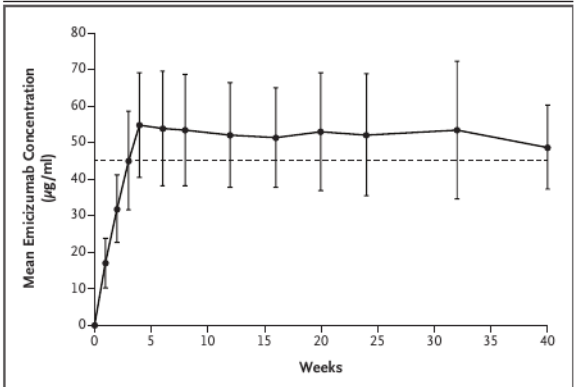

Figure 3. Observed Trough Plasma Concentrations of Emicizumab over Time with Once-Weekly Dosing (102 Patients).

As determined by pharmacokinetic and pharmacodynamic modeling, emicizumab doses of 1.5 mg per kilogram of body weight per week were predicted to result in trough plasma concentrations of emicizumab of 45 μg per milliliter (dashed line). I bars indicate standard deviations.

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alone. Thrombotic microangiopathy or thrombosis occurred only in patients who received high cumulative doses of activated prothrombin complex concentrate for breakthrough bleeding while receiving emicizumab prophylaxis; thus, the usefulness of this bypassing agent may be limited in patients who have bleeding events while receiving emicizumab prophylaxis. Emicizumab may provide a weekly, subcutaneous, prophylactic therapeutic option for patients with hemophilia A with inhibitors.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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[no notes on this page]

Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med 2017;377:809-18. DOI: 10.1056/NEJMoa1703068

[no notes on this page]

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

1

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PROTOCOL

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC RO5534262 VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
PROTOCOL NUMBER:	BH29884
VERSION NUMBER:	1
EUDRACT NUMBER:	2015-002866-21
IND NUMBER:	122,954
TEST PRODUCT:	RO5534262
MEDICAL MONITOR:	[redacted], M.D., M.Phil.
SPONSOR:	F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.*
DATE FINAL:	See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	02-Jul-2015 23:56:17

*Chugai will act as the Sponsor **only** in South Korea, Taiwan, and Japan. The specific details of the legal/regulatory entity within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and the Clinical Trial Application with the Competent Authority.

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC RO5534262 VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
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TEST PRODUCT:	RO5534262
MEDICAL MONITOR:	[redacted], M.D., M.Phil.
SPONSOR:	F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of this form to your local study monitor.

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PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC RO5534262 VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
PROTOCOL NUMBER:	BH29884
VERSION NUMBER:	1
EUDRACT NUMBER:	2015-002866-21
IND NUMBER:	122,954
TEST PRODUCT:	RO5534262
PHASE:	Phase III
INDICATION:	Hemophilia A with inhibitors
SPONSOR:	F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.

Objectives and Endpoints

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of prophylactic RO5534262 compared with no prophylaxis in patients with hemophilia A with inhibitors on the basis of the following endpoint:

- Number of bleeds over time (i.e., bleed rate)

Secondary Efficacy Objectives

The secondary efficacy objectives and endpoints for this study are as follows:

- Prophylactic RO5534262 compared with no prophylaxis
  - To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate over the last 24 weeks prior to study entry or for the duration of their participation in the non-interventional study, whichever is longer
  - To evaluate the efficacy in reducing the number of joint bleeds over time
  - To evaluate the efficacy in reducing the number of target joint bleeds over time (target joints are defined as joints with ≥3 bleeds occurring in the same joint over the last 24 weeks prior to study entry)
  - To evaluate the health-related quality of life (HRQoL) of patients according to Haem-A-QoL (age ≥ 18) or Haemo-QoL-Short Form (ages 12–17) scores at 24 and 48 weeks
  - To evaluate the health status of patients according to EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) scores at 24 and 48 weeks
- Open-label prophylactic RO5534262 for patients previously treated with prophylactic bypassing agents (e.g., activated prothrombin complex concentrate [aPCC] and recombinant activated factor VII [rFVIIa])
  - To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate over the last 24 weeks prior to study entry

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Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of prophylactic RO5534262 compared with no prophylaxis on the basis of the following endpoints:

- To assess differences in number of days away from school/work
- To assess differences in number of days hospitalized
- To assess potential pharmacodynamic (PD) biomarkers of RO5534262, including but not limited to aPTT, thrombin generation, and FVIII activity, at timepoints throughout the study

Safety Objective

The safety objective for this study is as follows:

- To evaluate the overall safety of prophylactic RO5534262 compared with no prophylaxis in patients with hemophilia A with inhibitors on the basis of the following endpoints:
  - The incidence and severity of adverse events
  - The incidence and severity of thromboembolic events
  - Changes in physical examination findings and vital signs
  - Incidence of laboratory abnormalities
  - Incidence and severity of injection-site reactions
  - Incidence of adverse events leading to drug discontinuation
  - Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events
  - The incidence and clinical significance of anti-RO5534262 antibodies

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the exposure (C_{trough}) of RO5534262 prior to drug administration on Day 1 at the following timepoints:

- Every week during Weeks 1–4 on RO5534262
- Every 2 weeks during Weeks 5–8 on RO5534262
- Every 4 weeks during Weeks 9–24 on RO5534262
- Every 8 weeks during Weeks 25–48 on RO5534262
- Every 12 weeks thereafter while on RO5534262, until the end of the study

Study Design

Description of Study

This randomized, multicenter, open-label, Phase III clinical study will enroll patients aged 12 years or older with hemophilia A who have inhibitors against factor VIII (FVIII). Approximately 51 patients with inhibitors who received episodic treatment (i.e., administered following bleeds) with bypassing agents prior to study entry will be enrolled globally and randomized in a 2:1 ratio (see protocol) to receive either prophylactic RO5534262 at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously thereafter (Arm A), or to the control arm (Arm B), which will consist of no prophylaxis. Given the potential heterogeneity of bleed rates in the study patient population, randomized patients will be stratified according to the number of bleeds they experienced over the last 24 weeks prior to study entry (< 9 or ≥ 9 bleeds) to ensure a balance of inhibitor patients with lower versus higher number of bleeds, respectively, at baseline across the two randomized arms of the proposed Phase III study. All patients will continue to receive standard of care/background treatment with their usual episodic bypassing agent therapy to treat breakthrough bleeds, as needed.

In addition, given that some patients with hemophilia A with inhibitors are also currently treated with bypassing agents on a prophylactic basis, approximately 10–20 patients with inhibitors on prophylactic bypassing agents will be enrolled in a separate therapeutic arm (Arm C) to receive prophylactic RO5534262 at the same dose and schedule (see protocol).

The primary efficacy analysis, defined as comparing the number of bleeds over time for patients randomized to receive prophylactic RO5534262 versus no prophylaxis, will be conducted after

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the last randomized patient completes 24 weeks in the study or discontinues study participation, whichever occurs first. An interim analysis (see protocol), in which an independent Data Monitoring Committee (iDMC) will evaluate safety and efficacy, will be conducted after approximately 50% of the randomized population has completed at least 24 weeks in the study.

To obtain additional safety and efficacy data, prior episodic bypassing agent patients who had been randomized to not receive RO5534262 (control arm, Arm B) will crossover to receive prophylactic RO5534262, at the same dose and schedule as patients who started Study BH29884 on RO5534262, once they complete 24 weeks in the study. In addition, after 24 weeks on prophylactic RO5534262, all patients will be able to continue on their 1.5 mg/kg/week maintenance dose or may be provided the option to increase their dose to 3 mg/kg/week if they meet protocol-defined criteria of suboptimal response and receive approval from the Medical Monitor to do so (see protocol). Patients who continue to derive clinical benefit will be given the opportunity to continue receiving prophylactic RO5534262 [redacted].

During the study, individual bleeds will be captured as they occur, while HRQoL, health status, patient safety, and days of school or work missed will be assessed every 4 weeks for approximately 24 weeks and every 4–12 weeks thereafter, as outlined in the schedule of assessments in the protocol. Patients (or their legally authorized representative) will be asked on a daily basis via their electronic patient-reported outcome (ePRO) device whether a bleed has occurred and whether treatment for a bleed or treatment to prevent a bleed has been given. In addition, health status information will be collected whenever a bleed is reported.

Physical examinations, vital sign assessments, ECG, and laboratory assessments will be collected as per the schedule of assessments and will be the same for all patients receiving RO5534262, regardless of whether they are enrolled in the randomized portion of the study or in the separate non-randomized arm. Adverse events will be captured on an ongoing basis, as they occur during the study.

All patients who receive RO5534262 in the study will undergo a PK assessment. As RO5534262 is intended in this study for prophylactic use only (i.e., not to treat bleeds that have already occurred), neither aPCC nor rFVIIa interfere with RO5534262 PK assessments, and some patients with hemophilia A with inhibitors require frequent dosing with bypassing agents due to having many bleeds or being on prophylaxis, a washout period is not required prior to inclusion so that new bleeds are minimized and treatment for any ongoing bleeds is not interrupted.

Exploratory PD biomarkers (e.g., aPTT, FVIII activity, thrombin generation assay) will be collected as per the schedule of assessments. As values for these tests are normalized by even low plasma concentrations of RO5534262 (see protocol), a variety of assay formats (one-stage, chromogenic) and modifications (pre-dilution of patient plasma) will be investigated for assessment of PD response at higher RO5534262 plasma concentrations. [redacted] In addition, factor IX and factor X antigen levels will be monitored.

Throughout the study, biomarkers related to thromboembolism (e.g., D-dimer, prothrombin 1.2 fragment) and RO5534262 trough concentrations will be collected as per the schedule of assessments. Immunologic biomarkers (i.e., anti-RO5534262 antibodies) will also be measured as per the schedule of assessments (see protocol).

An iDMC composed of, at minimum, hemostasis/thrombosis experts and a statistician will be in place throughout the duration of the study and will monitor patient safety at pre-specified intervals and ad hoc as needed throughout the study. Stopping rules for the study will be included for select adverse events of special interest, which are outlined in the protocol, and will be specified in the iDMC Charter.

Breakthrough bleeds will be treated with bypassing agents according to standard of care and captured as they occur on the ePRO device. Of note, the clinical experience in the ongoing Phase I/II clinical studies includes the treatment of over [redacted] breakthrough bleeds in patients receiving RO5534262 with either FVIII or bypassing agents without any related safety concerns reported. Investigators will be asked to contact the Medical Monitor in the event of suspected lack or loss of efficacy of RO5534262 in order to discuss potential laboratory evaluations (e.g.,

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anti-RO5534262 antibodies, coagulation tests) to be performed as well as to re-evaluate the patient's benefit-risk of continued treatment. When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, category of bleed, time of each individual bleed (day, start time), symptoms of bleed, and treatment for bleed. Health status information will also be collected on the day a bleed occurs.

The reason for the use of coagulation products (e.g., aPCC or rFVIIa will be documented (e.g., bleeding, prophylaxis, pain, etc.). A thorough documentation of the treatments for bleeds will be requested, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed.

As mentioned in the protocol, a non-interventional study (Study BH29768) has been initiated to document the number and types of bleeds and current treatment with episodic or prophylactic bypassing agents, as well as collect information on HRQoL, health status, and safety in patients with hemophilia A with FVIII inhibitors. The assessments in the non-interventional study will mitigate the risk of underreporting of bleeds that oftentimes occurs in the real world, and the resulting data will serve as a source of comparator information for some analyses conducted in the Phase III clinical study (Study BH29884). The non-interventional study will also allow an investigation of the feasibility of using an ePRO device that has been developed to record data related to bleeds, HRQoL, and health status. In addition, the non-interventional study will enable earlier identification and confirmation of patients who may qualify for the Phase III clinical study. It is anticipated that a significant number of patients participating in Study BH29768 will enroll in Study BH29884, as long as they meet the inclusion and exclusion criteria of the study and are able to enroll at a participating site while the study is open for enrollment.

Number of Patients

Approximately 61−71 patients with hemophilia A with inhibitors—approximately 51 who previously received episodic bypassing agents and approximately 10−20 who previously received prophylactic bypassing agents (depending on the timing of the primary efficacy analysis)

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of patient-reported outcomes questionnaires and daily bleed questionnaire through the use of an electronic device
- Aged 12 years or older at the time of informed consent
- Body weight ≥ 40 kg at the time of screening
- Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (i.e., ≥ 5 Bethesda Units)
- Documentation of treatment with episodic or prophylactic bypassing agents for at least the last 24 weeks
- ≥ 6 (if on an episodic bypassing agent regimen) or ≥ 2 (if on a prophylactic bypassing agent regimen) bleeds in the last 24 weeks
- Adequate hematologic function, defined as platelet count ≥ 100,000/μL and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin ≤ 1.5 × the upper limit of normal (ULN) (excluding Gilbert's syndrome) and AST and/or ALT ≤ 3 × ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine ≤ 2.5 × ULN and creatinine clearance by Cockcroft-Gault formula ≥ 30 mL/min

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- For women who are not postmenopausal (≥48 weeks of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined highly effective non-hormonal contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of non-hormonal contraceptive methods with a failure rate of <1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of <1% per year. Barrier methods must always be supplemented with the use of a spermicide.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Inherited or acquired bleeding disorder other than hemophilia A
- Ongoing (or plan to receive during the study) immune tolerance induction therapy or prophylaxis with FVIII
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Previous or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which antithrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Previous or concurrent autoimmune or connective tissue disease
- History of hypersensitivity associated with monoclonal antibody therapies or components of the RO5534262 injection
- Known HIV infection with CD4 count <200 cells/μL within 24 weeks prior to screening
- Use of systemic immunomodulators (e.g., interferon or rituximab) at enrollment or planned use during the study, with the exception of antiretroviral therapy
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study or that would, in the opinion of the investigator or Sponsor, preclude the patient's safe participation in and completion of the study or interpretation of the study results
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Receipt of

  RO5534262 in a prior investigational study

  An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration

  A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter

  An investigational drug concurrently
- Unwillingness to use highly effective contraception methods for the specified duration in the protocol (females only, unless required otherwise by the local health authority)
- Clinically significant abnormality on screening evaluations or laboratory tests that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient

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- Pregnancy or lactation, or intent to become pregnant during the study

  Women who are not postmenopausal (≥48 weeks of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

End of Study and Length of Study

The approximate length of the entire study from the first patient enrolled to the Last Patient Last Visit (i.e., 24-week follow-up visit after discontinuing RO5534262) is approximately 108 weeks.

The end of this study is defined as the date when the last patient completes the end of study, safety follow-up visit 24 weeks after discontinuing RO5534262, [redacted], or is lost to follow-up.

Investigational Medicinal Products

Test Product (Investigational Drug)

RO5534262 3 mg/kg/week subcutaneously for 4 weeks when initiating treatment, followed by 1.5 mg/kg/week subcutaneously for a minimum of 24 weeks total. There will be an option to increase the dose after 24 weeks of treatment to 3 mg/kg/week if a patient meets criteria for insufficient control of bleeds on the 1.5 mg/kg/week RO5534262 dose and with approval from the Medical Monitor.

To support home administration of the drug, patients/caregivers will be required to complete in-person, instructional training on how to administer RO5534262 as a subcutaneous (SC) injection. Patients/caregivers will be taught to perform the injections utilizing the Instructions for Use document. They will observe at least one SC injection performed by a healthcare provider (HCP) and will need to successfully administer at least one SC injection under an HCP's watch prior to starting home administration. The first five weekly treatments will be administered in a monitored setting, such as an infusion center, clinic, or hospital, in conjunction with RO5534262 PK assessments. Patients will be observed for a minimum of 60 minutes after the first three doses. Patients/caregivers will be instructed on how to recognize signs/symptoms of hypersensitivity (including anaphylaxis) and obtain emergency care in the event of such reactions occurring. Each site will have the discretion to provide additional training or include additional observation (e.g. after the fourth and fifth doses), if deemed appropriate, and each patient/caregiver will be able to ask any question they may have prior to being deemed capable of performing SC RO5534262 injections at home. If, despite additional training, the investigator determines that the patient/caregiver is unable to inject RO5534262, a trained and proficient caregiver or HCP should be identified to administer the SC injections. Patients/caregivers will be provided with contact information for the clinic in case they have questions related to self-administration between visits.

Compliance in the home setting is to be monitored by use of a hemophilia medication log on the ePRO device, as well as by the return of used and unused medication.

Statistical Methods

Efficacy Analyses

The primary and secondary efficacy analyses to evaluate the clinical effect of prophylactic RO5534262 compared with no prophylaxis will include all randomized patients, with patients grouped according to the treatment assigned at randomization. For patients previously treated with prophylactic bypassing agents, the efficacy analysis will include all enrolled patients.

Primary Efficacy Endpoint

The primary efficacy objective is to evaluate the clinical effect of prophylactic RO5534262 compared with no prophylaxis on the number of bleeds over time. The definition of a bleed is described in the protocol.

The primary efficacy analysis will be conducted after all randomized patients have reached 24 weeks in the study or discontinue study participation, whichever occurs first, and using an intent-to-treat principle. The comparison of the number of bleeds over time between the randomized treatment arms will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study included as an offset in the

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model. The model also includes the number of bleeds (<9 or ≥ 9) in the last 24 weeks prior to study entry as a stratification factor in the randomization. This analytic model estimates the rate ratio, λ_t / λ_c., which quantifies the risk of bleeding associated with prophylactic RO5534262 (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level, and the estimated risk ratio is compared with 1, assuming the following statistical hypothesis:

H_0 (null hypothesis): Rate Ratio $= 1$ versus H_1 (alternative hypothesis): Rate Ratio $\neq 1$

The treatment effect therein is based on a contrast statement in the model with use of the SAS GENMOD procedure. Statistical significance at the pre-specified alpha level will be based on a Wald testing procedure. Bleed rates for prophylactic RO5534262 and no prophylaxis and the rate ratio will be presented and include 95% confidence intervals.

The number of bleed episodes can also be annualized for each patient using the following formula: Annualized bleeding rate (ABR) = (Number of bleeds during the efficacy period/Total number of days during the efficacy period) $\times$ 365.25. If the negative binomial model converges, an analysis of variance (ANOVA) to compare the mean ABR between the randomized arms will be provided only as a sensitivity analysis. However, if the convergence of the negative binomial model is not achieved or is questionable, the primary efficacy analysis will be based on the ANOVA of ABR.

A detailed description of the statistical methods that will be used for the primary and secondary efficacy analyses will be provided in the Statistical Analysis Plan (SAP).

Secondary Efficacy Endpoint

For all patients, the number of bleeds over time will be compared with the patient's bleed rate over the last 24 weeks prior to study entry recorded in the medical record and/or for the duration of their participation in the non-interventional study, whichever is longer.

In addition, the number of joint and target joint bleeds over 24 weeks' time between the RO5534262 prophylaxis and no prophylaxis arms will be evaluated. Adherence with the HRQoL and health status measures captured in the ePRO device will be summarized at the end of the study.

HRQoL (using the Haem-A-QoL or the Haemo-QoL-SF) and health status (using the EQ-5D-5L) will be assessed on a regular basis as per the schedule of assessments (scheduled). Health status will also be assessed in the event of a bleed (unscheduled).

Because different HRQoL measures (Haem-A-QoL and the Haemo-QoL-SF) are being used for the adult and adolescent patients, all calculations and analyses will be conducted separately for adults and adolescents. Scale scores for the Haem-A-QoL and Haemo-QoL-SF will be calculated and summarized descriptively. The HRQoL scale scores for all patients will be evaluated at 24 weeks in the study, a timepoint that is consistent with other recent registrational studies in hemophilia and analyses of such data. An additional sensitivity analysis will be performed utilizing patients' HRQoL scale scores at 48 weeks or the time of the most recent HRQoL assessment, whichever occurs later. For each treatment arm, paired t-tests will be used to compare the 24-week and final assessments with the baseline scale scores for each HRQoL measure. Statistical significance will be set at $p < 0.05$. Within-subject and between-group changes from baseline on the different HRQoL scale scores will also be calculated at 24 weeks and the final HRQoL assessment.

For the assessments of the EQ-5D-5L performed every 4 weeks, the number and percentage of patients in each of the five categories for each question for each group will be assessed. Changes in the EQ-5D-5L index utility score from baseline will also be compared between groups. In addition, summary statistics including mean, standard deviation, median, minimum and maximum will be displayed for the patients' health state using the EQ-VAS both within and between groups. The proportion of patients who report changes in each group exceeding the clinically meaningful threshold on the EQ-5D-5L index and EQ-VAS scores in each group will be reported at 24 weeks and the final, scheduled EQ-5D-5L assessment.

Separately, for each EQ-5D-5L completed in connection with a bleed, the level of pain associated with that episode, as well as the utility score and general health score, will be reported.

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Secondary endpoints used for labeling and those that are solely for scientific interest will be specified in the SAP. The method used for controlling the type 1 error rate will also be described.

Safety Analyses

The safety analyses population will be based on all enrolled patients grouped according to the actual treatment received. Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology, including complete blood count with differential), ECGs, vital signs, and antibodies to RO5534262.

To evaluate the overall safety of prophylactic RO5534262 compared to no prophylaxis, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade for each treatment arm.

For clinical laboratory data, summary statistics will be presented by treatment arm. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

Data on the impact of immunogenicity (anti-RO5534262 antibodies) on safety, efficacy, and/or clinical pharmacology and PK will be summarized adopting standard language/terminology.

Pharmacokinetic Analysis

For all patients, pre-dose (trough) plasma concentrations of RO5534262 will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will be used to analyze the dose-concentration-time data of RO5534262 following SC administration. Population PK parameters, such as clearance and volume of distribution, will be estimated, and the influence of various covariates, such as age, gender, and body weight, on these parameters will be investigated graphically. Secondary PK parameters, such as area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies. These analyses will be reported in a dedicated report.

Exploratory Analyses

Summary statistics of the number of work/school days missed and days hospitalized will be presented by treatment arm.

PD parameters (e.g., aPTT, parameters derived from thrombin generation, FVIII activity) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Interim Analysis

Although this is an open-label study, Sponsor personnel will not have access to by-arm efficacy and safety summaries prior to the formal reporting of the study results. HCPs at participating study sites, as well as the Sponsor's drug safety and medical monitoring staff, will have access to the treatment assignments of patients for safety monitoring purposes only.

The iDMC (see protocol) will evaluate efficacy and safety at one formal interim analysis, as well as at periodic safety reviews, and will recommend to the Sponsor if the study should be stopped early. All summaries and analyses will be prepared by the independent Data Coordinating Center (iDCC) and presented by treatment arm for the iDMC's review. Members of the iDMC will be external to the Sponsor and the study team and will follow a charter that outlines their roles and responsibilities.

The planned interim analysis will occur during the execution of the primary efficacy period (after the 25th randomized patient completes 24 weeks in the study [i.e., after 50% of the information has been collected] or discontinues study participation, whichever occurs first). The primary efficacy analysis will take place after the last randomized patient completes 24 weeks in the study or discontinues study participation, whichever occurs first. No information from the remaining patients who will have been enrolled but followed for $<$24 weeks will be included in the interim analysis; the data from these patients will be included in the primary efficacy analysis.

The statistical evaluation of the interim analysis dataset will be performed on the primary efficacy endpoint—number of bleeds over time—and a Wald's test from a negative binomial regression model will be used to compare the treatment arms. However, if the convergence of

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the negative binomial model is not achieved or is questionable at the time of the interim analysis, the interim and primary efficacy analyses will be based on a Wald's test from an ANOVA of the ABR. The interim analysis will follow a group sequential design proposed by Lan-DeMets with an alpha-spending function according to O'Brien and Fleming. This method allows for interim analyses at flexible information fractions without destroying the integrity of the calculated boundaries. To maintain an overall two-sided alpha level of 5%, this approach results in the two-sided boundaries of approximately 2.9626 (nominal p-value $=0.0031$) for the interim analysis, which will take place after approximately 50% of the required patients (i.e., 25 patients) have been observed for at least 24 weeks, and 1.9686 (nominal p-value $=0.049$) for the primary efficacy analysis. At the time of the interim analysis, the iDMC may recommend unblinding and fully analyzing the study if the observed p-value is < 0.0031 and in favor of RO5534262.

Additional details about the interim analyses will be provided in the iDMC Charter and interim SAP.

Determination of Sample Size

The sample size for this study is based on clinical rather than statistical considerations, taking into account the limited number of patients with hemophilia A with inhibitors available for participation in clinical studies and in an effort to collect sufficient data to assess the safety and efficacy of RO5534262.

The sample size calculation is based on the evaluation of the primary efficacy endpoint, defined as the number of bleeds over time with RO5534262 (treatment group, λ_t) versus no prophylaxis (control group, λ_c), which are said to follow a negative binomial distribution, with γ_t and γ_c described as shape parameters for treatment and control groups, respectively. With consideration of enrollment feasibility, a sample size of 45 patients, assuming an allocation ratio of 2:1 (30 patients in treatment group and 15 patients in control group), will achieve a power of more than 95% for λ_t and λ_c ranging from 1 to 4 and 18 to 30, respectively. Here, the patients from the two groups are followed up to 0.5 units of time (i.e., 24 weeks). Sample size calculations were performed with East®, Version 6 (Cytel, Cambridge, MA), which allows specific shape parameters for both the treatment and control groups.

However, the above approach to sample size calculation assumes similar follow-up for each patient. Because this is unlikely to be seen in the study, power was also estimated by simulation to account for different follow-up times among patients. Conducting simulations on the basis of a negative binomial regression model including an offset variable to account for variable follow-up times, with all other assumptions remaining the same as previously described, the sample size is projected to have greater than 95% power at the 2-sided 0.05 level of significance.

Assuming a drop-out rate of 10% in the control group with 2:1 treatment to control randomization, approximately 34 RO5534262 treatment and approximately 17 control patients (approximately 51 patients, in total) will be enrolled.

During the study, a re-assessment of the initially specified sample size based on aggregated (not by treatment arm) data to-date (and potentially from the non-interventional study [BH29768] findings) may be performed. This may result in an increase in sample size, if necessary, to maintain adequate power without affecting the type 1 error rate. Study integrity will be upheld, as access to information via aggregated analyses and their results will be minimized to limit operational bias.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	annualized bleeding rate
ADA	anti-drug antibody
aPCC	activated prothrombin complex concentrate
AUC	area under the curve
BA	bioavailability
C_{max}	maximum plasma concentration
CVAD	central venous access device
[redacted]	[redacted]
[redacted]	[redacted]
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
FDA	U.S. Food and Drug Administration
FEIBA	Factor Eight Inhibitor Bypassing Activity
FIX	factor IX
FIX:Ag	factor IX antigen
FIXa	activated factor IX
FVIII	factor VIII
FX	factor X
FX:Ag	factor X antigen
HCP	healthcare provider
[redacted]	[redacted]
[redacted]	[redacted]
HIPAA	Health Insurance Portability and Accountability Act
HN	home nursing
HRQoL	Health-Related Quality of Life
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
ICH	International Conference on Harmonisation
IFU	Instructions For Use
IgG4	immunoglobulin G4
IMP	investigational medicinal product
IND	Investigational New Drug (application)

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Abbreviation	Definition
IRB	Institutional Review Board
ITI	immune tolerance induction
IV	intravenous
IxRS	interactive voice or Web Response System
LPLV	last patient, last visit
MAD	multiple ascending dose
NB	negative binomial
[redacted]	[redacted]
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient-reported outcome
QTcF	QT interval corrected using Fridericia's formula
QOL	quality of life
RCR	Roche Clinical Repository
rFVIII	recombinant FVIII
rFVIIa	recombinant activated factor VII
SAD	single ascending dose
SAP	Statistical Analysis Plan
SC	subcutaneous
$t_{1/2}$	half-life
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
VAS	visual analog scale

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1. BACKGROUND

1.1 BACKGROUND ON HEMOPHILIA A WITH INHIBITORS

Hemophilia A is an X-linked recessive bleeding disorder that occurs in approximately 1 in 5000 live male births. Patients with hemophilia A have a deficiency or absence of blood coagulation factor VIII (FVIII), an essential component of the intrinsic pathway in the coagulation cascade (Mannucci and Tuddenham 2001; Franchini and Mannucci 2013).

Hemophilia A is most commonly caused by an inherited FVIII gene mutation within the Xq28 region of the X chromosome. It occurs almost exclusively in males having one defective copy of the relevant gene on their X chromosome. Because an affected male will transmit a normal Y chromosome to all his sons and an abnormal X chromosome to all his daughters, his sons will not be affected and all of his daughters will be carriers. For female carriers, with each birth there is a 50% chance to transmit the disorder to male infants and a 50% chance for female infants to be a carrier. Females who are carriers of hemophilia A may experience bleeding symptoms similar to those seen in men with mild hemophilia A, as approximately 10% of carriers have a FVIII activity that is less than 35% (Plug and Mauser-Bunschoten 2006). Rarely, women can have more severe bleeding symptoms requiring treatment and may develop FVIII inhibitors. Approximately 30% of patients with hemophilia A do not have a family history of the disorder; these cases arise from spontaneous FVIII gene mutations.

The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical signs of hemophilia A include easy bruising; prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial hemorrhage. The severity of the disease roughly correlates with the residual endogenous level of FVIII activity. Approximately 68% of people with hemophilia A have moderate (25%) or severe (43%) forms, characterized by FVIII activity levels $<5\%$ or $<1\%$, respectively, leading to frequent bleeding events with the sequelae of musculoskeletal complications, such as arthropathy, local functional deficits, hemorrhagic shock, neurocognitive defects, or even death (World Federation of Hemophilia 2013). These disease-related issues can have a significant impact on the health-related quality of life (HRQoL) of both adult and adolescent patients (Brown et al. 2009).

Prophylactic FVIII replacement therapy (i.e., administered on a scheduled basis with the intent to prevent bleeds) has been proven to minimize bleeding events and complications (Manco-Johnson et al. 2007). Since the 1990s, recombinant FVIII concentrates have been standard-of-care treatment options for patients with hemophilia A (Kingdon and Lundblad 2002). Treatment regimens to achieve optimal prevention of bleeding events vary individually; some patients tolerate nadir FVIII levels of 1%, whereas others require higher nadir FVIII levels to achieve the desired therapeutic outcome (Ahnstrom et al. 2004; Collins et al. 2010). Current standard prophylactic

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regimens commonly use infusion therapy administered three times weekly; other regimens require every other day administration, depending on the patient's needs (Shapiro 2013).

The required adherence to demanding therapeutic regimens that include frequent morning infusions to achieve adequate hemostatic coverage during periods of highest activity makes these regimens less effective and compromises their cost-benefit ratio (Thornburg 2010). Major issues with current regimens are the need for adequate venous access and patient/family compliance with regular prophylaxis, especially in the very young pediatric population, in whom central venous access devices (CVADs) have been used to overcome technical difficulties. Although CVADs make prophylaxis feasible in young children, CVADs are associated with complications, including mechanical failure, dehiscence of the skin over the reservoir, infection, and thrombosis (Ewenstein et al. 2004). In addition, significant healthcare provider efforts are required to manage optimal treatment solutions and to overcome identified issues (Schrijvers et al. 2013). Thus, both the disease and its treatment have the potential to affect HRQoL, the latter through limitations on daily activities that treatment may impose.

The development of inhibitory alloantibodies (inhibitors) occurs in approximately 20%–30% of patients with severe hemophilia A and in 3%–13% of those with moderate or mild disease (Franchini and Mannucci 2013). Inhibitors neutralize the activity of endogenous FVIII as well as of FVIII administered as replacement therapy. For patients with a history of a high-titer (≥5 BU/mL) inhibitor following a re-challenge with FVIII administration (high-responding inhibitor), the only hemostatic options currently available are pro-thrombotic coagulation factors that augment other parts of the coagulation cascade (i.e., "bypassing agents"). Bypassing products include Factor Eight Inhibitor Bypassing Activity (FEIBA), an activated prothrombin complex concentrate (aPCC; FEIBA will be referred to as aPCC throughout this document), and NovoSeven® (recombinant activated human FVIIa [rFVIIa]; NovoSeven® will be referred to as rFVIIa throughout this document) (Srivastava et al. 2013). Both have been used as prophylaxis to prevent bleeding in patients with inhibitors against FVIII ("inhibitor patients"); however, the only available product for this indication in most countries is the aPCC FEIBA. Of note, treatment of patients with congenital hemophilia A with any severity with high-titer inhibitors is similar, and their severity, as defined at diagnosis based on FVIII activity (mild, moderate, or severe), no longer is prognostic of their clinical phenotype and risk of bleeding.

APCCs may be associated with side effects, such as thromboembolic events, hypersensitivity reactions, myocardial infarction, and disseminated intravascular coagulation. Both aPCC and rFVIIa are administered intravenously, with aPCC prophylaxis requiring every other day dosing and rFVIIa requiring daily (or more frequent) dosing.

The development of effective prophylactic treatment options with decreased immunogenicity and less frequent dosing requirements is a high, unmet medical need in

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the patient population of hemophilia A patients with FVIII inhibitors. Reducing the time and burden associated with frequent intravenous dosing and the impact of the disease on aspects of physical health and other areas of function, while promoting increased efficacy, may further improve HRQoL, as suggested by a study in which patients receiving a prophylactic treatment with FEIBA had improved HRQoL than those who received episodic therapy (i.e., administered following bleeds) with FEIBA (Gringeri et al. 2013). Therefore, despite major therapeutic advances in the treatment of hemophilia A, opportunities remain to optimize and transform therapy, in particular for patients with inhibitors.

1.2 BACKGROUND ON RO5534262

RO5534262 is a recombinant, humanized, bispecific, immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX), mimicking the co-factor function of FVIII. In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors, as RO5534262 shares no sequence homology with FVIII. In addition, RO5534262 offers the possibility of subcutaneous (SC) administration, removing the need for venous access. Finally, because of the expected pharmacokinetic properties of this antibody, markedly extending the dosing interval to once weekly or even less frequently, this novel compound has the potential to dramatically change the treatment of patients with hemophilia A with and without FVIII inhibitors who are in need of effective, safe, and convenient prophylactic therapy.

RO5534262 binds with moderate affinity in the low μM range to FIXa and FX and mimics the co-factor activity of FVIIIa. This in turn, promotes the activation of FX by FIXa and downstream hemostasis for patients with hemophilia A who have hypofunctional levels of or entirely lack FVIII, irrespective of the presence of FVIII inhibitors. [redacted] Mechanistic in vitro studies were conducted in human and cynomolgus FVIII-neutralized plasma and in various coagulation factor-specific assay testing systems, which revealed that RO5534262 shortened aPTT and promoted thrombin generation. [redacted]

In vivo pharmacology experiments in cynomolgus monkeys were conducted in a hemophilia A model where endogenous FVIII levels were neutralized by a FVIII specific monoclonal antibody. This model mimics essential characteristics of patients with hemophilia A and was used to test in vivo pharmacodynamics and efficacy under spontaneous or local trauma-induced bleeding conditions. In summary, RO5534262 demonstrated the ability to significantly reduce bleeding tendency under both sets of conditions.

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Potential prothrombotic risks associated with RO5534262-induced FVIII mimetic activity were further explored in [redacted]

Overall, the preclinical pharmacology program is considered to have fully characterized the nonclinical profile of RO5534262. The conducted in vitro and in vivo studies demonstrated the mode of action of RO5534262 and provided supportive data on efficacious dose levels in a relevant hemophilia A disease model which were used for dose extrapolation to humans.

[redacted]

See the RO5534262 Investigator's Brochure for additional details on nonclinical studies with RO5534262.

Currently available experience with RO5534262 in humans includes data from one Phase I study (ACE001JP) and its ongoing extension, a Phase I/II study (ACE002JP). ACE001JP was a single study conducted in 3 parts, including both healthy patients (Part A and Part B) and patients with hemophilia A (Part C). The objective of Parts A and B in healthy patients was to investigate the tolerability, safety, pharmacokinetic (PK), and pharmacodynamics (PD) response of SC administered RO5534262 in adult

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Japanese and Caucasian males and to evaluate for racial differences, if any, in their PK and PD response. Healthy male volunteers aged 20–44 were eligible for enrollment. A total of 64 healthy volunteers were enrolled in Parts A and B from August 2012 to April 2013. In Part C, the objective was to investigate the tolerability, safety, PK, and PD response of SC administered RO5534262 in patients with hemophilia A. Patients were eligible for enrollment if they were 12–59 years of age, >40 kg in weight, had a diagnosis of severe congenital hemophilia A, and had documentation of bleeds and treatment with coagulation factor in the last 6 months. For those with inhibitors, patients must have had ≥6 bleeds in the 6 months prior to enrollment, and for those without inhibitors, patients were required to have received ≥150 lifetime doses of FVIII replacement, including in the last 6 months. A total of 18 patients with hemophilia A were enrolled from May 2013 to June 2014.

In the single ascending dose (SAD) portion of the Study ACE001JP, healthy volunteers (Japanese [Part A] and Caucasian [Part B]) received a single SC injection of RO5534262 (48 patients) or placebo (16 patients), at dose levels ranging from 0.001 to 1 mg/kg. Six patients received RO5534262 and 2 patients received placebo at each dose level. In Part C (the multiple ascending dose [MAD] portion) of the Study ACE001JP, a total of 18 patients with hemophilia A were enrolled in three cohorts of 6 patients each for each dose level (1 mg/kg loading dose followed by weekly SC injections of 0.3 mg/kg [0.3 mg/kg/week group]; 3 mg/kg loading dose followed by weekly SC injections of 1 mg/kg [1 mg/kg/week group]; and 3 mg/kg weekly SC injections [3 mg/kg/week group]).

Study ACE002JP is an extension study that allows for continued treatment with RO5534262 of patients enrolled in Part C of Study ACE001JP. [redacted]

Both Study ACE001JP and Study ACE002JP are currently in progress; data from the completed Parts A and B, as well as interim data from Part C of the Study ACE001JP and Study ACE002JP are presented here. The median age and body mass index (BMI) of the healthy volunteers across the dose groups in Part A ranged from 25.5 to 35.5 years and 20.28 to 21.44 kg/m^2, respectively. In Part B, the median age ranged from 28.5 to 30.5 years, and the median BMI ranged from 21.60 to 22.56 kg/m^2 across the dose groups. Among the 0.3, 1, and 3 mg/kg/week groups in Part C, the median age was 32, 30, and 33 years, respectively; the median BMI was 22.54, 22.87, and 22.31 kg/m^2, respectively. There were 5 adolescent patients (12–18 years): 1 patient (17 years old) in the 0.3 mg/kg/week group; 2 patients (12 years old and 18 years old) in the 1 mg/kg/week group; and 2 patients (12 years old and 18 years old) in the 3 mg/kg/week group. There were 11 patients with inhibitors: 4 patients in the

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0.3 mg/kg/week group; 4 patients in the 1 mg/kg/week group; and 3 patients in the 3 mg/kg/week group. All patients in Part C of Study ACE001JP have completed the treatment period [redacted]. Study ACE001JP will be completed when the last patient completes the protocol-defined observation period of 28, 32, or 36 weeks if they were assigned to receive 0.3, 1, or 3 mg/kg/week of RO5534262, respectively. Study ACE002JP will enable patients from Study ACE001JP to continue receiving RO5534262 [redacted].

[redacted]

The Phase I and I/II studies have shown promising results for RO5534262 prophylaxis in reducing the annualized bleeding rate (ABR) in Japanese patients with hemophilia A with and without inhibitors against FVIII. Overall, three cohorts of 6 patients each were treated with 0.3 mg/kg (Cohort C-1), 1 mg/kg (Cohort C-2), or 3 mg/kg (Cohort C-3) RO5534262 weekly. The number of patients with inhibitors against FVIII was 4 (Cohort C-1), 4 (Cohort C-2), and 3 (Cohort C-3). In 4 of 4 patients with inhibitors against FVIII, treatment with 0.3 mg/kg RO5534262 weekly for 12 weeks resulted in a 64.7%–100% reduction in ABR compared with that reported for the previous 6 months, during which time patients received episodic treatment with bypassing agents. In 4 of 4 patients with inhibitors against FVIII, treatment with 1 mg/kg RO5534262 weekly for 12 weeks resulted in an 88.9%–100% reduction in ABR compared with that reported for the previous 6 months, during which time patients' episodic treatment with bypassing agents. In 3 of 3 patients with inhibitors against FVIII, treatment with 3 mg/kg RO5534262 weekly for 12 weeks resulted in a 100% reduction in ABR compared with that reported for the previous 6 months, during which time patients received prophylactic and episodic treatment with bypassing agents (Shima et al. 2014). For patients without inhibitors against FVIII (n=2 in Cohort C-1/Cohort C-2; n=3 in Cohort C-3), the reduction in ABR was 22.8%–100% when treated with 0.3 mg/kg RO5534262 and 100% when

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treated with 1 mg/kg RO5534262 weekly for 12 weeks. In Cohort C-3 (n=3), one patient had a reduction in ABR of 100%, another patient who previously had an ABR of 0 on FVIII prophylaxis continued to have an ABR of 0 on RO5534262 prophylaxis, and a third patient had a reduction in ABR of 48% when treated with 3 mg/kg RO5534262 weekly for 12 weeks. [redacted]

RO5534262 was safe and well-tolerated in these patients (see Investigator's Brochure). [redacted] There were no dose dependent increase in adverse events; and the majority of the adverse events were not considered related to RO5534262. One adverse event (injection-site erythema) in the 1 mg/kg weekly group resulted in discontinuation of treatment; the event was mild in intensity and resolved. [redacted] No thromboembolic adverse events have been reported when RO5534262 has been administered alone or concomitantly with FVIII products or bypassing agents as episodic therapy.

In terms of PK, RO5534262 exhibited linear PK after single SC administration. Following single SC injection, its mean elimination t1/2 (4–5 weeks) [redacted]. Furthermore, comparison of PK profiles between Japanese and Caucasian patients did not reveal racial differences. In patients with hemophilia A, RO5534262 trough plasma concentrations increased in a dose-dependent manner with weekly dosing to achieve a plateau (steady state) after approximately 12 weeks in the first two dosing groups, while they continued to increase in the highest

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dose group where no loading dose was administered and steady state was expected later.

To-date, RO5534262 has been administered to 48 healthy subjects and 18 patients with hemophilia A. [redacted]

Based on these compelling Phase I/II data, a clinical development program in adult and pediatric patients with hemophilia A (both with and without FVIII inhibitors) has been developed. See the RO5534262 Investigator's Brochure for additional details on clinical studies with RO5534262.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

For patients with hemophilia A who are diagnosed with inhibitors, permanent eradication of inhibitors is the ultimate goal. This can be achieved by means of intensive FVIII administration over many months with immune tolerance induction (ITI), which is successful in approximately 60%–80% of treated inhibitor patients (Hay and DiMichele 2012; Santagostino et al. 2009). However, hemostatic management may be challenging during the time interval required to achieve ITI success. Furthermore, ITI is not viewed as a viable option for inhibitor patients in many countries, owing to its high cost, the scarce local supply of FVIII concentrates, practical issues and potential complications associated with CVADs, and psychological stress on patients and their families for this highly demanding therapeutic endeavor. Finally, even with successful implementation, ITI will fail to eradicate inhibitors in approximately 20%–40% of treated patients (Mariani et al. 2003).

Therefore, for those inhibitor patients who are unable to eradicate their inhibitors or are not candidates for ITI, bypassing agents are required to treat or prevent bleeds. Unfortunately, the hemostatic effect of bypassing agents is unstable in comparison with that of FVIII concentrates. In addition, as opposed to the 8–12-hour half-life and 15–20-minute infusion time of FVIII, rFVIIa has a short half-life of only 2–3 hours, and aPCC requires 25–50 minutes to infuse (with a half-life of 4–7 hours), requiring frequent and extended IV infusions, respectively. In practice, some inhibitor patients will have bleeds that respond better to rFVIIa while others will respond better to aPCC. Several recent publications evaluating the efficacy of prophylactic therapy in adults and children with the bypassing agents rFVIIa (Konkle et al. 2007) and aPCC (Leissinger et al. 2007; Ettingshausen et al. 2010; Leissinger et al. 2011; Antunes et al. 2014) showed decreased bleeding rates compared to episodic treatment.

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In the FEIBA prophylaxis pivotal study (PROOF study), inhibitor patients on episodic bypassing agents were eligible for participation if they had a minimum historical ABR of ≥12. On prophylactic aPCC, their median ABR (interquartile range) decreased from 28.7 (32.3) to 7.9 (8.1) (Antunes et al. 2014), suggesting that while this treatment was partially efficacious for some, there still exists suboptimal control of bleeds and unmet medical need in this population.

Given the hemostatic management challenges in adults and children with inhibitors, there is an urgent need for therapeutics that have more reliable efficacy, an extended half-life, and less treatment burden to prevent bleeding for patients with hemophilia A with inhibitors.

The nonclinical and clinical data related to RO5534262 to-date support a positive benefit-risk assessment. As described in Section 1.2, evaluation of in vivo pharmacodynamics and efficacy under spontaneous or local trauma-induced bleeding conditions in cynomolgus monkeys using a hemophilia A model demonstrated the ability of RO5534262 to significantly reduce bleeding tendency under both sets of conditions. This was corroborated in the Phase I/II studies, where significant and stable ABR reductions [redacted] in the 1 and 3 mg/kg RO5534262 weekly dose cohorts have been seen to-date. [redacted] In the Phase I/II studies, no thromboembolic or systemic hypersensitivity adverse events were seen. The majority of adverse events were of mild intensity, with the most common being injection-site reactions and the majority of the adverse events were not considered related to RO5534262.

Given the significant unmet medical need among patients with hemophilia A with FVIII inhibitors and positive benefit-risk assessment, initiation of a larger, confirmatory Phase III study is indicated.

2. OBJECTIVES AND ENDPOINTS

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of prophylactic RO5534262 compared with no prophylaxis in patients with hemophilia A with inhibitors on the basis of the following endpoint:

- Number of bleeds over time (i.e., bleed rate)

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives and endpoints for this study are as follows:

- Prophylactic RO5534262 compared with no prophylaxis

  To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate over the last 24 weeks prior to study entry or for the duration of their participation in the non-interventional study, whichever is longer

  To evaluate the efficacy in reducing the number of joint bleeds over time

  To evaluate the efficacy in reducing the number of target joint bleeds over time (target joints are defined as joints with ≥3 bleeds occurring in the same joint over the last 24 weeks prior to study entry)

  To evaluate the HRQoL of patients according to Haem-A-QoL (age ≥ 18) or Haemo-QoL-Short Form (ages 12–17) scores at 24 and 48 weeks

  To evaluate the health status of patients according to EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) scores at 24 and 48 weeks

- Open-label prophylactic RO5534262 for patients previously treated with prophylactic bypassing agents

  To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate over the last 24 weeks prior to study entry

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of prophylactic RO5534262 compared with no prophylaxis on the basis of the following endpoints:

- To assess differences in number of days away from school/work
- To assess differences in number of days hospitalized
- To assess potential PD biomarkers of RO5534262, including but not limited to aPTT, thrombin generation, and FVIII activity, at timepoints throughout the study

2.2 SAFETY OBJECTIVE

The safety objective for this study is as follows:

- To evaluate the overall safety of prophylactic RO5534262 compared with no prophylaxis in patients with hemophilia A with inhibitors on the basis of the following endpoints:

  The incidence and severity of adverse events

  The incidence and severity of thromboembolic events

  Changes in physical examination findings and vital signs

  Incidence of laboratory abnormalities

  Incidence and severity of injection-site reactions

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Incidence of adverse events leading to drug discontinuation

Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events

The incidence and clinical significance of anti-RO5534262 antibodies

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the exposure (C_{trough}) of RO5534262 prior to drug administration on Day 1 at the following timepoints:

- Every week during Weeks 1–4 on RO5534262
- Every 2 weeks during Weeks 5–8 on RO5534262
- Every 4 weeks during Weeks 9–24 on RO5534262
- Every 8 weeks during Weeks 25–48 on RO5534262
- Every 12 weeks thereafter while on RO5534262, until the end of the study

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This randomized, multicenter, open-label, Phase III clinical study will enroll patients aged 12 years or older with hemophilia A who have inhibitors against FVIII. Approximately 51 patients with inhibitors who received episodic treatment with bypassing agents prior to study entry will be enrolled globally and randomized in a 2:1 ratio (see Figure 1) to receive either prophylactic RO5534262 at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously thereafter (Arm A), or to the control arm (Arm B), which will consist of no prophylaxis. Given the potential heterogeneity of bleed rates in the study patient population, randomized patients will be stratified according to the number of bleeds they experienced over the last 24 weeks prior to study entry (<9 or ≥ 9 bleeds) to ensure a balance of inhibitor patients with lower versus higher number of bleeds, respectively, at baseline across the two randomized arms of the proposed Phase III study. All patients will continue to receive standard of care/background treatment with their usual episodic bypassing agent therapy to treat breakthrough bleeds, as needed.

In addition, given that some patients with hemophilia A with inhibitors are also currently treated with bypassing agents on a prophylactic basis, approximately 10–20 patients with inhibitors on prophylactic bypassing agents will be enrolled in a separate therapeutic arm (Arm C) to receive prophylactic RO5534262 at the same dose and schedule (see Figure 1).

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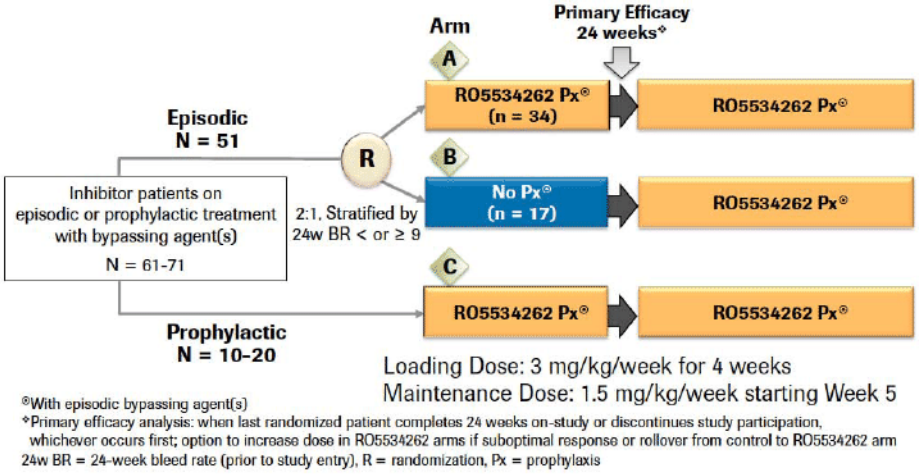
Figure 1 Study Schema



®With episodic bypassing agent(s)
*Primary efficacy analysis: when last randomized patient completes 24 weeks on-study or discontinues study participation, whichever occurs first; option to increase dose in RO5534262 arms if suboptimal response or rollover from control to RO5534262 arm
24w BR = 24-week bleed rate (prior to study entry), R = randomization, Px = prophylaxis

The primary efficacy analysis, defined as comparing the number of bleeds over time for patients randomized to receive prophylactic RO5534262 versus no prophylaxis, will be conducted after the last randomized patient completes 24 weeks in the study or discontinues study participation, whichever occurs first. An interim analysis (see Section 6.9), in which an independent Data Monitoring Committee (iDMC) will evaluate safety and efficacy, will be conducted after approximately 50% of the randomized population has completed at least 24 weeks in the study.

To obtain additional safety and efficacy data, prior episodic bypassing agent patients who had been randomized to not receive RO5534262 (control arm, Arm B) will crossover to receive prophylactic RO5534262, at the same dose and schedule as patients who started Study BH29884 on RO5534262, once they complete 24 weeks in the study. In addition, after 24 weeks on prophylactic RO5534262, all patients will be able to continue on their 1.5 mg/kg/week maintenance dose or may be provided the option to increase their dose to 3 mg/kg/week if they meet protocol-defined criteria of suboptimal response and receive approval from the Medical Monitor to do so (see Section 4.3.1.2). Patients who continue to derive clinical benefit will be given the opportunity to continue receiving prophylactic RO5534262 [redacted].

During the study, individual bleeds will be captured as they occur, while HRQoL, health status, patient safety, and days of school or work missed will be assessed every 4 weeks for approximately 24 weeks and every 4–12 weeks thereafter, as outlined in the schedule of assessments in protocol. Patients (or their legally authorized representative) will be asked on a daily basis via their electronic patient-reported outcome (ePRO)

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device whether a bleed has occurred and whether treatment for a bleed or treatment to prevent a bleed has been given In addition, health status information will be collected whenever a bleed is reported.

Physical examinations, vital sign assessments, ECG, and laboratory assessments will be collected as per the schedule of assessments and will be the same for all patients receiving RO5534262, regardless of whether they are enrolled in the randomized portion of the study or in the separate non-randomized arm. Adverse events will be captured on an ongoing basis, as they occur during the study.

All patients who receive RO5534262 in the study will undergo a PK assessment. As RO5534262 is intended in this study for prophylactic use only (i.e., not to treat bleeds that have already occurred), neither aPCC nor rFVIIa interfere with RO5534262 PK assessments, and some patients with hemophilia A with inhibitors require frequent dosing with bypassing agents due to having many bleeds or being on prophylaxis, a washout period is not required prior to inclusion so that new bleeds are minimized and treatment for any ongoing bleeds is not interrupted.

Exploratory PD biomarkers (e.g., aPTT, FVIII activity, thrombin generation assay) will be collected as per the schedule of assessments. As values for these tests are normalized by even low plasma concentrations of RO5534262 (see Section 1.3), a variety of assay formats (one-stage, chromogenic) and modifications (pre-dilution of patient plasma) will be investigated for assessment of PD response at higher RO5534262 plasma concentrations. [redacted] In addition, FIX and FX antigen levels will be monitored.

Throughout the study, biomarkers related to thromboembolism (e.g., D-dimer, prothrombin 1.2 fragment) and RO5534262 trough concentrations will be collected as per the schedule of assessments. Immunologic biomarkers (i.e., anti-RO5534262 antibodies) will also be measured as per the schedule of assessments (see Appendix 1 and Appendix 2).

An iDMC composed of, at minimum, hemostasis/thrombosis experts and a statistician will be in place throughout the duration of the study and will monitor patient safety at pre-specified intervals and ad hoc as needed throughout the study. Stopping rules for the study will be included for select adverse events of special interest, which are outlined in Section 4.6.1, and will be specified in the iDMC Charter.

Breakthrough bleeds will be treated with bypassing agents according to standard of care and captured as they occur on the ePRO device. Of note, the clinical experience in the ongoing Phase I/II clinical studies includes the treatment of over [redacted] breakthrough bleeds in patients receiving RO5534262 with either FVIII or bypassing agents, without any

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related safety concerns reported. Investigators will be asked to contact the Medical Monitor in the event of suspected lack or loss of efficacy of RO5534262 in order to discuss potential laboratory evaluations (e.g., anti-RO5534262 antibodies, coagulation tests) to be performed as well as to re-evaluate the patient's benefit-risk of continued treatment. When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, category of bleed, time of each individual bleed (day, start time), symptoms of bleed, and treatment for bleed. Health status information will also be collected on the day a bleed occurs.

The reason for the use of coagulation products (e.g., aPCC or rFVIIa) will be documented (e.g., bleeding, prophylaxis, pain, etc.). A thorough documentation of the treatments for bleeds will be requested, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed.

A non-interventional study (Study BH29768) has been initiated to document the number and types of bleeds and current treatment with episodic or prophylactic bypassing agents, as well as collect information on HRQoL, health status, and safety in patients with hemophilia A with FVIII inhibitors. The assessments in the non-interventional study will mitigate the risk of underreporting of bleeds that oftentimes occurs in the real world, and the resulting data will serve as a source of comparator information for some analyses conducted in the Phase III clinical study (Study BH29884). The non-interventional study will also allow an investigation of the feasibility of using an electronic patient ePRO device that has been developed to record data related to bleeds, HRQoL, and health status. In addition, the non-interventional study will enable earlier identification and confirmation of patients who may qualify for the Phase III clinical study. It is anticipated that a significant number of patients participating in Study BH29768 will enroll in Study BH29884, as long as they meet the inclusion and exclusion criteria of the study and are able to enroll at a participating site while the study is open for enrollment.

3.2 END OF STUDY AND LENGTH OF STUDY

LENGTH OF STUDY

The approximate length of the entire study from the first patient enrolled to the Last Patient Last Visit (LPLV) (i.e., 24-week follow-up visit after discontinuing RO5534262) is approximately 108 weeks.

END OF STUDY

The end of this study is defined as the date when the last patient completes the end of study, safety follow-up visit 24 weeks after discontinuing RO5534262, [redacted], or is lost to follow-up.

3.3 RATIONALE FOR STUDY DESIGN

Current standard-of-care treatment for patients with FVIII inhibitors involves treatment with bypassing agents (e.g., aPCC and rFVIIa). Despite EU approval of prophylactic

aPCC as early as 2007 in the United Kingdom and approval in the United States in 2013, the majority of adult and adolescent patients with hemophilia A with inhibitors worldwide are still treated with episodic bypassing agents (Carcao et al. 2015). Uptake of current prophylactic treatment may be limited by the occurrence of associated adverse events, including CVAD-related thrombosis and infection, perceived and actual problems with treatment adherence, and treatment cost (Leissinger et al. 2015a; Leissinger et al. 2015b).

In designing Study BH29884, the study designs of the pivotal studies for both aPCC (in inhibitor patients) and FVIII concentrates (in non-inhibitor patients) were extensively reviewed. The pivotal FEIBA study (Antunes et al. 2014) was conducted as a comparison of episodic versus prophylactic FEIBA. It may be argued that there was no prophylactic regimen available at the time this study was conducted that could have served as an alternative comparison. However, review of the prior approvals for FVIII concentrates, where FVIII prophylaxis is utilized in the majority of patients, revealed that the standard clinical trial design for novel FVIII concentrates has been to compare episodic to prophylactic regimens (Manco-Johnson et al. 2013; Valentino et al. 2012; Mahlangu et al. 2014) rather than performing a comparison to a previously marketed FVIII prophylactic regimen. This precedent has likely been maintained even for more recent clinical study designs (e.g., long-acting FVIII products N8-GP and BAX855) due to operational feasibility concerns, design complexities such as the definition of the appropriate non-inferiority margin, and the large number of patients continuing to receive treatment with episodic regimens despite the availability of prophylactic ones.

Therefore, given the high unmet need for patients with hemophilia A with inhibitors, the current patterns of utilization of bypassing agents, and the regulatory precedent, a study comparing prophylactic RO5534262 to no prophylaxis in patients with hemophilia A with inhibitors who were treated with episodic bypassing agents prior to study entry is deemed to be appropriate for the first pivotal study and will provide clinical data that is clinically meaningful to the hemophilia community. If efficacy of RO5534262 is demonstrated in the inhibitor population that has the highest unmet need (i.e., patients who are treated with episodic bypassing agents and experience upwards of 30 bleeds per year), this should translate to the smaller subset of the inhibitor population whose bleeds are better, albeit still not completely controlled (i.e., annual bleed rate of 8–10) on prophylactic bypassing agents.

Acknowledging that the treatment landscape may evolve in the future (e.g., more patients with hemophilia A with inhibitors may be treated with prophylactic bypassing agents), the proposed study will evaluate prophylactic RO5534262 in patients previously treated with prophylactic bypassing agents in an additional, non-randomized arm.

In conclusion, based on the current treatment landscape, regulatory precedent, operational considerations, and taking into account the desire not to delay access to a

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potentially efficacious therapy to the population of highest unmet need, the proposed design for Study BH29884 is considered to be the most appropriate.

3.3.1 Rationale for RO5534262 Dose and Schedule

RO5534262 prophylaxis has been administered subcutaneously in 18 Japanese patients with hemophilia A (with and without FVIII inhibitors) in Study ACE001JP [redacted]. Three dose groups (of 6 patients each) received the following treatment for at least 12 weeks:

- A loading dose of 1 mg/kg followed by weekly doses of 0.3 mg/kg
- A loading dose of 3 mg/kg followed by weekly doses of 1 mg/kg
- Weekly doses of 3 mg/kg

RO5534262 was safe and well-tolerated in these patients (see Section 1.2 and the RO5534262 Investigator's Brochure). [redacted]

A substantial reduction in bleeding events has been observed with prophylactic RO5534262 treatment, [redacted] ABR decreased in all patients, regardless of age or the presence of FVIII inhibitors.

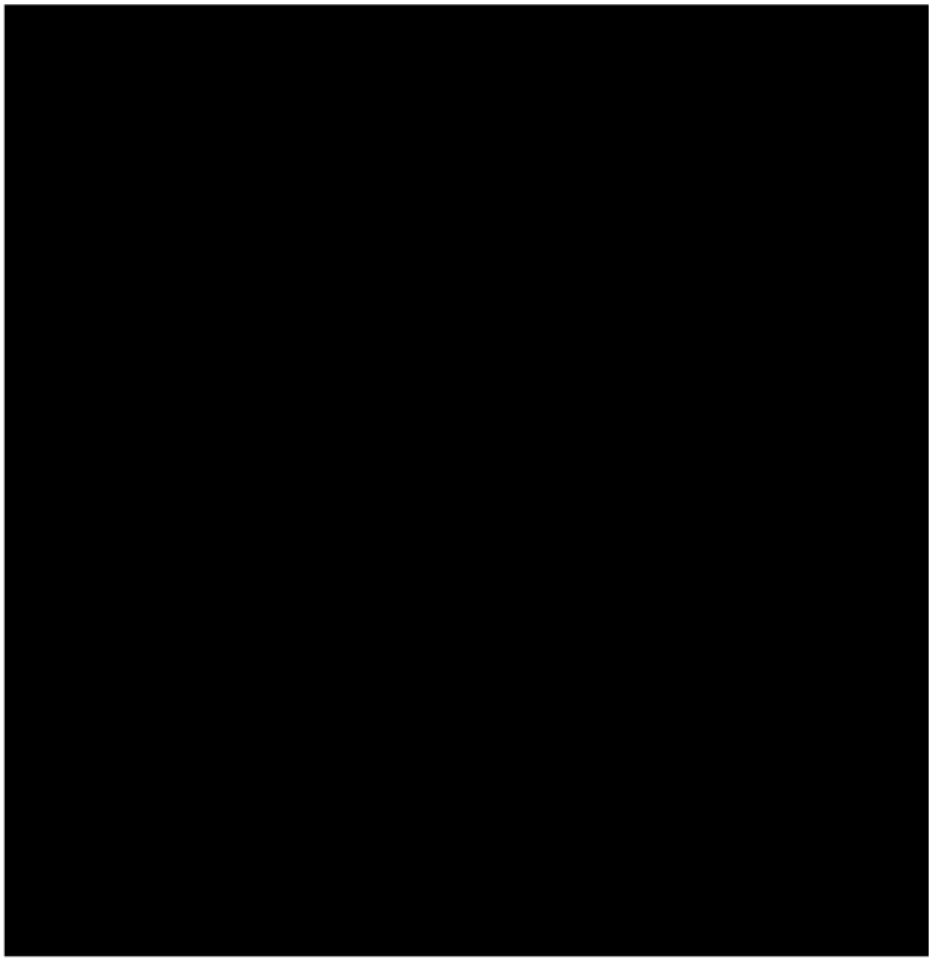
Table 1 Mean Reduction (%) of Annualized Bleeding Rates in Inhibitor and Non-Inhibitor Patients Enrolled in ACE001JP/ACE002JP

RO5534262 dose	0.3 mg/kg weekly	1 mg/kg weekly	3 mg/kg weekly
ABR reduction	[redacted]%	[redacted]%	[redacted]%

ABR = annualized bleeding rate.

[redacted]

Figure 2 Individual Pharmacokinetic Profile with Corresponding Bleeding Event



The exposure-response relationship of RO5534262 was quantitatively characterized and simulations suggested that a median ABR of 0 is achieved for RO5534262 trough plasma ≥ 45 μg/mL. On the basis of population PK modeling, a median trough plasma concentration of 45 μg/mL is predicted to be achieved after treatment with 4 weekly doses of 3 mg/kg and maintained, thereafter, with weekly doses of 1.5 mg/kg. The loading doses of 3 mg/kg weekly for 4 weeks were chosen in order to rapidly achieve the effective trough concentration of 45 μg/mL without exceeding the maximum dose of 3 mg/kg weekly investigated in the Phase I/II studies. Thereafter, a dose and schedule of 1.5 mg/kg weekly was chosen in order to reduce the peak-trough fluctuations and to

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maintain RO5534262 plasma concentrations above 45 μg/mL over the entire dosing interval. This dosing regimen (i.e., 3 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly) will, therefore, be investigated in this study.

3.3.2 Rationale for Patient Population

As described in Section 3.3, patients with hemophilia A and inhibitors against FVIII who were treated with episodic bypassing agents prior to study entry will comprise the primary population for this Phase IIII study of prophylactic RO5534262 compared with no prophylaxis in investigating the efficacy, safety, and PK of RO5534262.

Although the initial severity of a patient's hemophilia A may be directly related to his or her endogenous FVIII activity, the treatment of patients of any severity (mild, moderate, or severe) with high-titer inhibitors is similar (i.e., with bypassing agents). Because their initial severity of hemophilia A, which is defined at diagnosis on the basis of their FVIII activity, no longer is prognostic of their clinical phenotype and risk of bleeding, this will not be used to determine study eligibility.

Instead, inhibitor patients previously treated with episodic bypassing agents will be required to have at least 6 bleeds in the last 24 weeks prior to study entry to be eligible for enrollment in the randomized portion of Study BH29884. This is to select a group of patients with hemophilia A with inhibitors who have a high, unmet medical need and to enable detection of a clinically and statistically significant difference in bleed rates in this subset of an orphan disease population.

Inhibitor patients previously treated with episodic bypassing agents also comprised the control arm in prior prophylaxis studies involving inhibitor patients (Leissinger et al. 2011; Antunes et al. 2014). In both the PRO-FEIBA and PROOF studies, inhibitor patients ranging in age from 2–68 years old on episodic bypassing agents were eligible for participation if they had a minimum historical ABR of ≥12 (Leissinger et al. 2011; Antunes et al. 2014), which defines a group with high unmet medical need and is also an inclusion criterion for Study BH29884. Based on its mechanism of action (mimetic of FVIII's co-factor activity) and clinical study results to-date, prophylactic RO5534262 is expected to provide significant and clinically meaningful benefit to this inhibitor population that is in need of a reliably efficacious therapy to prevent bleeds.

Based on current treatment algorithms for patients with hemophilia A with inhibitors (Srivastava et al. 2013; Kempton and White 2009), it is anticipated that the majority of adults and adolescents treated with RO5534262 will have previously undergone ITI without success or are not candidates for ITI, although prior ITI will not be required.

As clinical safety data related to the concomitant use of prophylactic RO553462 during ITI are not available at this time, patients currently receiving ITI will not be eligible for Study BH29884. Because the presence or amount of FVIII inhibitors in their plasma does not impact the efficacy of RO5534262, patients' inhibitor titers at the time of study

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entry will not influence their study eligibility. However, patients will be required to have a history of a high-titer inhibitor documented in the medical record in order to be eligible for the study.

Inhibitor patients previously treated with prophylactic bypassing agents are included in a separate arm in Study BH29884, as combining them with those previously treated with episodic bypassing agents would have introduced significant heterogeneity in baseline bleed rates.

3.3.3 Rationale for Control Group

There will be two types of control groups in this Phase III clinical study. The first will be a concurrent, no prophylaxis "usual care" arm, to which patients who were on episodic bypassing agents prior to study entry will be randomized (2:1 prophylactic RO5534262:no prophylaxis), which will enable an inter-patient comparison of the treatment and control groups. All patients, whether assigned to receive prophylactic RO5534262 or no prophylaxis, will continue to receive bypassing agents on an episodic basis for the treatment of breakthrough bleeds during the study. Specific doses of bypassing agents will not be mandated in the study but rather should be administered according to the respective prescribing information or as previously used per each individual patient.

The second type of control group will be an individual patient's ABR calculated over the 24 weeks prior to study entry, from the medical record and/or Study BH29768. This will enable intra-patient analyses of bleed rates to be performed as well.

Both control groups are appropriate, as episodic bypassing agent therapy represents the regimen that the majority of patients with hemophilia A with FVIII inhibitors are currently receiving and because these control groups have been utilized in previous prophylaxis inhibitor studies (Leissinger et al. 2011; Antunes et al. 2014) (see Section 3.3).

3.3.4 Rationale for the Primary Efficacy Analysis

The objective of the primary efficacy analysis is to evaluate the clinical effect of prophylactic RO5534262 compared with no prophylaxis on the number of bleeds over time (i.e., bleed rate). As mentioned in Section 3.1, the primary efficacy analysis will occur after the last randomized patient completes 24 weeks in the study or discontinues study participation, whichever occurs first. This timepoint in the study will lead to a range of observation periods from 24–48 weeks (estimated at n=28 patients) or longer (estimated at n=6 patients) in the prophylactic RO5534262 arm and is deemed to be sufficient to reliably assess the effect of prophylactic RO5534262 on bleed rate reduction. In the multiple ascending dose Phase I study involving Japanese patients with hemophilia A (Study ACE001JP), a statistically significant reduction in median ABR to 0 after 12 weeks of treatment (approximately 3 months) in the 1 and 3 mg/kg/week RO5534262 dose cohorts was demonstrated. [redacted]

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[redacted] consistent with evidence suggesting longer duration of prophylactic therapy in inhibitor patients is associated with maintenance of ABR reduction (Antunes et al. 2014). The duration of safety follow-up for all patients in the 1 and 3 mg/kg/week cohorts in Study ACE001JP/Study ACE002JP ranges from [redacted], respectively.

A recent publication of hemophilia B patients with factor IX (FIX) activity levels ≤ 2% who received episodic therapy showed no distinguishable trend in prospectively collected ABRs over approximately 59 weeks in the study (Shafer et al. 2014). As the number of bleeds over time is not expected to differ between patients with hemophilia A or B, it is reasonable to extrapolate this study's findings to the hemophilia A population.

In addition, because this will be a global study with enrollment from different continents occurring over time, all seasons will be represented in the bleed rate data.

3.3.5 Rationale for Patient-Reported Outcome Assessments

The study design utilizes the electronic capture of bleeds, HRQOL, and health status using an ePRO device whose feasibility will already have been assessed in a previous study (Study BH29768). HRQoL is an important outcome in the care of patients with hemophilia (Brown et al. 2009). HRQoL in hemophilic patients is multifaceted and impacted by:

- Disease symptoms

  Pain, arthropathy, disability, swelling, bleeding
- Outcome perception

  Orthopedic outcomes, survival outcomes
- Treatment both prophylactic and on demand, as well as pain management

  Painfulness, risk of infections, side effects, risk of complications
- Limitations on daily functioning
- Increased anxiety and depression
- Significant time spent in the hospital, emergency room, and receiving treatments to manage both diseases symptoms and treatment effects

The goal of measuring HRQoL is to quantify the benefit of treatment from the patient perspective. Previous studies that have used the Haemo-QoL, a measure of different dimensions of HRQoL affected by hemophilia in children and adolescents, have reported improvements in physical health, feelings, view of self, family relations, friend relations, perceived support, relation with others, participation in sports, dealing with hemophilia, views of treatment, views of the future, and relationships (Santagostino et al. 2014). Improvements in physical health, feelings, view of self, and participation in work and

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school have also been observed on the adult version of the measure, the Haem-A-QoL (Stasyshyn et al. 2014).

The inclusion of HRQoL measures in the current study will allow for the assessment of the impact of prophylactic treatment with RO5534262 in adolescents and adults with Hemophilia A and an evaluation of the changes in HRQoL in patients receiving prophylaxis with RO5534262 compared with that of patients receiving only episodic treatment for breakthrough bleeds. It will also allow for an assessment of pain associated with bleeding episodes.

3.3.6 Rationale for Biomarker Assessments

Biomarkers to measure the PD effect of RO5534262 on hemostasis have not been validated to-date [redacted]. Plasma samples will be collected for PD biomarker assessment in parallel with PK samples at all clinic visits to demonstrate evidence of biologic activity of RO5534262 in patients and to support selection of a recommended dose. These PD biomarkers include but are not limited to coagulation assays such as aPTT, thrombin generation, and FVIII activity assays. All of these assays were previously shown in the Phase I/II study to exhibit a dose-response relationship to RO5534262 concentration (for more information, see the RO5534262 Investigator's Brochure). The aPTT assay will be run [redacted] to ensure that the assay range covers all levels of RO553426 exposure. [redacted]. Exploratory plasma biomarkers will include factor IX antigen (FIX:Ag) and factor X antigen (FX:Ag) to assess whether drug treatment causes a change in the circulating levels of these coagulation factors, which are the binding targets of RO5534262, and may include measurement of other coagulation or hemophilia-related factors as well. Finally, residual plasma samples will be banked for future disease-related assays.

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population will be patients with hemophilia A with FVIII inhibitors who have been treated with bypassing agents to control or prevent bleeds with suboptimal success.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of patient-reported outcomes questionnaires and daily bleed questionnaire through the use of an electronic device

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- Aged 12 years or older at the time of informed consent
- Body weight ≥40 kg at the time of screening
- Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (i.e., ≥5 Bethesda Units)
- Documentation of treatment with episodic or prophylactic bypassing agents for at least the last 24 weeks
- ≥6 (if on an episodic bypassing agent regimen) or ≥2 (if on a prophylactic bypassing agent regimen) bleeds in the last 24 weeks
- Adequate hematologic function, defined as platelet count ≥100,000/μL and hemoglobin ≥8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin ≤1.5×the upper limit of normal (ULN) (excluding Gilbert's syndrome) and AST and/or ALT ≤3×ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine ≤2.5×ULN and creatinine clearance by Cockcroft-Gault formula ≥30 mL/min
- For women who are not postmenopausal (≥48 weeks of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined highly effective non-hormonal contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of non-hormonal contraceptive methods with a failure rate of <1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of <1% per year. Barrier methods must always be supplemented with the use of a spermicide.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Inherited or acquired bleeding disorder other than hemophilia A
- Ongoing (or plan to receive during the study) immune tolerance induction therapy or prophylaxis with FVIII
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment

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- Previous or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which antithrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Previous or concurrent autoimmune or connective tissue disease
- History of hypersensitivity associated with monoclonal antibody therapies or components of the RO5534262 injection
- Known HIV infection with CD4 count $<$200 cells/μL within 24 weeks prior to screening
- Use of systemic immunomodulators (e.g., interferon or rituximab) at enrollment or planned use during the study, with the exception of antiretroviral therapy
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study or that would, in the opinion of the investigator or Sponsor, preclude the patient's safe participation in and completion of the study or interpretation of the study results
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Receipt of

  RO5534262 in a prior investigational study

  An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration

  A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter

  An investigational drug concurrently
- Unwillingness to use highly effective contraception methods for the specified duration in the protocol (females only, unless required otherwise by the local health authority)
- Clinically significant abnormality on screening evaluations or laboratory tests that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient
- Pregnancy or lactation, or intent to become pregnant during the study

  Women who are not postmenopausal ($\geq$48 weeks of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

4.2 METHOD OF TREATMENT ASSIGNMENT

Patients who received episodic treatment with bypassing agents prior to study entry will be randomized in a 2:1 ratio to receive either prophylactic RO5534262 at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously, or to the control arm (no prophylaxis). A central randomization procedure will be used for all patients that fulfill the entry criteria at screening. A block-based randomization method

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will be used, stratified by the number of bleeds in the last 24 weeks (<9 or ≥ 9). The proposed randomization method is designed to balance treatment group assignment within the prognostic stratification factor.

Patients on prophylactic bypassing agents prior to study entry will be enrolled in a separate therapeutic arm to receive prophylactic RO5534262, at the same dose and schedule as described above.

In order to ensure the integrity of study results, the Sponsor, with the exception of the bioanalytical manager, bioanalytic laboratory, biomarker laboratory, and pharmacometrician, will remain blinded to the randomization assignments throughout the conduct of the study.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 RO5534262

RO5534262 Drug Product will be supplied by the Sponsor as a sterile liquid for SC injection, contains no preservatives, and requires storage at 2–8° Celsius (do not freeze and protect from light). Each single-use vial contains [redacted] mg (nominal) of RO5534262 at pH [redacted]. The Drug Product is formulated as [redacted] mg/mL RO5534262 in [redacted] mmol/L [redacted], [redacted] mg/mL [redacted], [redacted] mmol/L [redacted] (pH [redacted]). For information on the formulation and handling of RO5534262, see the Investigator's Brochure.

4.3.1.2 Dosage, Dose Adjustment, and Administration

As discussed in Section 3.3.1, when each patient starts on prophylactic RO5534262, they will receive 3 mg/kg weekly for 4 weeks as loading doses, followed by 1.5 mg/kg weekly, as long as they continue to derive sufficient clinical benefit. After 24 weeks on prophylactic RO5534262, patients will have the opportunity to increase their RO5534262 dose to 3 mg/kg weekly if they meet one or more of the following criteria **and** receive approval from the Medical Monitor:

- ≥2 bleeds in 24 weeks on RO5534262
- Lack of breakthrough bleed control despite hemostatic agents administered according to approved dosing and schedule

If a patient has a systemic hypersensitivity reaction or severe adverse reaction that may be attributable to RO5534262, subsequent doses should be held until the situation is discussed with the Medical Monitor and approval to resume dosing is given. Should certain, unanticipated events occur during the study that require treatment with multiple daily administrations of bypassing agents or FVIII concentrates for multiple days, such as non-elective surgery or severe/life-threatening bleeds, the investigator should contact the Medical Monitor immediately to discuss such cases and the management of future

RO5534262 doses. Any other RO5534262 dose adjustment request will require discussion of the clinical case with and approval from the Medical Monitor.

Study site healthcare providers (HCPs) will be trained on how to properly prepare the study medication and administer the correct calculated dose subcutaneously as described in the “Instructions for Use” (IFU) document. Patients will in turn be trained on study medication preparation and self-administration by an HCP, using the IFU as support. In the event that a caregiver will ultimately administer study drug to the patient in the home setting, the caregiver is to be trained. The HCP is to inform the patient/caregiver of the volumetric dose to be administered and dosing frequency.

Details on the devices to be used for study medication withdrawal and SC injection are provided in the Pharmacy Manual.

RO5534262 will be administered as a SC injection in the home setting, with one dose every week, after a period of in-clinic administration and training. The first five drug administrations must be performed in a monitored setting, such as an infusion center, clinic, or hospital, with a 60-minute observation period following each of the first three doses. For patients with a previous history of a clinically significant hypersensitivity reaction, additional precautions as described in Section 5.1.2.2 should be considered. The fourth and fifth scheduled study drug administrations must also be performed in the monitored setting. At that time, the patient/caregiver will also have the opportunity to ask any questions to the HCP before the scheduled start of home administration. The patient/caregiver will observe at least one SC injection performed by the HCP and successfully administer at least one SC injection while being observed by the HCP prior to starting home administration. Each site will have the discretion to provide additional training if deemed appropriate. If, despite additional training, the investigator determines that the patient/caregiver is unable to inject RO5534262, then arrangements may be made to identify a trained caregiver or HCP to administer the SC injections. At applicable sites, study drug may be administered by a trained home nursing (HN) professional at the patient's home or another suitable location, if the patient has given written informed consent to participate in HN visits.

Patients/caregivers will be provided with the clinic contact information, to use in case they have questions related to self-administration between visits.

Medication errors during training will be recorded and competence of the patient or caregiver to administer at home will be documented in the eCRF. If necessary, patients or their HCP may choose to continue administration of study drug in the clinic. Compliance in the home setting is to be monitored by review of hemophilia medication log on the ePRO device and recording of used and unused vials at each site.

If the patient forgets or cannot administer study medication on the scheduled dosing day, study medication should be administered as soon as possible within a window of 3 days

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from the scheduled dosing date. If more than 3 days has passed, the patient should take their next dose at the next scheduled time with the study medication dosing resumed in accordance with the original dosing schedule. All dosing should be clearly documented.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Patients and/or the caregiver will be provided with alert cards, which they will be requested to carry at all times. These will include guidance on recognizing signs/symptoms of thromboembolic events or allergic/anaphylactic/anaphylactoid reactions and how to obtain emergency care.

Guidelines for dosage modification are discussed in Section 3.1, and those for treatment interruption or discontinuation are provided in Section 4.6.

4.3.2 Investigational Medicinal Product Accountability

RO5534262, the only investigational medicinal product (IMP) in Study BH29884, is required for completion of this study and will be provided by the Sponsor, and accountability for each vial is required throughout the study. The study site will acknowledge receipt of IMPs using the interactive voice or Web response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

Used and unused IMP vials will be returned by study patients to the Sponsor and appropriately accounted for. Used vials will then be disposed of at the study site according to the study site's institutional standard operating procedure. Instructions regarding how to handle unused vials should be obtained from the Sponsor. If indicated, the site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.3 Post-Trial Access to RO5534262

The Sponsor will offer post-trial access to the study drug (RO5534262) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

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A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for hemophilia A with FVIII inhibitors
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for hemophilia A with FVIII inhibitors
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT AND RESCUE THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Concomitant use of the following drugs and therapies will be permitted:

- Drugs intended to control bleeds, including bypassing agents as standard of care/background treatment. Specific dosages of bypassing agents will not be mandated in the study but rather should be administered according to the respective prescribing information or as previously used per each individual patient (for information on the formulation, packaging, and handling of bypassing agents, see the local prescribing information for the marketed bypassing agent in question).
- Drugs and therapies to treat adverse events and use of topical antiseptics, anesthetics, eye drops, etc., that are not considered to result in systemic exposure

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 4 weeks prior to initiation of study treatment:

- Use of drugs that would affect hemostasis (e.g., aspirin, non-steroidal anti-inflammatory drugs, or anticoagulants [other than to flush, dwell, or de-clot a CVAD]) but excluding drugs intended to control bleeding episodes or used in the context of minor surgery (e.g., tooth extraction) or injuries (e.g., concussion) to prevent deterioration
- Use of systemic immunomodulators (e.g., rituximab, interferon) other than antiretroviral therapy from enrollment to last observation
- Elective surgery (excluding minor procedures such as tooth extraction or incision and drainage as well as emergency surgeries) from enrollment to last observation
- Use of other investigational drugs from enrollment to last observation

If prohibited therapy is administered for any reason, it should be recorded on the eCRF. If prohibited treatment is prescribed or considered medically necessary, the medical monitor should be consulted to discuss any changes in the benefit/risk and determine whether the patient should continue on the study.

4.5 STUDY ASSESSMENTS

See Appendix 1 for the schedule of assessments performed during the study.

At applicable sites, certain study assessments may be performed by an HN professional at the patient's home or another suitable location, such as their school or office, to improve access and convenience for patients participating in the study. The Sponsor may select a healthcare company that will be responsible for providing HN services for participating sites (the HN vendor). The HN vendor is responsible for ensuring that all HN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that HN services are appropriate for a patient and the patient gives written informed consent to participate in HN visits, the HN network will communicate with the patient and the patient's site. HN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the HN professional. The schedule of assessments (see Appendix 1) will specify the assessments that may be performed by an HN professional.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not enrolled will be maintained at the study site. For adolescents (i.e., 12–17 years of age), an Informed Assent Form will be completed instead. Parents or caregivers of adolescents will also complete an Informed Consent Form.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, procedures, use of alcohol and drugs of abuse within the past year, and medication allergies. In particular, sites should record whether the patient has any history of prior immune tolerance induction, anaphylaxis, or known thrombophilia. It should also include all medication taken in the 4 weeks prior to screening (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies). Finally, all bleed information (i.e., start date, cause, type, location), number of school/work days missed, and number of days hospitalized during the 24 weeks prior to study entry should be documented.

Demographic data will include age, sex, and self-reported race and ethnicity.

4.5.3 Physical Examinations

A complete physical examination should include but not necessarily be limited to the evaluation of head, eye, ear, nose, and throat and include cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified during screening should be recorded on the General Medical History and Baseline Conditions eCRF. Subsequently, a targeted (i.e., musculoskeletal, dermatological) and/or symptom-driven examination should be conducted as noted in the schedule of assessments or as clinically indicated. New or worsened abnormalities from screening should be recorded as adverse events, if appropriate.

4.5.4 Vital Signs

Vital signs will include measurement of heart and respiratory rate, temperature, systolic and diastolic blood pressure, and weight and should be recorded before study drug administration. Frequency of vital sign assessments should follow the schedule of assessments but may also be taken anytime as unscheduled assessments as judged by the investigator.

4.5.5 Laboratory, Biomarker, and Other Biological Samples

Local laboratory assessments will be performed as indicated on the schedule of assessments. On days of study drug administration, laboratory samples should be drawn before the administration of study drug. Laboratory assessments will include the following:

- Hematology (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells], mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width)
- Serum chemistries (sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, and uric acid)
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening.

  Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

The following samples will be sent to the Sponsor or a designee for centralized analysis:

- Plasma samples for PK analysis
- Plasma samples for immunogenicity assessment
- Plasma for PD and exploratory PD biomarker assessments (aPTT, PT, FVIII activity, thrombin generation, FIX:Ag, FX:Ag, and others as listed in Appendix 2)

In certain instances, blood draws may be performed by an HN professional.

4.5.6 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of assessments (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The following parameters will be obtained (and reported by the instrument): QT, RR, HR, QTcB, QTcF, PR and QRS and T- and U-wave morphology. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including

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environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

Any ECG changes that are associated with symptoms or lead to a change in study treatment or concomitant treatment, or discontinuation from study treatment, must be reported as an adverse event on the adverse event eCRF. The investigator or designee must review, sign, and date all ECG tracings. The ECG may be repeated if investigator deems it appropriate. Paper copies will be kept as part of the patient's permanent study file at the site. The site should also make a copy to be submitted to the Sponsor or Central Vendor. The Sponsor or Central Vendor will collect and store these copies until the end of the study. Centralized ECG reading and interpretations will not be performed unless safety concerns arise.

4.5.7 Patient-Reported Outcomes

An ePRO data collection modality will be employed. To capture PRO data during study treatment, patients will complete the questionnaires on an ePRO device that has been provided to them during their baseline visit at the site. The ePRO device and instructions for completing the PRO questionnaires electronically will be provided by the investigator staff. The data will be transmitted via a pre-specified transmission method (e.g., Web or wireless) automatically after entry to a centralized database at the ePRO vendor. The data can be accessed securely by appropriate study personnel via the Internet.

HRQoL:

The Haem-A-QoL and the Haemo-Qol-SF will be used to measure HRQOL in adults and adolescents, respectively (see Appendix 3 and Appendix 4). The Haem-A-QoL was designed for adult patients with hemophilia. It consists of 46 items comprising 10 dimensions (physical health, feelings, view, sport and leisure time, work and school, dealing, treatment, future, family planning, and relationships/partners) and a scale representing total score. Items are rated along 5 response options, although for some items there is also a 'not applicable' option (von Mackensen and Gringeri 2005; 2010).

The Haemo-QoL has been developed in a series of age-related questionnaires to measure health-related quality of life in children and adolescents with hemophilia (Bullinger et al. 2002; von Mackensen and Bullinger 2004; Pollak et al. 2006). These versions include a 77-item long form, a 35-item short form, and an 8-item index form. The short version of the Haemo-QoL was also developed: long versions for three age groups contain 21–77 items and cover 8–12 dimensions of quality of life (QOL). Furthermore, two age-specific short form measures containing 16 and 35 items were developed. The short version for older children (8–16 years) containing 35 items was selected for this study. This version contains 35 items, which cover nine dimensions considered relevant for the children's HRQoL (physical health, feelings, view of yourself, family, friends, other people, sports and school, dealing with hemophilia and treatment).

Items are rated with five respective response options: never, seldom, sometimes, often, and always.

Health Status:

The EQ-5D-5L (see Appendix 5) is a generic, preference-based health utility measure that assesses health status and is used to inform pharmacoeconomic evaluations. The EQ-5D-5L consists of two parts. The first part, health state classification, contains five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman et al. 2011; Janssen et al. 2013). Published weights are available that allow for the creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The second part is a 0 to 100 point visual analog scale (VAS), which assesses current health status; higher scores are reflective of better health.

4.5.8 Bleed Definitions

DEFINITION OF A BLEED

A standardized definition of bleed, adapted from standard criteria defined by the Subcommittee on Standards and Criteria, FVIII/FIX subcommittee of the International Society of Thrombosis and Hemostasis and similar to that used in a recent clinical study, will be utilized in this study (Blanchette et al. 2014; Mahlangu et al. 2014).

- An event is considered a bleed if coagulation factors are administered to treat signs or symptoms of bleeding (pain, swelling, etc.).
- Bleeds starting from the first sign of bleed and ending 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections $\leq$72 hours apart, are considered the same bleed.
- Any injection to treat the bleed, taken $>$72 hours after the preceding injection, is considered the first injection to treat a new bleed at the same location.
- Any bleed at a different location is considered a separate bleed regardless of time from last injection.

DEFINITIONS OF BLEED SITES

- Target joints: defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (frequency of $\geq$3 bleeds into the same joint over the last 24 weeks prior to study entry)
- Joint bleeds (other joint except target joints) defined as an unusual sensation (“aura”) in the joint, in combination with any of the following:

  Increasing swelling or warmth of the skin over the joint

  Increasing pain

  Progressive loss of range of motion or difficulty in using the limb as compared with baseline
- Muscle bleeds (sites as per the ePRO Bleed Questionnaire)
- Bruise/hematoma (sites as per the ePRO Bleed Questionnaire)

- Miscellaneous (sites as per the ePRO Bleed Questionnaire)

DEFINITIONS OF BLEED TYPES

In addition, the assessment of a bleed will be separated into spontaneous bleeds, traumatic bleeds and bleeds related to procedure/surgery. Both spontaneous bleeds (i.e., the occurrence of hemorrhage where neither the patient nor a caregiver can identify a reason) and traumatic bleeds (i.e., hemorrhage occurring secondary to an event such as trauma, "strenuous" activity, or "overuse") will be collected.

- Spontaneous bleeds: Bleeds should be classified as spontaneous if a patient records a bleed when there is no known contributing factor such as definite trauma, antecedent "strenuous" activity or "overuse." The determination of what constitutes "strenuous" or "overuse" will be at the discretion of the patient. For example, light jogging may be considered "non-strenuous" while sprinting may be considered "strenuous," lifting of weights for a short period of time may be considered "moderate use" while repetitive weightlifting may be considered "overuse."
- Traumatic bleeds: Bleeds should be classified as traumatic if a patient records a bleed when there is a known or believed reason for the bleed. For example, if a patient were to exercise "strenuously" and then have a bleed in the absence of any obvious injury, the bleed would be recorded as a traumatic bleed because, although no injury occurred, there was antecedent "strenuous" activity. Injuries preceding bleeds would certainly be classified as traumatic.
- Bleeds related to procedure/surgery: such as hematomas resulting from any surgeries or invasive procedures (e.g., tooth extractions, venipuncture, or SC drug administrations) or invasive diagnostic procedures (e.g., lumbar puncture, arterial blood gas determination, or any endoscopy with biopsy, etc.) would not be counted as bleeds. Bleeds related to procedure/surgery are not associated with any trauma except procedure/surgery-induced trauma.

Patients (or patient's legally authorized representative) will complete an ePRO questionnaire on a daily basis that asks whether they have had a bleed. If they have had a bleed, they are to answer questions on the above topics as well as medication they took to treat the bleed.

4.5.9 Samples for Roche Clinical Repository

4.5.9.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (see Section 4.5.9) will not be applicable at that site.

4.5.9.3 Sample Collection

The following samples will be collected for research purposes, including but not limited to research on genetic (inherited) biomarkers related to RO5534262, hemophilia A, or other coagulation disorders:

- Whole blood for DNA extraction (at Week 1)

For all samples, dates of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.9.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, the whole blood sample is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and

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considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.9.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient or patient guardian the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.9.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal

Form and, if the study is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. A patient's withdrawal from Study BH29884 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study BH29884.

4.5.9.7 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Patient's inability or unwillingness to comply with protocol requirements non-compliance despite appropriate education measures taken by the clinical site. Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn.

4.6.2 Study Treatment Discontinuation

Patients must stop study treatment if they experience the following:

- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced. Patients who become pregnant should immediately stop treatment and be managed as per local guidelines.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

- Incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence (e.g., ePRO data not checked by investigator/co-investigator for >8 weeks)
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

RO5534262 is not approved and is currently in clinical development. Thus, the complete safety profile is not known at this time. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

5.1.1 Patient Selection

The inclusion and exclusion criteria in this study are designed to select patients who are not at increased risk based on the current understanding of the investigational medication. See Section 4.1.1, Section 4.1.2 for full inclusion and exclusion criteria, respectively.

5.1.2 Risks Associated with RO5534262

5.1.2.1 Injection-Site Reactions

In the completed and ongoing Japanese studies, injection-site reactions have been observed in some patients with hemophilia A. These local injection-site reactions included injection-site erythema, injection-site hematoma, injection-site rash, injection-site discomfort, and injection-site pruritus. All local injection-site reactions were of mild intensity. Further details of the observed injection-site reactions are available in the Investigator's Brochure.

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Directions for RO5534262 administration should be followed, as outlined in Section 3.3.1, Section 4.3.1.2.

5.1.2.2 Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid Reaction

Since RO5534262 is a biological product, acute, systemic hypersensitivity reactions, including anaphylaxis and anaphylactic reactions, may occur. In completed and ongoing clinical studies of RO5534262, no severe hypersensitivity reactions have been reported. These events should be reported as Serious Adverse Events or Adverse Events of Special Interest as described in Section 5.2.3.

HCPs administering the study medication in the clinic must be trained in the appropriate administration procedures, be able to recognize the signs and symptoms associated with potential hypersensitivity, anaphylactic, and anaphylactoid reactions, and should be familiar with Sampson's criteria for defining anaphylaxis (Sampson et al. 2006; see Appendix 7). HCPs should also instruct patients how to recognize the signs and symptoms of hypersensitivity, anaphylactic, and anaphylactoid reactions and to contact an HCP or seek emergency care in case of any such occurrence. Patients/caregivers will also receive two alert cards to remind them of this information and these instructions should any of these reactions occur.

For patients with a previous history of a clinically significant hypersensitivity reaction, after each of the first three doses, the site will call the patient 24 hours after each dose to assess the status of the patient. Additional precautions following each of these doses may also be considered including having an extended observation period or IV access prior to dosing, etc. The investigator may include these or other precautions, as deemed appropriate.

5.1.2.3 Hypercoagulation and Thromboembolic Events

The bypassing agents (e.g., aPCC and rFVIIa) have the unwanted potential to induce thromboembolism. Though thrombus formation was seen in some animal venous stasis models with RO5534262, subsequent pre-clinical results suggested that the risk does not substantially exceed those seen with bypassing agents alone. In completed and ongoing clinical studies of RO5534262, no thromboembolic events have been reported.

These events should be reported as Serious Adverse Events or Adverse Events of Special Interest as described in Section 5.2.3. HCPs should educate patients/caregivers to recognize signs and symptoms of potential thromboembolism (i.e., dyspnea, chest pain, leg pain or swelling, etc.) and ensure that they understand the importance of seeking appropriate medical attention. Patients/caregivers will also receive two alert cards to remind them of this information and these instructions should thromboembolism be suspected.

5.1.3 Management of Specific Adverse Events

Table 2 Guidelines for Management of Specific Adverse Events

Event	Actions to Be Taken
Injection-Site Reaction	• Injection-site reactions should be treated as clinically indicated. • RO5534262 should not be injected into areas where the skin is red, bruised, tender, or hard or into areas where there are moles or scars. • In the clinic setting, patients will be monitored for signs of injection-site reactions in the period immediately following injections. Patients will be given guidance on reporting injection-site reactions when administering drug at home or after they leave the clinic.
Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid Reaction	• Suspected cases should be fully evaluated and treated as clinically indicated. • Medicinal products for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, and glucocorticoids) and resuscitation equipment must be available for immediate use during the initial administrations in the infusion center, clinic, or hospital. • If a patient has symptoms of anaphylaxis or severe hypersensitivity, administration of study drug must be immediately stopped and treatment of the reaction be initiated. • The investigator should contact the Medical Monitor to assess if the clinical benefit clearly outweighs the risk to determine if and when the patient should resume taking RO5534262 and discuss the patient's continued study participation. If patient continues in the study, the next two scheduled doses must be in a monitored setting with at least a 60-minute observation period and resuscitation treatment immediately available. After each of these two doses in the clinic, the site will call the patient 24 hours after each dose to assess status of the patient. • Investigators may order any pertinent laboratory tests, including an unscheduled anti-drug antibody, in the event any of these reactions occur.
Hypercoagulation and Thromboembolic Events	• HCPs should be vigilant for patients who exhibit signs/symptoms consistent with thromboembolic events and immediately begin work-up and treatment, as per local guidelines. • If a patient has a thromboembolic event, administration of study drug should be stopped. The investigator should contact the Medical Monitor to assess if the clinical benefit clearly outweighs the risk to determine if the patient should resume taking RO5534262 and discuss the patient's continued study participation.
Coagulation Disorder and Risk of Bleeding	• HCPs should be vigilant for abnormal or unusual bleeding tendencies. Coagulation tests or other work-up may be indicated if judged to be appropriate by the investigator. If bleeding is observed, appropriate action as per local guidelines must be taken immediately.

HCP = healthcare provider.

[no notes on this page]

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

Bleeds considered as serious adverse events should be reported as serious adverse events on the eCRF. Non-serious bleeds will not be considered adverse events and will not be recorded on the eCRF.

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

[no notes on this page]

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as grade 1–4, according to the World Health Organization [WHO] Toxicity Grading Scale for Determining The Severity of Adverse Events criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Systemic hypersensitivity reactions and anaphylactic and anaphylactoid reactions (see Sampson's Criteria in Appendix 7)
- Thromboembolic events

[no notes on this page]

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to randomization (randomized arms) or initiation of study drug (non-randomized arm)**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After randomization (randomized arms) or initiation of study drug (non-randomized arm), all adverse events will be reported until the patient completes his or her last study visit. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The WHO toxicity grading scale (see Appendix 6) will be used for assessing adverse event severity (WHO 2003). Table 3 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (<48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Notes: Developed by the Division of Microbiology and Infectious Diseases.
Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection-Site Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a diagnosis (e.g., injection-site erythema or injection-site rash) on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction. Associated signs and symptoms should be recorded on the dedicated Injection-Site Reaction eCRF. If a patient experiences both a local and systemic reaction to the same administration of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection-Site Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events, other than injection-site reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

[no notes on this page]

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$baseline value) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of hemophilia.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of hemophilia, "hemophilia progression" should be recorded on the Adverse Event eCRF.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Hemophilic Bleeds

Medical occurrences or symptoms of deterioration that are anticipated as part of hemophilia should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in terms of severity (e.g., increased number of doses of bypassing agents to stop bleeds with RO5534262, in the absence of neutralizing anti-RO5534262 antibodies, compared with before study entry), frequency of bleeds, or nature of hemophilia at any time during the study. Should any of these occur (according to the investigator's clinical assessment), they should be documented as an adverse event on the Adverse Event eCRF, conveying that the underlying condition has changed by including applicable descriptors (e.g., "increased clinical severity of hemophilia").

[no notes on this page]

Events that are clearly consistent with the expected pattern the underlying disease should not be recorded as adverse events. These data will be reflected in efficacy assessment data only. In most cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for drug administration)
- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing or drug administration error of RO5534262 are available, as no such instances have been observed to-date. To minimize the risk of errors associated with future home administration of RO5534262, data related to

[no notes on this page]

medication errors with observed patient/caregiver administration of RO5534262 during the first 5 weeks at the site by the investigator and/or clinical staff will be recorded and corrected at the time of occurrence. In addition, the recording of medication and handling errors associated with home administration, as well as drug compliance, will be collected at each clinic visit.

5.3.5.13 Patient-Reported Outcome Data

The patient-reported outcome (PRO) measurements are described in Section 4.5.9. The methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Because of these differences, PRO data will not be reported as adverse events and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF. The PRO data will be presented in separate tables, figures, and data listings from the adverse event data, and will be included in the appropriate section of the final study report.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

[no notes on this page]

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D., M.Phil. (primary)

Telephone No.: [redacted]

Medical Monitor: [redacted], M.D. (secondary)

Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Randomization or Study Drug Initiation

After informed consent has been obtained but prior to randomization (randomized arms) or initiation of study drug (non-randomized arm), only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Randomization or Study Drug Initiation

After randomization (randomized arms) or initiation of study drug (non-randomized arm), serious adverse events and non-serious adverse events of special interest will be reported until the last scheduled study visit (see Section 5.6). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

[no notes on this page]

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 24 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 24 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified

[no notes on this page]

as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 24 weeks after the last dose of study drug or rollover to an extension study), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest (see Section 5.2.3) against cumulative product experience to identify and

expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- RO5534262 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

The sample size for this study is based on clinical rather than statistical considerations, taking into account the limited number of patients with hemophilia A with inhibitors available for participation in clinical studies and in an effort to collect sufficient data to assess the safety and efficacy of RO5534262.

The sample size calculation is based on the evaluation of the primary efficacy endpoint, defined as the number of bleeds over time (i.e., bleed rate) with RO5534262 (treatment group, λ_t) versus no prophylaxis (control group, λ_c), which are said to follow a negative binomial (NB) distribution with γ_t and γ_c described as shape parameters for treatment and control groups, respectively. With consideration of enrollment feasibility, a sample size of 45 patients, assuming an allocation ratio of 2:1 (30 patients in treatment group and 15 patients in control group), will achieve a power of more than 95% for λ_t and λ_c ranging from 1 to 4 and 18 to 30, respectively (Table 4). Here, the patients from the two groups are followed up to 0.5 units of time (i.e., 24 weeks). Sample size calculations were performed with East®, Version 6 (Cytel, Cambridge, MA), which allows specific shape parameters for both the treatment and control groups.

However, the above approach to sample size calculation assumes similar follow-up for each patient. Because this is unlikely to be seen in the study, power was also estimated by simulation to account for different follow-up times among patients. Conducting simulations on the basis of a negative binomial regression model including an offset variable to account for variable follow-up times, with all other assumptions remaining the same as previously described, the sample size is projected to have greater than 95% power at the 2-sided 0.05 level of significance.

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Assuming a drop-out rate of 10% in the control group with 2:1 treatment to control randomization, approximately 34 RO5534262 treatment and approximately 17 control patients (approximately 51 patients, in total) will be enrolled.

During the study, a re-assessment of the initially specified sample size based on aggregated (not by treatment arm) data to-date (and potentially from the non-interventional study [BH29768] findings) may be performed. This may result in an increase in sample size, if necessary, to maintain adequate power without affecting the type 1 error rate. Study integrity will be upheld, as access to information via aggregated analyses and their results will be minimized to limit operational bias.

Table 4 Power Calculations

Rate for Control Treatment Arm (λ_c, n_c=15)	**Rate for Experimental Treatment Arm** (λ_t, n_t=30)			
	1 (γ_t=0.11)	2 (γ_t=0.22)	3 (γ_t=0.33)	4 (γ_t=0.44)
18 (γ_c=2)	**1** (λ_t / λ_c=0.056)	**0.999** (λ_t / λ_c=0.111)	**0.99** (λ_t / λ_c=0.167)	**0.952** (λ_t / λ_c=0.222)
25 (γ_c=2.78)	**1** (λ_t / λ_c=0.04)	**1** (λ_t / λ_c=0.08)	**0.994** (λ_t / λ_c=0.12)	**0.973** (λ_t / λ_c=0.16)
30 (γ_c=.33)	**1** (λ_t / λ_c=0.033)	**0.999** (λ_t / λ_c=0.067)	**0.995** (λ_t / λ_c=0.1)	**0.978** (λ_t / λ_c=0.133)

6.2 GENERAL

This section provides a general overview of the methods. If any of the items require a unique approach that differs from the general overview, then it will be noted in the appropriate section.

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum, and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

All summary tables will be structured with a column for each treatment arm and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

Analyses will follow the principle of intention-to-treat (i.e., based on randomized population).

[no notes on this page]

6.3 SUMMARIES OF CONDUCT OF STUDY

Flow of patients through the study will be displayed in a 'CONSORT' diagram. A clear account of all patients who entered the study, who were enrolled and randomized, and who entered and completed each phase of the study will be displayed. In addition, reasons for premature discontinuations from study treatment and reasons for withdrawing from the study (e.g., during follow-up) will be described.

Variables from the eCRF used to establish how many patients reached the various stages of the study, how many dropped out and for what reasons will be described in the Statistical Analysis Plan (SAP).

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Comparisons between the treatment arms of demographic data and baseline characteristics will be conducted to establish if any observed differences between the treatment arms are not due to imbalances in patient characteristics at baseline. Only descriptive analyses are planned, and no formal statistical tests will be applied.

6.5 EFFICACY ANALYSES

The primary and secondary efficacy analyses to evaluate the clinical effect of prophylactic RO5534262 compared with no prophylaxis will include all randomized patients, with patients grouped according to the treatment assigned at randomization. For patients previously treated with prophylactic bypassing agents, the efficacy analysis will include all enrolled patients.

6.5.1 Primary Efficacy Endpoint

The primary efficacy objective is to evaluate the clinical effect of prophylactic RO5534262 compared with no prophylaxis on the number of bleeds over time. The definition of a bleed is described in Section 4.5.8.

The primary efficacy analysis will be conducted after all randomized patients have reached 24 weeks in the study or discontinue study participation, whichever occurs first, and using an intent-to-treat principle. The comparison of the number of bleeds over time between the randomized treatment arms will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study included as an offset in the model. The model also includes the number of bleeds (<9 or ≥ 9) in the last 24 weeks prior to study entry as a stratification factor in the randomization. This analytic model estimates the rate ratio, λ_t / λ_c., which quantifies the risk of bleeding associated with prophylactic RO5534262 (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level, and the estimated risk ratio is compared with 1, assuming the following statistical hypothesis:

H_0 (null hypothesis): Rate Ratio $= 1$ versus H_1 (alternative hypothesis): Rate Ratio $\neq 1$.

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The treatment effect therein is based on a contrast statement in the model with use of the SAS GENMOD procedure. Statistical significance at the pre-specified alpha level will be based on a Wald testing procedure. Bleed rates for prophylactic RO5534262 and no prophylaxis and the rate ratio will be presented and include 95% confidence intervals.

The number of bleeds can also be annualized for each patient using the following formula: ABR = (Number of bleeds during the efficacy period/Total number of days during the efficacy period) × 365.25. If the negative binomial model converges, an analysis of variance (ANOVA) to compare the mean ABR between the randomized arms will be provided only as a sensitivity analysis. However, if the convergence of the negative binomial model is not achieved or is questionable, the primary efficacy analysis will be based on the ANOVA of ABR.

A detailed description of the statistical methods that will be used for the primary and secondary efficacy analyses will be provided in the SAP.

6.5.2 Secondary Efficacy Endpoints

For all patients, the number of bleeds over time will be compared with the patient's bleed rate over the last 24 weeks prior to study entry recorded in the medical record and/or for the duration of their participation in the non-interventional study, whichever is longer.

In addition, the number of joint and target joint bleeds over 24 weeks' time between the RO5534262 prophylaxis and no prophylaxis arms will be evaluated. Adherence with the HRQoL and health status measures captured in the ePRO device will be summarized at the end of the study.

HRQoL (using the Haem-A-QoL or the Haemo-QoL-SF) and health status (using the EQ-5D-5L) will be assessed on a regular basis, as per the schedule of assessments (scheduled). Health status will also be assessed in the event of a bleed (unscheduled).

Because different HRQoL measures (Haem-A-QoL and the Haemo-QoL-SF) are being used for the adult and adolescent patients, all calculations and analyses will be conducted separately for adults and adolescents. Scale scores for the Haem-A-QoL and Haemo-QoL-SF will be calculated and summarized descriptively. The HRQoL scale scores for all patients will be evaluated at 24 weeks in the study, a timepoint that is consistent with other recent registrational studies in hemophilia (Lentz et al. 2013; Powell et al. 2013; Mahlangu et al. 2014) and analyses of such data (Santagostino et al. 2014; Wyrwich et al. 2015). An additional sensitivity analysis will be performed utilizing patients' HRQoL scale scores at 48 weeks or the time of the most recent HRQoL assessment, whichever occurs later. For each treatment arm, paired t-tests will be used to compare the 24-week and final assessments with the baseline scale scores for each HRQoL measure. Statistical significance will be set at $p < 0.05$. Within-subject and between-group changes from baseline on the different HRQoL scale scores will also be calculated at 24 weeks and the final HRQoL assessment.

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For the assessments of the EQ-5D-5L performed every 4 weeks, the number and percentage of patients in each of the five categories for each question for each group will be assessed. Changes in the EQ-5D-5L index utility score from baseline will also be compared between groups. In addition, summary statistics including mean, standard deviation, median, minimum and maximum will be displayed for the patients' health state using the EQ-VAS both within and between groups. The proportion of patients who report changes in each group exceeding the clinically meaningful threshold on the EQ-5D-5L index and EQ-VAS scores in each group will be reported at 24 weeks and the final, scheduled EQ-5D-5L assessment.

Separately, for each EQ-5D-5L completed in connection with a bleed, the level of pain associated with that episode, as well as the utility score and general health score will be reported.

Secondary endpoints used for labeling and those that are solely for scientific interest will be specified in the SAP. The method used for controlling the type 1 error rate will also be described.

6.6 SAFETY ANALYSES

The safety analyses population will be based on all enrolled patients grouped according to the actual treatment received. Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology, including complete blood count with differential), ECGs, vital signs, and antibodies to RO5534262.

To evaluate the overall safety of prophylactic RO5534262 compared to no prophylaxis, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade for each treatment arm.

For clinical laboratory data, summary statistics will be presented by treatment arm. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

Data on the impact of immunogenicity (anti-RO5534262 antibodies) on safety, efficacy, and/or clinical pharmacology and PK will be summarized adopting standard language/terminology (Shankar et al. 2014).

6.7 PHARMACOKINETIC ANALYSES

For all patients, pre-dose (trough) plasma concentrations of RO5534262 will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will be used to analyze the dose-concentration-time data of RO5534262 following SC administration. Population PK parameters, such as

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clearance and volume of distribution, will be estimated, and the influence of various covariates, such as age, gender, and body weight, on these parameters will be investigated graphically. Secondary PK parameters, such as area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies. These analyses will be reported in a dedicated report.

6.8 EXPLORATORY ANALYSES

Summary statistics of the number of work/school days missed and days hospitalized will be presented by treatment arm.

PD parameters (e.g., aPTT, parameters derived from thrombin generation, FVIII activity) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

6.9 INTERIM ANALYSIS

Although this is an open-label study, Sponsor personnel will not have access to by-arm efficacy and safety summaries prior to the formal reporting of the study results. HCPs at participating study sites, as well as the Sponsor's drug safety and medical monitoring staff, will have access to the treatment assignments of patients for safety monitoring purposes only.

The iDMC (Section 9.4.2) will evaluate efficacy and safety at one formal interim analysis, as well as at periodic safety reviews, and will recommend to the Sponsor if the study should be stopped early. All summaries and analyses will be prepared by the independent Data Coordinating Center (iDCC) and presented by treatment arm for the iDMC's review. Members of the iDMC will be external to the Sponsor, and the study team and will follow a charter that outlines their roles and responsibilities.

The planned interim analysis will occur during the execution of the primary efficacy period (after the 25th randomized patient completes 24 weeks in the study [i.e., after 50% of the information has been collected] or discontinues study participation, whichever occurs first). The primary efficacy analysis will take place after the last randomized patient completes 24 weeks in the study or discontinues study participation, whichever occurs first. No information from the remaining patients who will have been enrolled but followed for $<$24 weeks will be included in the interim analysis; the data from these patients will be included in the primary efficacy analysis.

The statistical evaluation of the interim analysis dataset will be performed on the primary efficacy endpoint—number of bleeds over time—and a Wald's test from a negative binomial regression model will be used to compare the treatment arms. However, if the convergence of the negative binomial model is not achieved or is questionable at the time of the interim analysis, the interim and primary efficacy analyses will be based on a Wald's test from an ANOVA of the ABR (Section 6.5). The interim analysis will follow a group sequential design proposed by Lan-DeMets (DeMets and Lan 1994) with an

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alpha-spending function according to O'Brien and Fleming (O'Brien and Fleming 1979). This method allows for interim analyses at flexible information fractions without destroying the integrity of the calculated boundaries. To maintain an overall two-sided alpha level of 5%, this approach results in the two-sided boundaries of approximately 2.9626 (nominal p-value = 0.0031) for the interim analysis, which will take place after approximately 50% of the required patients (i.e., 25 patients) have been observed for at least 24 weeks, and 1.9686 (nominal p-value = 0.049) for the primary efficacy analysis. At the time of the interim analysis, the iDMC may recommend unblinding and fully analyzing the study if the observed p-value is < 0.0031 and in favor of RO5534262.

Additional details about the interim analyses will be provided in the iDMC Charter and interim SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

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7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patient-reported data will be collected electronically with use of electronic devices provided by an ePRO vendor. The electronic device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 Code of Federal Regulations, Part 11). The data will be transmitted electronically in real-time to a centralized database at the ePRO vendor. The data from the ePRO devices are available for view access only via secure access to a Web portal provided by the ePRO vendor. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. Regular data transfers will occur from the centralized database at the vendor to the database at the Sponsor. The Sponsor will receive all data entered by patients on the ePRO devices and all relevant study documentation.

Once the study is complete, the ePRO data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for study-related

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monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and additional local regulatory requirements.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Adolescent's Informed Assent Form or Home Nursing Informed

Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other

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processes outlined above apply except that IRB review and approval may not be required per study site policies.

Patients who are declared legally incompetent or who are physically or mentally incapable of providing informed consent but otherwise meet the qualifications for participation in Study BH29884 will be included, as RO5534262 prophylaxis may directly benefit this population with high unmet medical need. In such cases, investigators will obtain informed consent from a guardian or legally authorized representative of the patient in accordance with applicable law. In addition, the investigator must also obtain the assent of the patient when they are able to give assent to decisions made on their behalf. Any indication on the part of the patient that they are not willing to participate in the study will be honored.

In cases where there is reason to question the competence of a patient who has not been declared incompetent (e.g., a patient in the early stages of Alzheimer's disease), a patient advocate will be involved in the consent process and throughout the duration of the patient's participation in the study.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This global study will enroll approximately 61–71 patients.

Randomization and drug assignment will be performed by an IxRS, which will also manage RO5534262 inventory for all sites globally.

Patient-reported outcomes will be captured on an ePRO device provided by a third-party vendor for all patients globally.

Central laboratories will be used for a subset of laboratory assessments specified in Section 4.5.5.

9.4.1 Steering Committee

A Steering Committee, consisting of medical experts in the field of bleeding disorders who collectively have the scientific, medical, and clinical study management experience to evaluate and provide guidance on the conduct of clinical studies, will monitor and supervise the progress of the study towards meeting its objectives (e.g., provide input on scientific decisions, propose solutions for overcoming operational challenges, and consider modifications to the protocol). The policies and procedures will be detailed in a separate Steering Committee Charter document.

9.4.2 Independent Data Monitoring Committee and Independent Data Coordinating Center

An iDMC will be assembled to review the safety and efficacy data collected during the study. The iDMC members will consist of, at minimum, independent hemostasis/thrombosis experts and a statistician, none of whom will be otherwise involved in the conduct of study. All analyses for review by the iDMC will be prepared by an iDCC that is independent of the Sponsor. At the beginning of the study, intensive monitoring and analysis of all significant safety events will be performed. Safety analyses of significant safety events will be conducted after the first 12 patients receiving RO5534262 have completed 12 weeks in the study. Thereafter, the iDMC will meet at a frequency determined by the iDMC and the Sponsor to conduct the interim analysis, but this schedule may be adjusted according to the emerging safety profile.

An iDCC will perform unblinded analyses and provide tables and listings to support the iDMC reviews of safety data and interim efficacy analysis. The safety data will include demographic data, adverse events, serious adverse events, and laboratory abnormalities (coagulation, hematology, and chemistry). Further information will be given on request. The efficacy data will include bleed rate.

Following each meeting, the iDMC will recommend to the Sponsor whether the study should continue according to the protocol or may suggest changes to the protocol based on the outcome of the data review. In exceptional cases, the iDMC may recommend stopping the study or closing a treatment arm for safety reasons. The iDMC will monitor the incidence of the anticipated adverse events, as well as the overall safety of patients, during the study.

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Stopping for a compelling benefit-risk for patients is possible only during the planned interim analysis (i.e., after approximately 25 randomized patients have completed 24 weeks in the study). The meeting schedule and all other iDMC-related activities will be specified in a separate iDMC charter. All results will be confidential and will not be divulged to non-members of the iDMC, including the Sponsor. All closed meetings will be summarized in written minutes available only to iDMC members and the iDCC statistician and kept by the iDCC statistician until the end of the study. The recommendations can be communicated to the Sponsor verbally but have to be confirmed in writing according to a pre-defined timeframe. Strict confidentiality rules will be applied to avoid any dissemination of either safety or efficacy interim results outside the iDMC.

The final decision of acting upon the iDMC's recommendations will rest with the Sponsor. The policies and procedures will be detailed in a separate iDMC Charter document.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on both the interim and final analyses of the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Website:
http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf.

The results of this study may be published or presented at scientific congresses. For all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments
Schedule of Assessments–Arms A and C

	Screen-ing	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Every 8 weeks from Wk 33	Wk 49	Every 12 weeks from Wk 61	Daily [a]	Study Com-pletion/ ET	Safety F/U Visit [b]
Informed consent [c]	x																	
Inclusion/exclusion criteria	x																	
Medical history & demographics [d]	x																	
Targeted physical exam [e]		x				x						x		x			x	x
Vital signs [f]	x	x [f]	x	x	x	x		x	x	x	x	x [f]	x	x [f]	x		x [f]	x [f]
Concomitant medications [g]		x				x		x	x	x	x	x	x	x	x		x	x
ECG [h]	x	x [h]				x						x	x [h]				x	
Safety laboratory assessments [i]	x [i]	x	x	x	x	x		x	x	x	x	x	x	x	x		x	x
Anti-FVIII antibodies [j]	x																	x
Anti-RO5534262 antibodies [k]		x [k]				x		x [k]	x	x [k]	x	x [k]	x [k]	x [k]	x [k]		x	x [k]
Bleed/injection questionnaire [l]																x		
Bleed/injection data review [m]		x				x		x	x	x	x	x	x	x	x		x	x
Adverse events [n]		x	x	x	x	x		x	x	x	x	x	x	x	x		x	x
IMP management [o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
HRQoL [p]		x				x		x	x	x	x	x	x	x	x		x	
Health status (EQ-5D-5L) [q]		x				x		x	x	x	x	x	x	x	x	x [q]	x	
PK assessment [r]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
PD biomarkers assessment [s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
RCR whole blood DNA sample [t]		x																

[no notes on this page]

Appendix 1
Schedule of Assessments (cont.)

Schedule of Assessments–Arm B

	Screen-ing	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Daily [a]
Informed consent [c]	x											
Inclusion/exclusion criteria	x											
Medical history & demographics [d]	x											
Targeted physical exam [e]		x										
Vital signs [f]	x	x [f]				x		x	x	x	x	
Concomitant medications [g]		x				x		x	x	x	x	
ECG [h]	x	x [h]										
Safety laboratory assessments [i]	x [i]	x										
Anti-FVIII antibodies [j]	x											
Bleed/injection questionnaire [l]												x
Bleed/injection data review [m]		x				x		x	x	x	x	
Adverse events [n]		x				x		x	x	x	x	
HRQoL [p]		x				x		x	x	x	x	
Health status (EQ-5D-5L) [q]		x				x		x	x	x	x	x [q]
PD biomarkers assessment [s]	x	x										
RCR whole blood DNA sample [t]		x										

[no notes on this page]

Appendix 1
Schedule of Assessments (cont.)

Schedule of Assessments–Arm B (continued)

	Wk 25	Wk 26	Wk 27	Wk 28	Wk 29	Wk 31	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	Every 8 weeks from Wk 57	Every 12 weeks from Wk 85	Daily[a]	Study Completion/ ET	Safety F/U Visit[b]
Targeted physical exam[e]	x				x						x				x	x
Vital signs[f]	x[f]	x	x	x	x		x	x	x	x	x[f]	x	x		x[f]	x[f]
Concomitant medications[g]	x				x		x	x	x	x	x	x	x		x	x
ECG[h]	x				x						x	x[h]			x	
Safety laboratory assessments[i]	x	x	x	x	x		x	x	x	x	x	x	x		x	x
Anti-FVIII antibodies[j]	x[j]															x
Anti-RO5534262 antibodies[k]	x[k]				x		x[k]	x	x[k]	x	x[k]	x[k]	x[k]		x	x[k]
Bleed/injection questionnaire[l]														x		
Bleed/injection data review[m]	x				x		x	x	x	x	x	x	x		x	x
Adverse events[n]	x	x	x	x	x		x	x	x	x	x	x	x		x	x
IMP management[o]	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
HRQoL[p]	x				x		x	x	x	x	x	x	x		x	
Health status (EQ-5D-5L)[q]	x				x		x	x	x	x	x	x	x	x[q]	x	
PK assessment[r]	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
PD biomarkers assessment[s]	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x

eCRF=electronic Case Report Form; EQ-5D-5L=EuroQoL Five-Dimension-Five Levels Questionnaire; eCRF=electronic Case Report Form; ePRO=electronic patient-reported outcome; ET=early termination; F/U=follow-up; FVIII=factor VIII; HRQoL=health-related Quality of Life;

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Appendix 1
Schedule of Assessments (cont.)

IMP = investigational medicinal product, PD = pharmacodynamics; PK = pharmacokinetic; RCR = Roche Clinical Repository; Wk = Week.

Notes: All assessments should be performed within ±2 days of the scheduled visit for the first 12 weeks, then ±7 days thereafter. Except for the bleed/injection questionnaire, HRQoL, and health status, all other patient data will be collected during office visits. On treatment days, pre-injection blood collection should be made 0–30 minutes before the injection.

[a] Patients will be prompted on a daily basis to complete the bleed/injection questionnaire.

[b] A safety follow-up visit will occur 24 weeks after discontinuing RO5534262.

[c] Obtain written informed consent (or patient assent and parent written informed consent if patient is an adolescent) before distribution of ePRO device and collection of any data. Randomization and enrollment form will be completed after informed consent and/or assent is obtained.

[d] Collected from patient medical records and documented in the eCRF, including information on target joint(s).

[e] Targeted physical exam of joints (for bleeds, evidence of arthropathy) and skin (for bruises, hematomas, and injection-site reactions), in addition to other organ systems as clinically indicated and/or report of new or worsening adverse event.

[f] Body temperature (oral or tympanic), blood pressure, pulse rate, respiratory rate, and weight; only to be used to monitor during and after injection for hypersensitivity reactions and not to be entered into eCRF, except at Weeks 1, 25, 49, at study completion/early termination, and at the safety follow-up visit (i.e., 24 weeks after discontinuing RO5534262) for patients in Arms A and C and additionally at Week 73 for patients in Arm B. Height will be measured at Screening only.

[g] Concomitant medications (e.g., extra pain medication with bleed) will be asked about at each clinic visit, excluding treatments for bleeds (i.e., bypassing agents and other medications to treat bleeds), which will be collected on the bleed questionnaire. Hemostatic medications to treat or prevent bleeds in the week prior to starting RO5534262 will also be collected.

[h] If screening ECG abnormal, repeat at Week 1. ECGs will also be performed 4–8 and 24 weeks after starting RO5534262 or dose up-titration, as well as at study completion/early termination.

[i] Laboratory data (performed locally) include: complete blood count with differential (i.e., neutrophils, hemoglobin, platelet count), serum chemistries (i.e., total protein, albumin, creatinine, total and direct bilirubin, alkaline phosphatase, ALT, AST, γ-glutamyl transferase). Blood samples may also be drawn to conduct biomarker assays at the central laboratory on an unscheduled basis (at the clinical judgment of the investigator) at any time. Female patients with childbearing potential will be required to have a negative serum pregnancy test result at screening and urine pregnancy tests performed at every clinic visit, with the exception of Weeks 2–4 and 7. If patients undergo up-titration of their dose after 24 weeks in the study, an additional safety laboratory assessment will be performed during Weeks 28–32.

[j] Anti-FVIII antibodies will be collected at screening (for all patients), at Week 25 pre-dose (for patients only in Arm B), and at the safety follow-up visit (i.e., 24 weeks after discontinuing RO5534262).

[k] Anti-RO5534262 antibodies will be collected every 4 weeks prior to RO5534262 administration but only the following samples will be analyzed: immediately prior to the first injection on Week 1, every 8 weeks from Weeks 5–48, every 12 weeks starting from Week 60, and at

[no notes on this page]

the 24-week, post-RO5534262 safety follow-up visit following initiation of RO5534262 in all patients; if any of these samples are positive and/or if there is suboptimal clinical response or low pharmacokinetic exposure, the remaining collected samples may be analyzed for anti-RO5534262 antibodies. Anti-RO5534262 antibodies may also be drawn at the time of hypersensitivity events.

[l] Reported by the patient; includes start date and time, reason, type, location, and associated symptoms of each bleed, as well as start date and time, reason, type, and dose of each injection, if any, excluding RO5534262.

[m] At the Week 1 visit, patients will be trained on how to use and be provided their own ePRO device. Investigator review of patient-reported bleed/injection questionnaire information. Information regarding trauma events in the preceding 4 weeks will be collected in the eCRF.

[n] Injection-site reaction adverse events will be collected on a separate form from the adverse event form. If there is unexpected worsening of the patient's hemophilia in terms of severity (e.g., increased number of doses of bypassing agents to stop bleeds compared to before study entry), frequency of bleeds, or nature at any time during the study, this should be documented as an adverse event on the Adverse Event eCRF, conveying that the underlying condition has changed by including applicable descriptors (e.g., "increased clinical severity of hemophilia").

[o] Drug accountability will not be performed at the first visit of RO5534262 receipt. Drug dispensation will not occur at the study completion/early termination visit.

[p] Haem-A-QoL questionnaire (age≥18) and Haemo-QoL-Short Form (ages 12–17). Patient-reported outcomes will be transmitted directly by the ePRO device to the ePRO database.

[q] On days that patients report having a new bleed and every 4 weeks, they will be prompted to also complete the EQ-5D-5L questionnaire on the ePRO device.

[r] RO5534262 concentration. Plasma samples for this assessment should be taken prior to injection.

[s] See Appendix 2 for detailed explanation of PD biomarker assessments (Sets 1 and 2). Blood samples will be banked for future exploratory PD biomarker analyses.

[t] Samples for the RCR are optional and require an additional signature.

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Appendix 2
Schedule of Pharmacodynamic Assessments

Sample	Visit [a]	Biomarker assays [b]
PD Set 1	**Starting on RO5534262 (Arms A and C):** Screening Every week during Weeks 1–4 Every 2 weeks during Weeks 5–8 Every 4 weeks during Weeks 9–24 Every 8 weeks during Weeks 25–48) Every 12 weeks thereafter, while on RO5534262 Study Completion/Early Termination Safety Follow-up Visit Unscheduled visit (at the discretion of the investigator), while on RO5534262 [c] **Starting on episodic bypassing agents, switch to RO5534262 after 24 weeks (Arm B):** Screening Week 1 Every week during Weeks 25–28 Every 2 weeks during Weeks 29–32 Every 4 weeks during Weeks 33–48 Every 8 weeks during Weeks 49–84 Every 12 weeks thereafter, while on RO5534262 Study Completion / Early Termination Safety Follow-up Visit Unscheduled visit (at the discretion of the investigator), while on RO5534262 [c]	Standard aPTT Modified aPTT PT FVIII activity Thrombin generation FIX antigen FX antigen D-dimer Prothrombin fragment 1.2
PD Set 2	**Starting on RO5534262 (Arms A and C):** Screening Week 1 Week 25 Study Completion/Early Termination Safety Follow-up Visit **Starting on episodic bypassing agents, switch to RO5534262 after 24 weeks (Arm B):** Screening Week 1 Week 25 Week 49 Study Completion/Early Termination Safety Follow-up Visit	FVIII activity VWF antigen Fibrinogen

[redacted] FIX = factor IX; FVIII = factor VIII; FX = factor X; PD = pharmacodynamics; VWF = von Willebrand factor.

Note: Except for Day 1 of Week 1, all other study visits and assessments during the treatment period should be performed within ± 2 days of the scheduled date for the first 12 weeks, then ± 7 days thereafter. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] All samples are to be collected on Day 1 of the indicated week, prior to RO5534262

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Appendix 2
Schedule of Pharmacodynamic and Pharmacokinetic Assessments (cont.)

injection (if applicable). All PD samples will be citrate or EDTA plasma. Refer to Appendix 1 for exact study visits.

[b] Biomarker assays will include, but are not limited to, those listed. [redacted] Blood volumes and processing procedures will be specified in the Laboratory Manual.

[c] Reasons for unscheduled visits may include evaluation or treatment for bleeds or hypersensitivity reactions.

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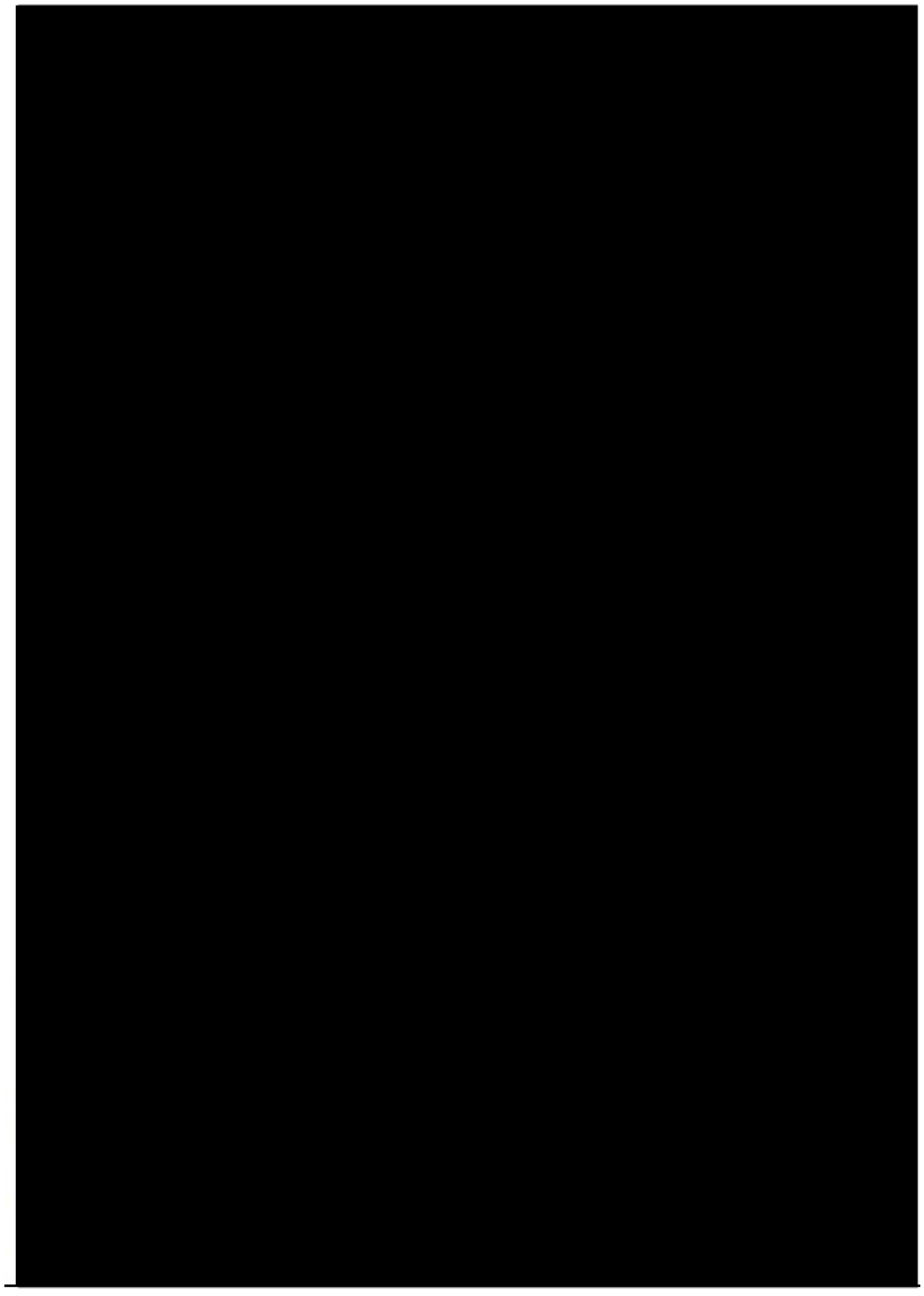
Appendix 3
Haemo-QoL-SF (United States/English)



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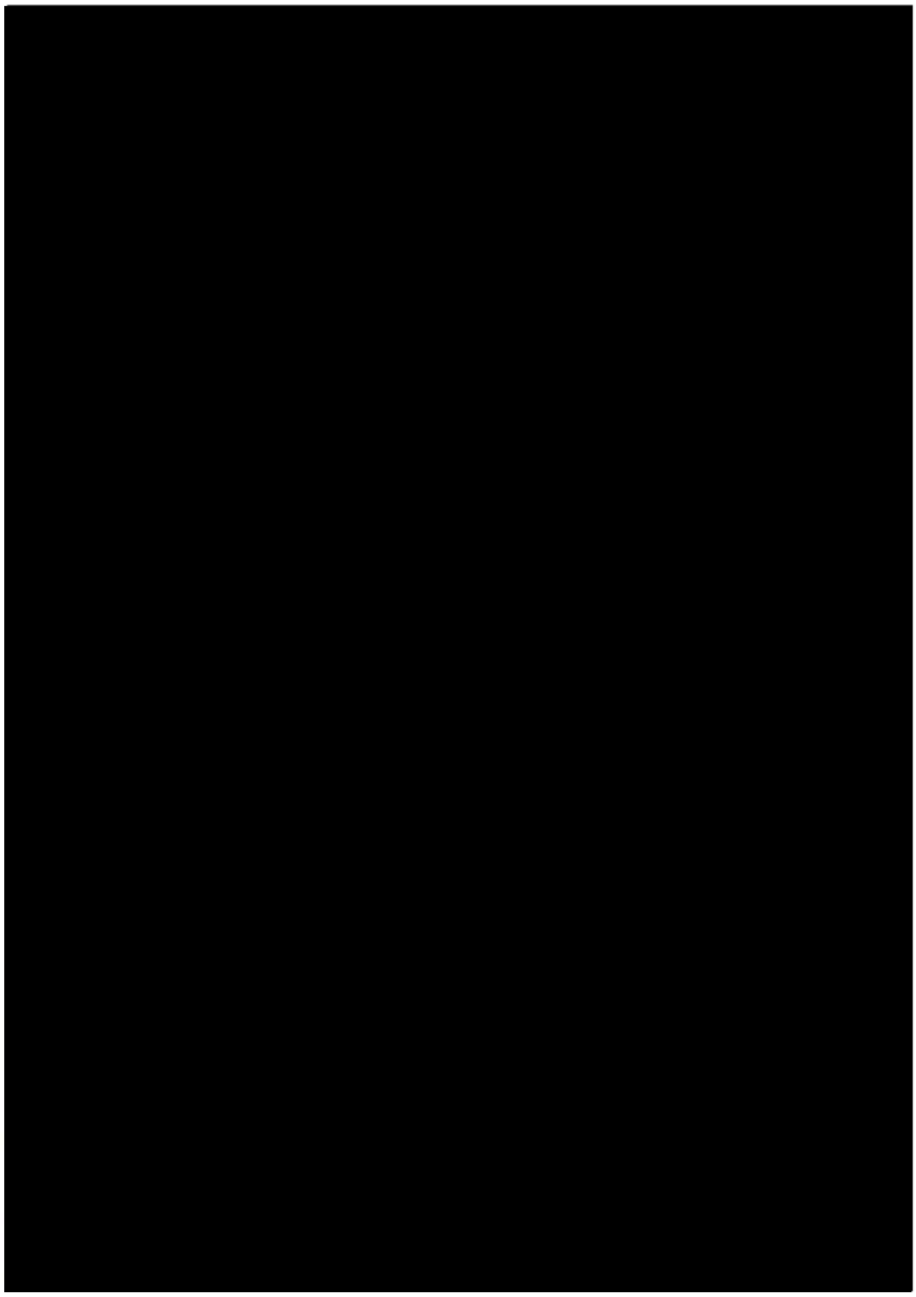
Appendix 3
Haemo-QoL-SF (United States/English)(Cont)



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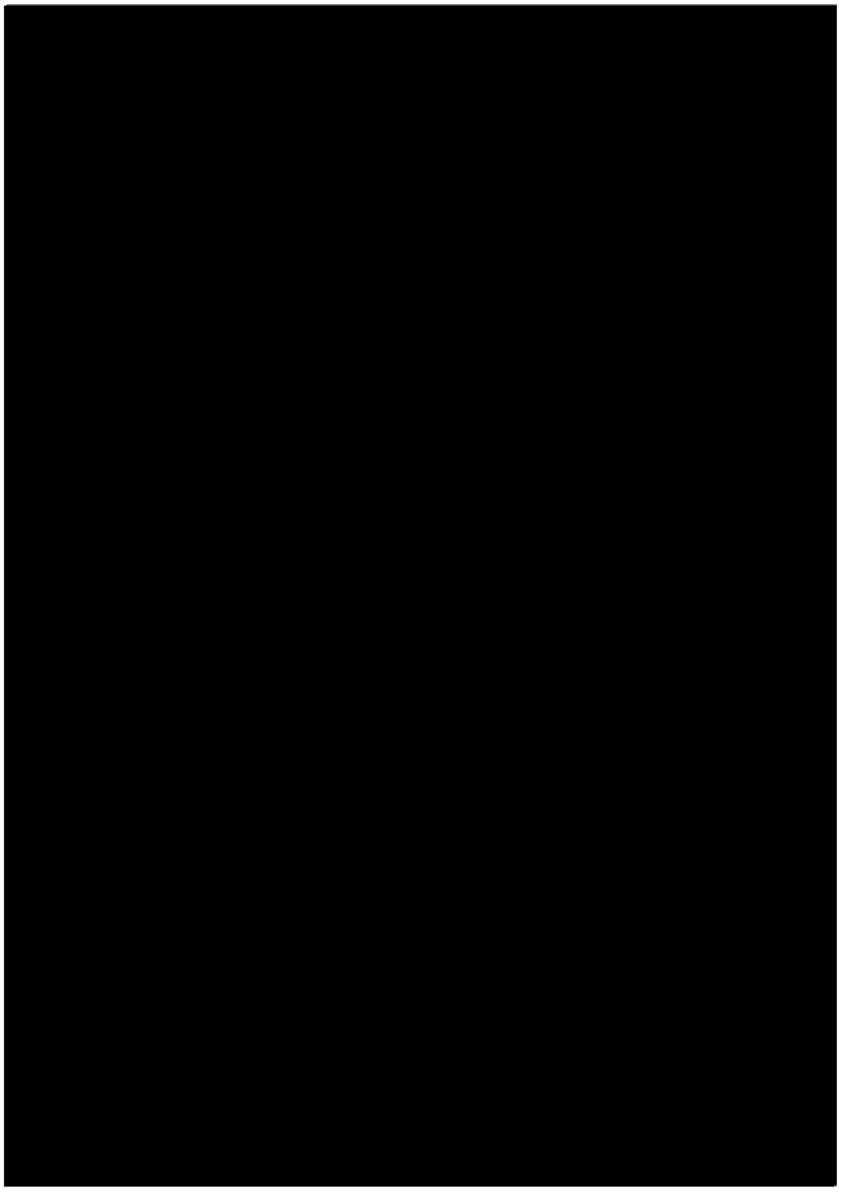
Appendix 4
Haem-A-QoL (United States/English)



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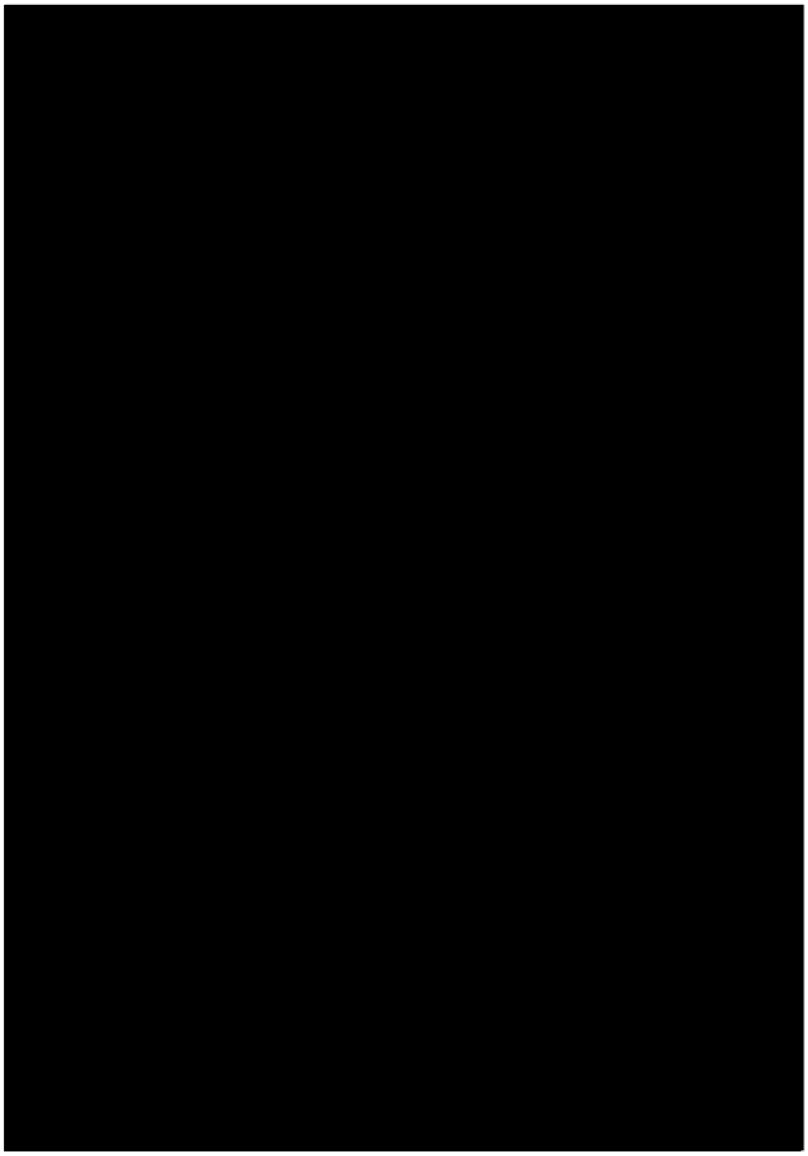
Appendix 4
Haem-A-QoL (United States/English) (cont.)



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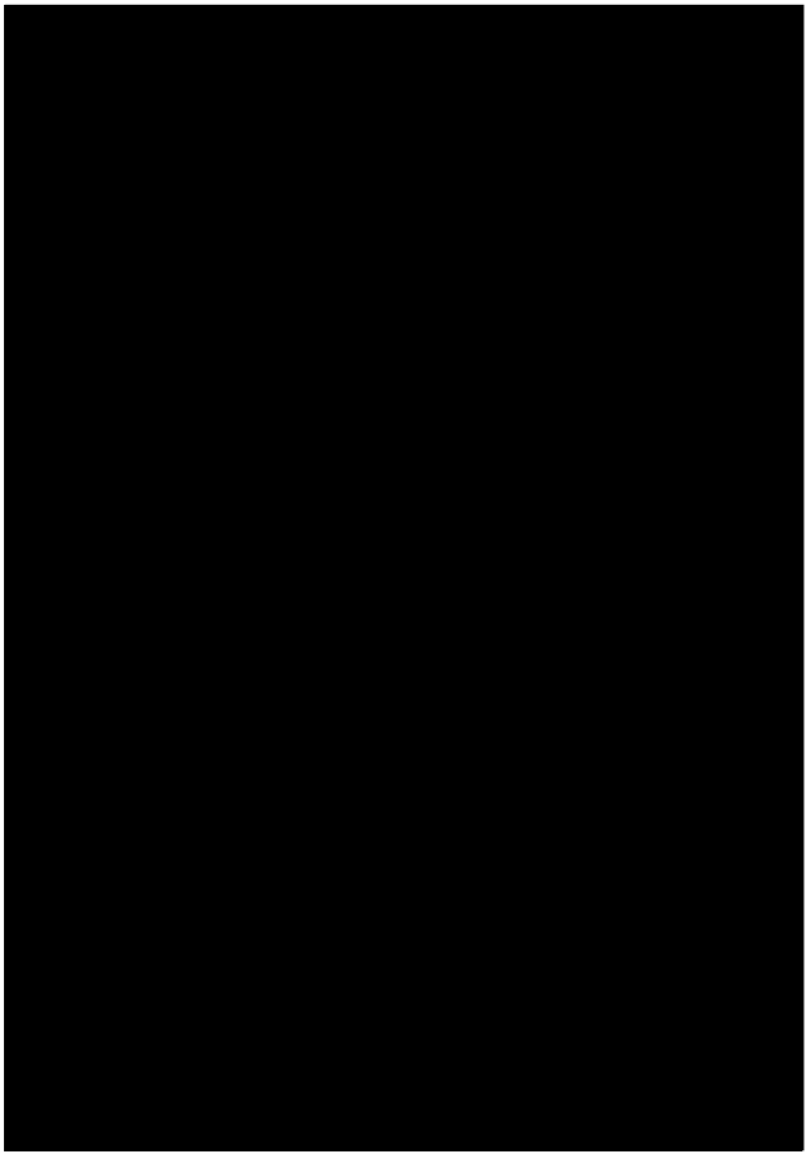
Appendix 4
Haem-A-QoL (United States/English) (cont.)



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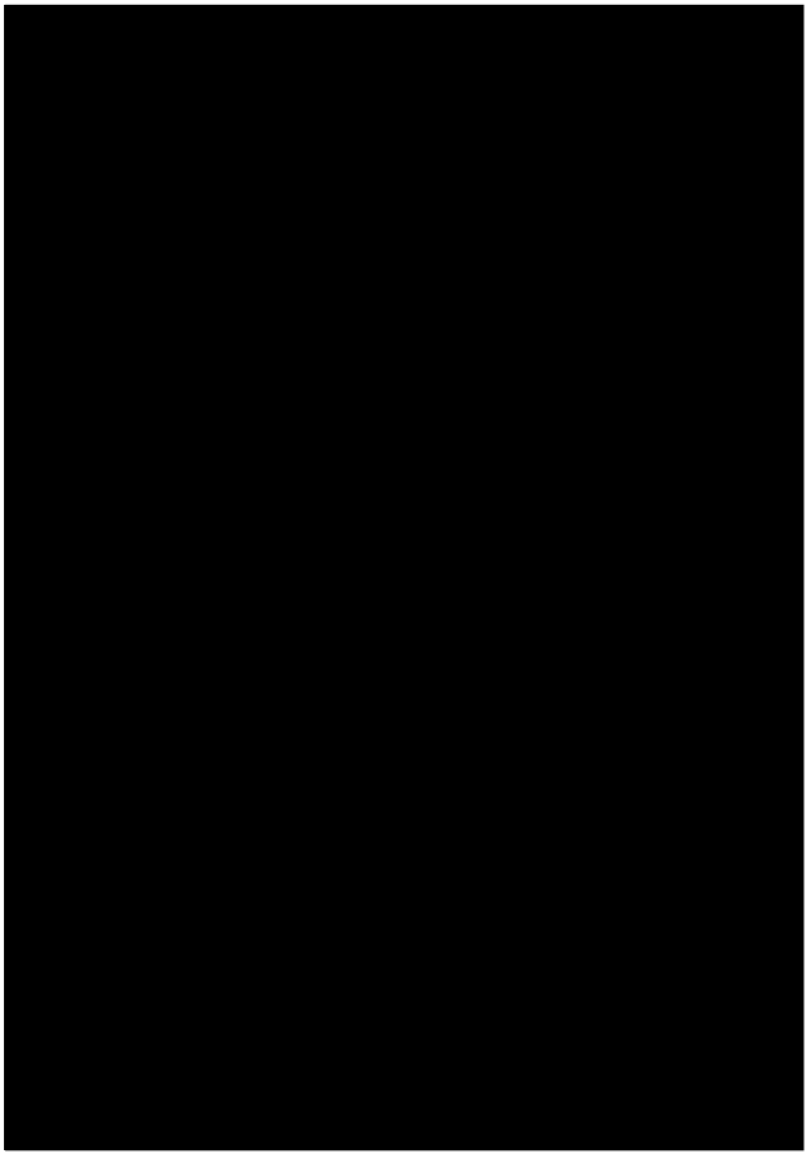
Appendix 4
Haem-A-QoL (United States/English) (cont.)



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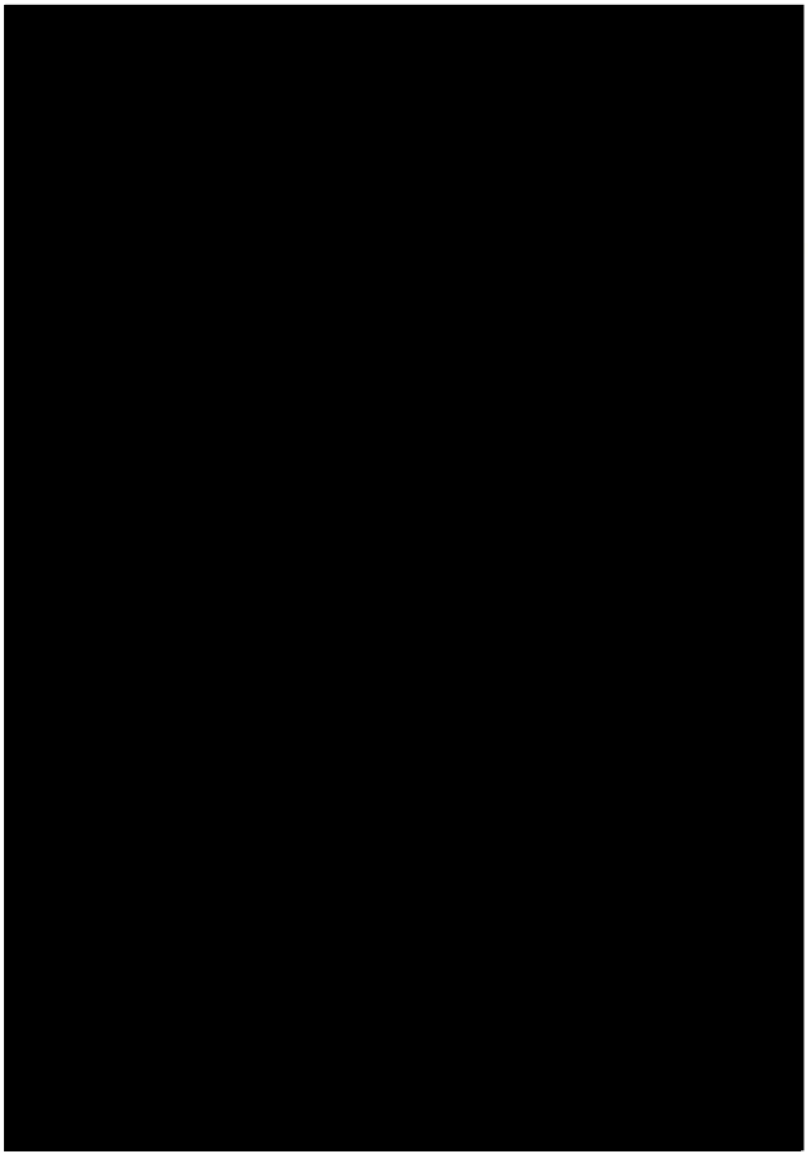
Appendix 4
Haem-A-QoL (United States/English) (cont.)



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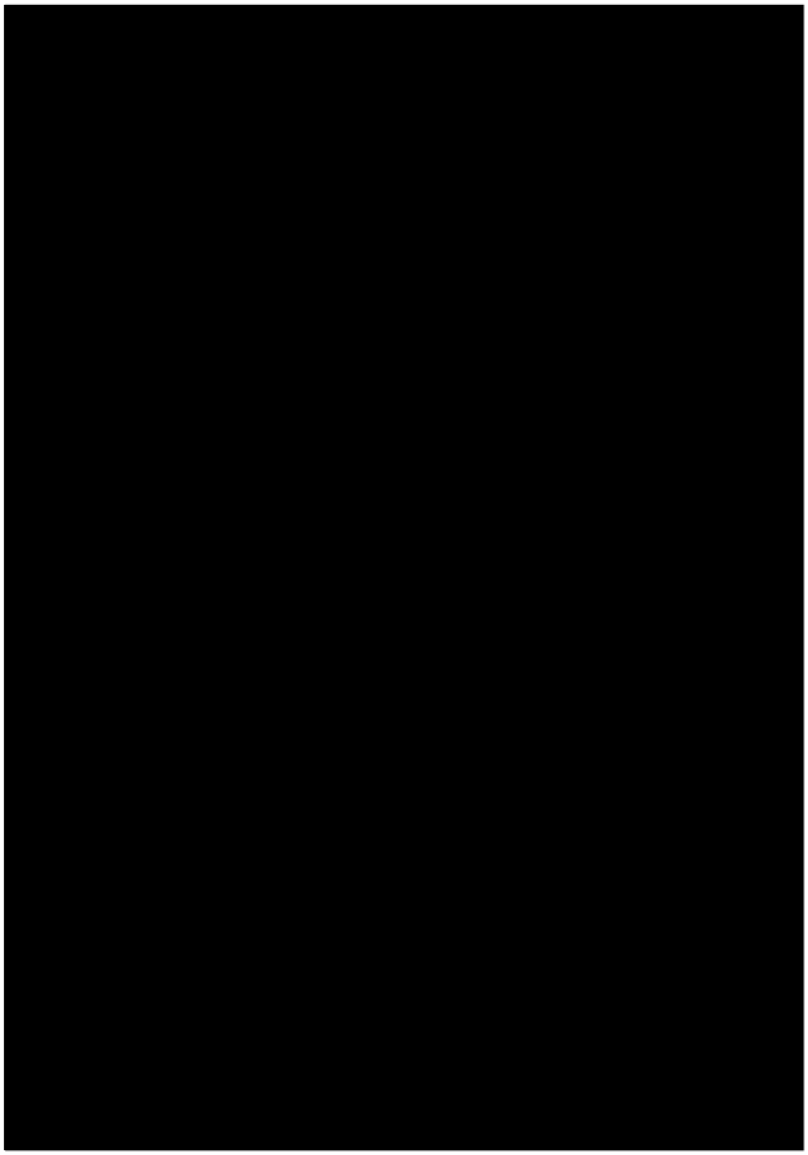
Appendix 4
Haem-A-QoL (United States/English) (cont.)



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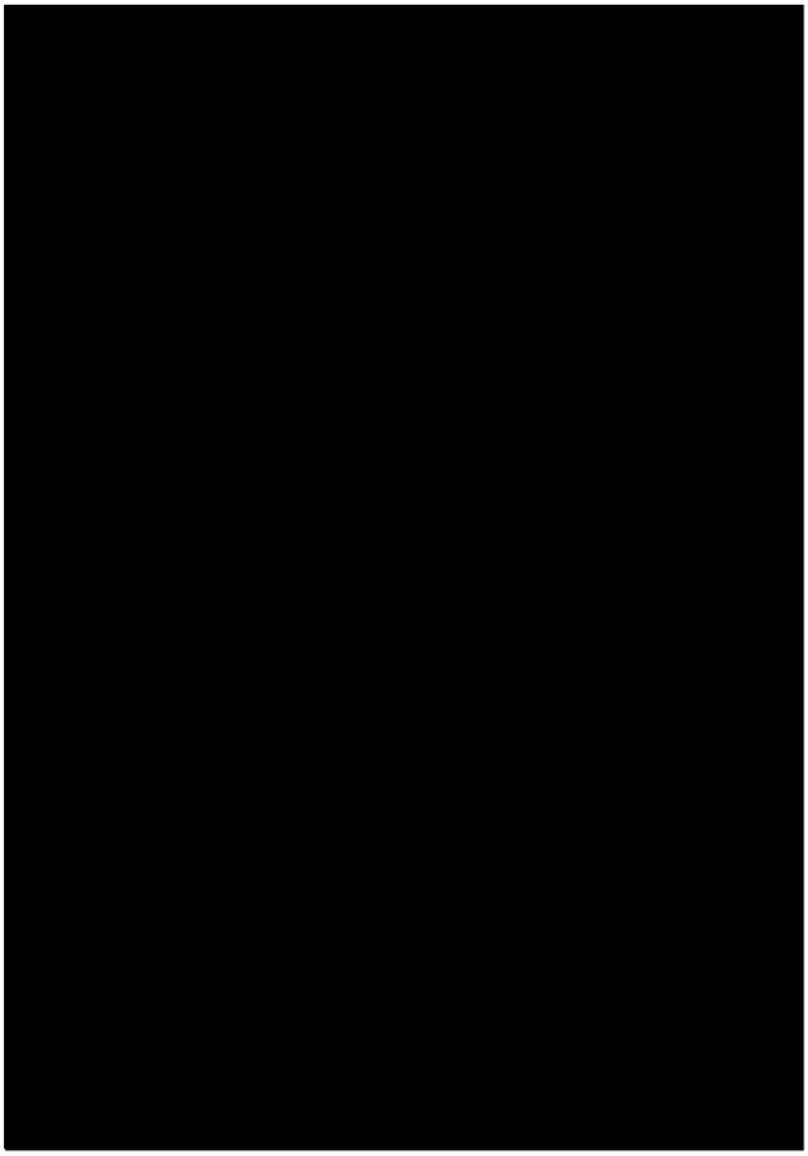
Appendix 4
Haem-A-QoL (United States/English) (cont.)



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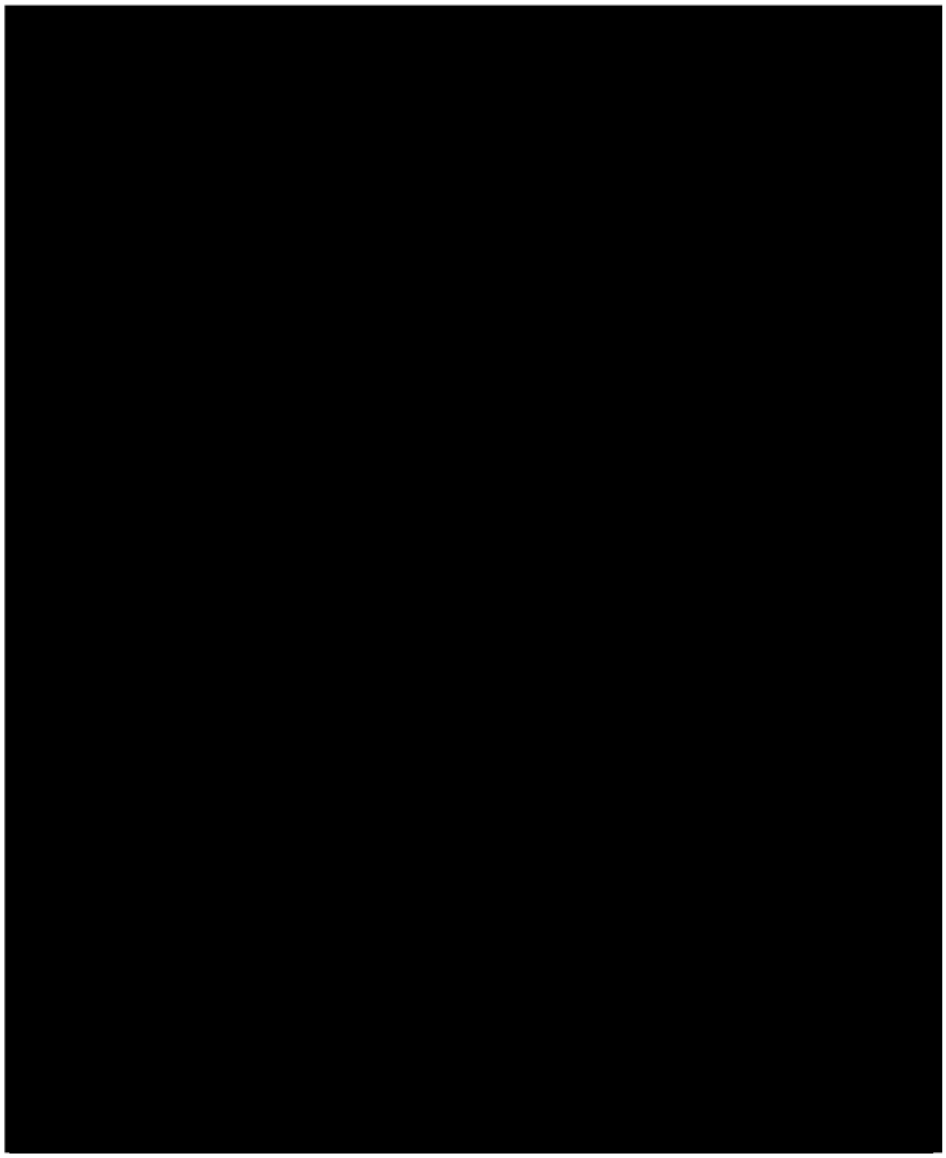
Appendix 5
EQ-5D-5L (United Kingdom/English)



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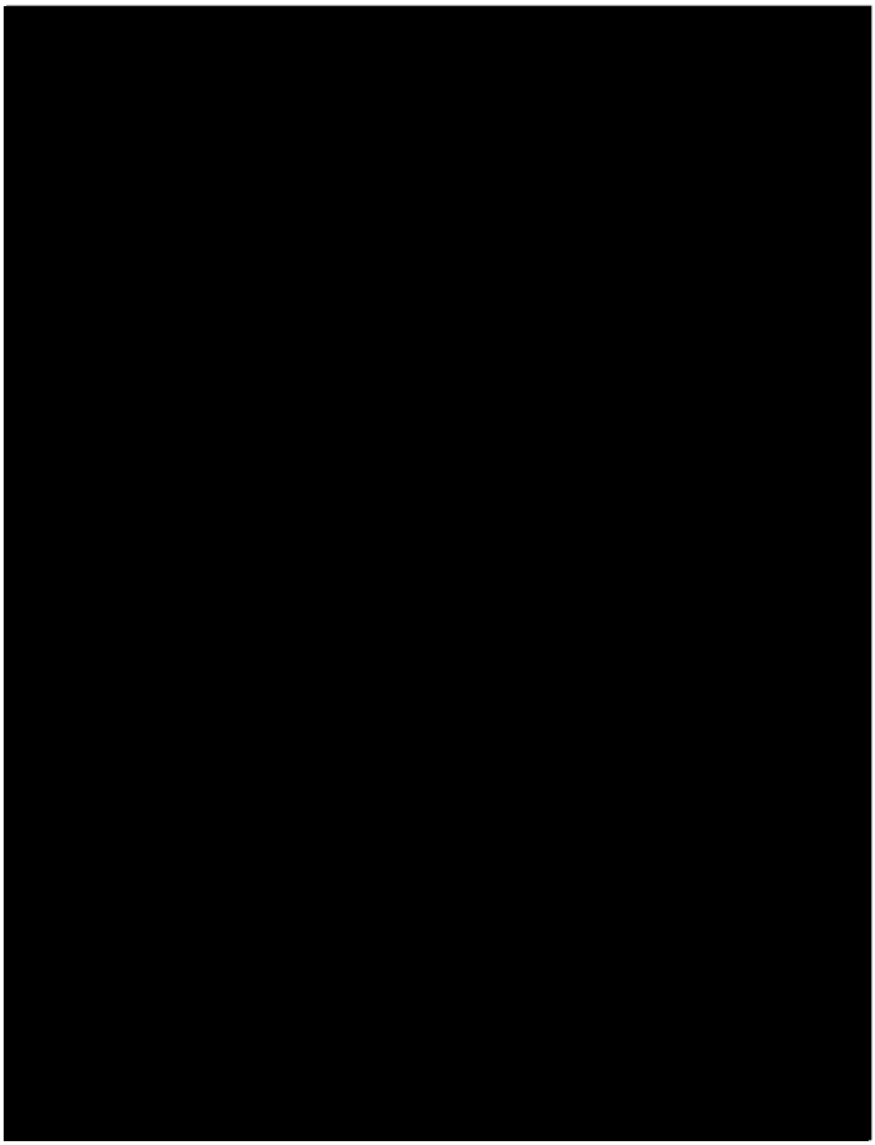
Appendix 5
EQ-5D-5L (United Kingdom/English) (cont.)



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Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events

HEMATOLOGY				
Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
Hemoglobin	9.5–10.5 g/dL	8.0–9.4 g/dL	6.5–7.9 g/dL	<6.5 g/dL
Absolute neutrophil count	1000–1500/mm^3	750–999/mm^3	500–749/mm^3	<500/mm^3
Platelets	75000–99000/mm^3	50000–74999/mm^3	20000–49000/mm^3	<20000/mm^3
Prothrombin time (PT)	1.01–1.25×ULN	1.26–1.5×ULN	1.51–3.0×ULN	>3×ULN
Activated partial thromboplastin (APPT)	1.01–1.66×ULN	1.67–2.33×ULN	2.34–3×ULN	>3×ULN
Fibrinogen	0.75–0.99×LLN	0.50–0.74×LLN	0.25 - 0.49×LLN	<0.25 x LLN
Fibrin split product	20–40 mcg/mL	41–50 mcg/mL	51–60 mcg/mL	>60 mcg/mL
Methemoglobin	5–9.9%	10.0–14.9%	15.0–19.9%	>20 %
LIVER ENZYMES				
AST (SGOT)	1.25–2.5×ULN	2.6–5×ULN	5.1–10×ULN	>10×ULN
ALT (SGPT)	1.25–2.5×ULN	2.6–5×ULN	5.1–10×ULN	>10×ULN
GGT	1.25–2.5×ULN	1.6–5×ULN	5.1–10×ULN	>10×ULN
Alkaline phosphatase	1.25–2.5×ULN	1.6–5×ULN	5.1–10×ULN	>10×ULN
Amylase	1.1–1.5×ULN	1.6–2.0×ULN	2.1–5.0×ULN	>5.1×ULN

[no notes on this page]

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

CHEMISTRIES				
Hyponatremia	130–135 mEq/L	123–129 mEq/L	116–122 mEq/L	< 116 or mental status changes or seizures
Hypernatremia	146–150 mEq/L	151–157 mEq/L	158–165 mEq/L	> 165 mEq/L or mental status changes or seizures
Hypokalemia	3.0–3.4 mEq/L	2.5–2.9 mEq/L	2.0–2.4 mEq/L or intensive replacement Rx required or hospitalization required.	<2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6–6.0 mEq/L	6.1–6.5 mEq/L	6.6–7.0 mEq/L	>7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55–64 mg/dL	40–54 mg/dL	30–39 mg/dL	<30 mg/dL or mental status changes or coma
Hyperglycemia (note if fasting)	116–160 mg/dL	161–250 mg/dL	251–500 mg/dL	>500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4–7.8 mg/dL	7.7–7.0 mg/dL	6.9–6.1 mg/dL	<6.1 mg/dL or life-threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6–11.5 mg/dL	11.6–12.5 mg/dL	12.6–13.5 mg/dL	>13.5 mg/dL life-threatening arrhythmia
Hypomagnesemia	1.4–1.2 mEq/L	1.1–0.9 mEq/L	0.8–0.6 mEq/L	<0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0–2.4 mg/dL	1.5–1.9 mg/dL or replacement Rx required	1.0–1.4 mg/dL intensive Rx or hospitalization required	<1.0 mg/dL or life-threatening arrhythmia

[no notes on this page]

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

CHEMISTRIES continued				
Hyperbilirubinemia	1.1–1.5 × ULN	1.6–2.5 × ULN	2.6–5 × ULN	> 5 × ULN
BUN	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Creatinine	1.1–1.5 × ULN	1.6–3.0 × ULN	3.1–6 × ULN	> 6 × ULN or required dialysis
URINALYSIS				
Proteinuria	1+ or < 0.3% or < 3g/L or 200 mg–1 g loss/day	2–3+ or 0.3–1.0% or 3–10 g/L 1–2 g loss/day	4+ or > 1.0% or > 10 g/L 2–3.5 g loss/day	nephrotic syndrome or > 3.5 g loss/day
Hematuria	microscopic only	gross, no clots	gross + clots	obstructive or required transfusion
CARDIAC DYSFUNCTION				
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; no Rx required	requires treatment
Hypertension	transient inc. > 20 mm; no Rx	recurrent, chronic, > 20 mm, Rx required	requires acute Rx; no hospitalization	requires hospitalization
Hypotension	transient orthostatic hypotension, no Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1–2 units transfused	massive blood loss; > 3 units transfused

[no notes on this page]

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

RESPIRATORY				
Cough	transient; no Rx	treatment-associated cough local Rx	uncontrolled	
Bronchospasm, Acute	transient; no Rx < 80%–70% FEV_1 (or peak flow)	requires Rx normalizes with bronchodilator; FEV_1 50%–70% (or peak Flow)	no normalization with bronchodilator; FEV_1 25%–50% (or peak flow retractions)	cyanosis: FEV_1 <25% (or peak flow) or intubated
GASTROINTESTINAL				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	severe discomfort; no significant intake; activities limited	minimal fluid intake
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3–4 loose stools/day	57 loose stools/day	orthostatic hypotension or >7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required

[no notes on this page]

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

NEURO AND NEUROMUSCULAR				
Neuro-cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and therapy required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization
Neuro control (ADL = activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/agitation some limitation of ADL; minimal Rx	severe confusion/agitation needs assistance for ADL; therapy required	toxic psychosis; hospitalization
Muscle strength	subjective weakness no objective symptoms/signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
OTHER PARAMETERS				
Fever: oral, >12 hours	37.7–38.5 C or 100.0–101.5 F	38.6–39.5 C or 101.6–102.9 F	39.6–40.5 C or 103–105 F	>40 C or >105 F
Headache	mild, no Rx therapy	transient, moderate; Rx required	severe; responds to initial narcotic therapy	intractable; required repeated narcotic therapy
Fatigue	no decrease in ADL	normal activity decreased 25–50%	normal activity decreased >50% can't work	unable to care for self
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis

[no notes on this page]

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

OTHER PARAMETERS continued				
Local Reaction	tenderness or erythema	induration < 10 cm or phlebitis or inflammation	induration > 10 cm or ulceration	necrosis
Mucocutaneous	erythema; pruritus	diffuse, maculo-papular rash, dry desquamation	vesiculation, moist desquamation, or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens- Johnson or necrosis requiring surgery

[no notes on this page]

Appendix 7
Clinical Criteria for Diagnosing Anaphylaxis

These criteria are taken from a summary report from the second symposium on the definition and management of anaphylaxis, conducted by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network.[1] Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue/uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
   - Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure*
   - Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

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[1] Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–7.

* Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

PROTOCOL

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC EMICIZUMAB VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
PROTOCOL NUMBER:	BH29884
VERSION NUMBER:	3
EUDRACT NUMBER:	2015-002866-21
IND NUMBER:	122,954
TEST PRODUCT:	Emicizumab (RO5534262)
MEDICAL MONITOR:	[redacted], M.D., M.Phil.
SPONSORS:	F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.*
DATE FINAL:	Version 1: 2 July 2015
DATE AMENDED:	Version 2: 21 April 2016 Version 3: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Clinical Science Leader	30-Nov-2016 19:46:18

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PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Changes to the protocol that modify the study design or analyses, along with a rationale for each change, are summarized below:

- Recent information on safety findings of thromboembolic events and thrombotic microangiopathy (TMA) observed in Study BH29884 has been added, including requirements for laboratory monitoring of coagulation status following bypassing agent use. The section for risks associated with emicizumab was updated accordingly and microangiopathic hemolytic anemia/TMA is newly classified as an adverse event of special interest. An exclusion criterion to exclude patients at high risk to experience TMA has been added (Sections 1.2, 1.3, 3.1, 4.1.2, 5.1.2.3, 5.1.2.4, 5.1.3, Table 2, and Appendix 1).
- A new efficacy objective to evaluate the clinical effect of prophylactic emicizumab on the number of spontaneous bleeds over time (spontaneous bleed rate) was added, because this is a bleed category that is impacted by an effective treatment (Section 2.1.2). Note that this new objective was already previously specified in the Statistical Analysis Plan.
- Arm D has been modified to also allow prophylactic bypassing agent patients who were unable to enroll in Arm C before it closed to enroll in Study BH29884, in order to further increase the collection of additional efficacy, safety, pharmacokinetic, and pharmacodynamic data and plasma samples [redacted] (Sections 3.1, 3.3, 3.3.2, 3.3.6, 4.2, 6.5, and 9.4). However, due to the limited number of patients that will be enrolled in this arm and the short follow-up they will have at the time of the primary efficacy analysis, the efficacy of patients in Arm D will be reflected only in analyses involving all patients treated with emicizumab (Section 2.1.2).
- The permitted treatment for breakthrough bleeds has been specified with guidance regarding the use of concomitant bypassing agents in patients being treated with emicizumab, in order to minimize the risk of thromboembolic and TMA events (Sections 3.1 and 3.3.3).

Other changes made to the protocol to further define and/or clarify include:

- The use of short-term prophylaxis with activated prothrombin complex concentrate concomitantly with emicizumab is prohibited, in order to minimize the risk of thromboembolic and TMA events (Section 4.4.2).
- Background information regarding the interference of some coagulation assays by emicizumab has been added (Section 5.1.4).
- Removal of the requirement for proactive collection of pregnancy information for female partners of male patients treated with emicizumab to be consistent with not requiring contraception use by male patients in Study BH29884 (Section 5.4.3.4).

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Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT, VERSION 3:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2.1: *Molecule and Preclinical Data*

Emicizumab (also known as ACE910 and RO5534262) is a recombinant, humanized, bispecific, immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX), mimicking the co-factor function of *activated* FVIII *(FVIIIa)*….

Potential prothrombotic risks associated with emicizumab-induced FVIII mimetic activity were further explored in [redacted]

SECTION 1.2.2: *Clinical Experience*

In Study BH29884, as of November 2016, thrombotic microangiopathy (TMA; atypical hemolytic uremic syndrome [*aHUS*]*) was observed in 2 patients receiving emicizumab and bypassing agents; and 2 cases of thromboembolic events were observed in 2 patients receiving emicizumab and bypassing agents. For more details refer to Sections 5.1.2.3 and 5.1.2.4.*

In the Phase I/II Studies ACE001JP and ACE002JP~~To date~~, emicizumab has been administered to 48 healthy subjects and 18 patients with hemophilia A.…

SECTION 1.3: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

…In the Phase I/II Studies *ACE001JP and ACE002JP*, no thromboembolic or systemic hypersensitivity adverse events were seen; *however, in Study BH29884, 2 cases of TMA (aHUS) and 2 thromboembolic events were observed in patients on emicizumab who received bypassing agents for the treatment of breakthrough bleeds. Three out of these 4 patients have fully recovered and the fourth patient's condition has improved (see Sections 5.1.2.3 and 5.1.2.4)*. ~~The majority of adverse events were of mild intensity, with the most common being injection site reactions and the majority of the adverse events were not considered related to emicizumab~~.

Given the significant unmet medical need among patients with hemophilia A with FVIII inhibitors and positive benefit-risk assessment, *the Sponsor believes that continuation* ~~initiation~~ of *this*~~a larger, confirmatory~~ Phase III study is indicated.

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SECTION 2.1.1: Primary Efficacy Objective

The primary definition of a bleed is a bleed for which coagulation factors are administered (*i.e., treated bleed;* see Section 4.5.8).

SECTION 2.1.2: Secondary Efficacy Objectives

Prophylactic emicizumab compared with no prophylaxis (Arms A and B):

- To evaluate the efficacy in reducing the number of *spontaneous* bleeds over time ~~compared with the patient's historical bleed rate~~
- ~~Non randomized, p~~*P*rophylactic emicizumab *compared with bleed rate prior to study entry (intra-patient comparison;* ~~(~~Arms *A*~~C~~ and *C*~~D)~~:
  - To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate *(both for treated bleeds and all bleeds)*
  - ~~To evaluate the efficacy in reducing the number of all bleeds) over time compared with the patient's historical bleed rate~~

SECTION 2.2: SAFETY OBJECTIVE

The safety objective for this study is as follows:

- To evaluate the overall safety of prophylactic emicizumab compared with no prophylaxis in patients with hemophilia A with inhibitors on the basis of the following endpoints:
  - *Incidence and severity of thrombotic microangiopathy*

SECTION 3.1: DESCRIPTION OF STUDY

…All patients will continue to receive ~~standard of care/background treatment with their usual~~ episodic bypassing agent therapy to treat breakthrough bleeds, *preferably with rFVIIa at the lowest expected dose to achieve hemostasis* ~~as needed~~.

Of note, all patients who participated in Study BH29768 (a non-interventional study; described at the end of this section) received priority to participate in a future emicizumab interventional study. A separate, therapeutic arm (Arm D) *has opened for*~~will open at a future timepoint if there remain~~ patients on episodic bypassing agents who participated in Study BH29768 but were unable to enroll in Arms A or B*, or for patients on prophylactic bypassing agents who were unable to enroll in Arm C,* before they closed to enrollment. Arm D will yield additional efficacy, safety, PK, and PD data and enable collection of plasma samples [redacted] (see Figure 1).

Breakthrough bleeds *should preferably*~~will~~ be treated with *rFVIIa at the lowest expected dose*~~bypassing agents according~~ to *achieve hemostasis*~~standard of care~~ and captured as they occur on the electronic, handheld device. Of note, the clinical experience in the ongoing Phase I/II clinical studies includes the treatment of over [redacted] breakthrough bleeds in patients receiving emicizumab with either FVIII or bypassing agents, without any related safety concerns reported. *However, in Study BH29884, 2 events of TMA*

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and 2 thromboembolic events were observed in patients who concomitantly used repeated doses of aPCC for the treatment of breakthrough bleeds (see Sections 1.2, 1.3, 5.1.2.4, and 5.1.3). Therefore, it is recommended that breakthrough bleeds are treated with rFVIIa only, if possible, and that the use of aPCC or other bypassing agents should be avoided or limited (see Sections 3.1 and 3.3.3). Also, local and central laboratory assessments are required to monitor the risk for thromboembolic events or TMA as per the schedule of assessments (see Section 4.5.5 and Appendix 1)….

SECTION 3.3: RATIONALE FOR STUDY DESIGN

In addition, a separate study arm (Arm D) *has*~~will be~~ opened *for*~~if there remain~~ patients on episodic bypassing agents who participated in Study BH29768 but were unable to enroll in Arms A or B*, or for patients on prophylactic bypassing agents who were unable to enroll in Arm C, prior to their closure*. The enrollment of these patients will provide additional data on the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab. [redacted]

SECTION 3.3.2: Rationale for Patient Population

Inhibitor patients previously treated with prophylactic bypassing agents are included in a separate arm (Arm C) in Study BH29884, as combining them with those previously treated with episodic bypassing agents would have introduced significant heterogeneity in baseline bleed rates. In order to collect additional safety and efficacy data on such patients, Arm C will remain open to enrollment for 24 weeks after Arms A and B close, or until 50 patients have enrolled, whichever occurs earlier. Also, *for*~~if there remain~~ patients on episodic bypassing agents who participated in Study BH29768 (and accordingly received priority to participate in a future emicizumab interventional study*) but were unable to enroll in Arms A or B, and for patients on prophylactic bypassing agents who were unable to enroll in Arm C, before they closed,*~~),~~ a separate therapeutic arm (Arm D) *has opened*~~comprised of up to approximately 35 patients will open at a future timepoint after the last randomized patient in Arms A and B has enrolled~~. In doing so, additional efficacy, safety, PK, and PD data will be collected, as well as blood samples [redacted].

SECTION 3.3.3: Rationale for Control Group

…Specific doses of bypassing agents will not be mandated in the study, but *patients receiving emicizumab must first receive approval from the investigator regarding what the appropriate dose and schedule of bypassing agents (preferably, rFVIIa)* ~~rather~~ should be ~~administered according~~ *used* to *treat a bleed, using the lowest effective dose to control a given bleed for*~~the respective prescribing information or as previously used per~~ each individual patient.

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SECTION 3.3.4: Rationale for the Primary Efficacy Analysis

…The duration of safety follow-up for all patients in the 1 and 3 mg/kg/week cohorts in Study ACE001JP/Study ACE002JP ranges [redacted].

SECTION 3.3.6: Rationale for Biomarker Assessments

Some ~~B~~*b*iomarkers to measure the PD effect of emicizumab on hemostasis have not been fully validated to date [redacted] *Refer to Section 5.1.4 for more information about the effects of emicizumab on existing laboratory assays….*

SECTION 4.1.1: Inclusion Criteria

Patients must meet the following criteria for study entry:

- Adequate hepatic function, defined as total bilirubin ≤1.5×the upper limit of normal (ULN) (excluding Gilbert's syndrome) and *both* AST and~~/or~~ ALT ≤3×ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis

SECTION 4.1.2: Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- *Patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgment*

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT

Patients on prophylactic bypassing agents prior to study entry will be enrolled in a separate therapeutic arm (Arm C) to receive prophylactic emicizumab, at the same dose and schedule as described above. Patients on episodic bypassing agents prior to study entry, who participated in Study BH29768 but were unable to enroll in Arms A or B*, or patients on prophylactic bypassing agents who were unable to enroll in Arm C, before they closed*, will have an opportunity to enroll in an additional, separate therapeutic arm (Arm D) to also receive prophylactic emicizumab.

SECTION 4.3.1.2: Dosage, Dose Adjustment, and Administration

Study site healthcare providers (HCPs) will be trained on how to properly prepare the study medication and administer the correct calculated dose subcutaneously as described in the "Instructions for Use" (IFU) document. Patients will in turn be trained *by an HCP* on study medication preparation and self-administration *at the recommended sites of injection, as detailed in*~~by an HCP, using~~ the IFU ~~as support~~. In the event that a caregiver will ultimately administer study drug to the patient in the home setting, the caregiver is to be trained. The HCP is to inform the patient/caregiver of the volumetric dose to be administered and dosing frequency.

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Patients and/or the caregiver will be provided with alert cards, which they will be requested to carry at all times. These will include guidance on recognizing signs/symptoms of thromboembolic events or allergic/anaphylactic/anaphylactoid reactions and how to obtain emergency care. *In addition, alert cards are designed to notify non-study HCPs that emicizumab will interfere with certain coagulation laboratory tests (see the RO5543262 [Emicizumab] Investigator's Brochure for more information) and that the investigator should be contacted for assistance in interpreting the test results.*

SECTION 4.4.1: Permitted Therapy

Concomitant use of the following drugs and therapies will be permitted:

- Drugs intended to control *or prevent* bleeds, including bypassing agents*, should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase patients' coagulation potential, the doses required to achieve hemostasis may be lower than the bypassing agent doses used prior to starting the study.*

  Caution should be taken for patients who are using rFVIIa (e.g., consideration of using no more than 90 µg/kg of rFVIIa as an initial dose).

  Use of aPCC in combination with emicizumab should be avoided completely in patients who have the option of using other bypassing agents to treat bleeds. In the event that aPCC is the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than 50 units/kg of aPCC to be administered as an initial dose.

  Other bypassing agents (e.g., Byclot®) should be avoided. In cases where such agents are the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than the lowest dose described in the prescribing information to be administered as an initial dose (e.g., no more than 60 µg/kg of Byclot®).
- *Exact dose and schedule of bypassing agents should be discussed with patients at the beginning and throughout the study. Repeated dosing of rFVIIa, aPCC, or other bypassing agents should be performed only under medical supervision, which includes laboratory monitoring by additional local and central laboratory assessments (see Appendix 1), and consideration should be given to verifying bleeds prior to repeated dosing.* ~~as standard of care/background treatment. Specific dosages of bypassing agents will not be mandated in the study but rather should be administered according to the respective prescribing information or as previously used per each individual patient (for information on the formulation, packaging, and handling of bypassing agents, see the local prescribing information for the marketed bypassing agent in question).~~
- *Caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients receiving emicizumab.*

[no notes on this page]

SECTION 4.4.2: Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 4 weeks prior to initiation of study treatment:

- Elective surgery (excluding minor procedures such as tooth extraction, *CVAD removal,* or incision and drainage as well as emergency surgeries)
- *Use of aPCC for short-term prophylaxis*
- Use of a concomitant prophylactic regimen with ~~bypassing agents or~~ FVIII *or rFVIIa*

  Intermittent, prophylactic doses *or short-term prophylaxis* (e.g., around the time of surgery), however, are permitted
- *Use of anti-fibrinolytics in conjunction with aPCC or Byclot®*

SECTION 4.5.1: Informed Consent Forms and Screening Log

…Parents or ~~caregivers~~*legally authorized representative* of adolescents will also complete an Informed Consent Form.

SECTION 4.5.5: Laboratory, Biomarker, and Other Biological Samples

Local laboratory assessments will be performed as indicated on the schedule of assessments. On days of study drug administration, laboratory samples should be drawn before the administration of study drug. Laboratory assessments will include the following:

- Serum chemistries (sodium, potassium, chloride, ~~bicarbonate,~~ glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, and uric acid)
- *In patients who receive bypassing agents, the following local laboratory tests will be performed within 24–48 hours of initial bypassing agent use so the investigator may monitor for potential thromboembolic events and thrombotic microangiopathy*:

  Platelet count

  Serum creatinine

  LDH

  Peripheral blood smear analysis to evaluate for schistocytes

  A plasma sample should also be provided for local (first aliquot) and central (second aliquot) laboratory monitoring of:

  Prothrombin fragment 1+2

  Fibrinogen

  D-dimer

  If the test for prothrombin fragment 1+2 is not available at the site, the sample should be sent to the local reference laboratory, if available and if the results from the local reference laboratory can be obtained within a reasonable timeframe to allow for decision-making.

[no notes on this page]

For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents administered to treat a given bleed.

If applicable, laboratory results should be recorded in the unscheduled visit eCRFs.

The following samples will be sent to the Sponsor or a designee for centralized analysis:

- Samples to detect anti-emicizumab antibodies will be collected prior to emicizumab administration, as indicated in the schedule of assessments (see Appendix 1), but only samples from the following visits will be analyzed:

  Arms A, C, and D

  Immediately prior to the injection *on Week* ~~every 8 weeks from Weeks~~ 1*, Week 5, Week 13, Week 21, Week 33, Week 41, Week* –49

  ~~At study termination~~

  At the 24-week, post-emicizumab safety follow-up visit ~~following initiation of emicizumab~~

SECTION 4.5.7: Patient-Reported Outcomes

To capture bleed and hemophilia medication use data, as well as HRQoL, ~~and~~ health status*, and* data *related to the number of missed days of school or work* during study treatment, patients will complete the questionnaires on an electronic, handheld device that will be provided to them during their Week 1 visit at the site. The electronic, handheld device and instructions for completing the questionnaires will be provided by the investigator staff. After bleed, medication, health status, or HRQoL entries have been saved, the data will be transmitted automatically from the device to a centralized, vendor database. Bleed and medication use data since the patient's previous clinic visit will be reviewed at subsequent clinic visits, as per the schedule of assessments, for completeness and accuracy. *In extenuating circumstances where patients/caregivers are unable to enter these data into the electronic, handheld device, sites may utilize an emergency back-up data entry system to record bleed and medication use on their behalf. However, this may only occur after first confirming the data's veracity with patients/caregivers.*

Missed Days of School or Work:
Patients will also be asked to document the number of days of school or work missed in the previous 4 weeks at the timepoints outlined in the Schedule of Assessments (see Appendix 1).

SECTION 4.6.2: Study Treatment Discontinuation

If the patient discontinues study treatment, bleed, hemophilia medication, health-related quality of life, health status, and missed days of school or work should be recorded by the patient on the electronic, handheld device until the safety follow-up visit (i.e., 24 weeks after the last study drug administration).

[no notes on this page]

SECTION 5.1.2.1: Injection-Site Reactions

In the completed and ongoing Japanese studies, injection-site reactions have been observed in some patients with hemophilia A. These local injection-site reactions included injection-site erythema, injection-site hematoma, injection-site rash, injection-site discomfort, *injection-site pain,* and injection-site pruritus. All local injection-site reactions were of mild intensity. Further details of the observed injection-site reactions are available in the Investigator's Brochure.

Directions for emicizumab administration should be followed, as outlined in Section 3.3.1, Section 4.3.1.2, and in the IFU. *This includes alternating the site of injection, from one injection to the next, in the recommended injection-site locations listed in the IFU.*

SECTION 5.1.2.3: Hypercoagulation and Thromboembolic Events

As of November 2016, there~~The bypassing agents (e.g., aPCC and rFVIIa)~~ have *been 2 thromboembolic events reported*~~the unwanted potential to induce thromboembolism. Though thrombus formation was seen~~ in 2 ~~some animal venous stasis models with emicizumab, subsequent pre-clinical results suggested that the risk does not substantially exceed those seen with bypassing agents alone.~~ *patients with hemophilia A with inhibitors while receiving emicizumab in Study BH29884.* [redacted]. ~~In completed and ongoing clinical studies of emicizumab, no thromboembolic events have been reported.~~

These events should be reported as Serious Adverse Events or Adverse Events of Special Interest as described in Section 5.2.3. HCPs should educate patients/caregivers to recognize signs and symptoms of potential thromboembolism (i.e., dyspnea, chest pain, leg pain or swelling*; or if in the head, headache, numbness in the face, eye pain or swelling, or vision impairment)*~~, etc.)~~ and ensure that they understand the importance of seeking appropriate medical attention. Patients/caregivers will also receive two alert cards to remind them of this information and these instructions should thromboembolism be suspected.

SECTION 5.1.2.4: *Thrombotic Microangiopathy*

Thrombotic microangiopathy is used to describe a group of disorders with clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage that can include the kidneys, gastrointestinal system, or central nervous system, etc. As of November 2016, 2 cases of TMA, diagnosed as aHUS, were observed in Study BH29884 involving patients receiving emicizumab. [redacted]

Any TMA event should be reported as an adverse event of special interest and also as a serious adverse event, if it meets criteria for such (see Sections 5.2.2 and 5.2.3).

SECTION 5.1.4: *Interpretation of Coagulation Assays for Patients Receiving Emicizumab*

Emicizumab interacts with standard laboratory assays used in the management of patients with hemophilia A. In one-stage assays, emicizumab is associated with a supra-physiologically short time to clot formation and thus normalization of aPTT at subtherapeutic levels and an overestimation of true FVIII activity. Emicizumab is not recognized or neutralized by FVIII inhibitors and, therefore, cannot be detected by a functional test such as Bethesda or Nijmegen-Bethesda assays, which use a one-stage clotting-based readout. Emicizumab activity cannot be detected by chromogenic assays using purified bovine coagulation proteins and can only be detected using an assay composed of human proteins. See the RO5543262 [Emicizumab] Investigator's Brochure for additional details on which tests can be used and how the test results can be interpreted.

SECTION 5.2.1: Adverse Events

Bleeds considered as serious adverse events should be reported *on the appropriate* ~~as serious~~ adverse event~~s both on the~~ eCRF *page, regardless of whether* ~~and~~ the *bleeds are consistent with patients' pre-study disease state (the* bleed *will remain recorded as well on the Bleed/*Medication Questionnaire). New, non-serious bleeds consistent with patients' pre-study disease state will not be considered adverse events and will not be recorded on the eCRF ~~(~~but *will* ~~should~~ be captured on the Bleed/Medication Questionnaire.~~).~~

SECTION 5.2.3: Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see

[no notes on this page]

Section 5.4.2 for reporting instructions). *These may include suspected or confirmed cases.* Adverse events of special interest for this study include the following:

- *Microangiopathic hemolytic anemia or thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura, hemolytic uremic syndrome)*

SECTION 5.3.5.1: Injection-Site Reactions

Local ~~A~~*a*dverse events that occur ~~during or~~ within 24 hours after study drug administration and ~~in the investigator's opinion~~ are judged to be related to study drug injection should be captured as an "injection-*site*~~related~~ reaction" on the Adverse Event eCRF. ~~An injection-related reaction that is localized should be marked as a "local injection-site reaction."~~ Associated signs and symptoms (e.g., injection-site erythema or injection-site rash) should be recorded on the dedicated Injection-Site Reaction eCRF. *If a patient experiences both a local and systemic reaction to the same administration of study drug, each reaction should* ~~Systemic reactions should~~ be recorded separately on the Adverse Event eCRF. *Only for local injection-site reactions should* ~~T~~*t*he dedicated Injection-Site Reaction eCRF ~~should only~~ be used to capture the individual signs/symptoms. ~~for local injection-site reactions.~~

SECTION 5.3.5.7: Abnormal Liver Function Tests

The finding of an elevated ALT or AST (>3×baseline value) in combination with either an elevated total bilirubin (>2×ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event *of special interest* the occurrence of either of the following:

- Treatment-emergent ALT or AST >3× baseline value in combination with clinical jaundice *in the absence of cholestasis or other causes of hyperbilirubinemia*

SECTION 5.3.5.10: Lack of Efficacy or Worsening of Hemophilic Bleeds

Events that are clearly consistent with the *anticipated*~~expected~~ pattern of the underlying disease *and do not indicate an unexpected worsening in severity or frequency* should not be recorded as adverse events. These data will be reflected in efficacy assessment data only.

SECTION 5.4.3.3: Abortions

Any ~~spontaneous~~ abortion should be classified as a serious adverse event (as the Sponsor considers ~~spontaneous~~ abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

SECTION 5.4.3.4: Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female ~~patient exposed to study drug or the female partner of a male~~ patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the

[no notes on this page]

Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

SECTION 5.5.1: Investigator Follow-Up

All pregnancies reported during the study should be followed until pregnancy outcome. *At the time of pregnancy outcome, reporting instructions provided in Section 5.4.3.1 should be followed.*

SECTION 6.5: EFFICACY ANALYSES

The primary and secondary efficacy analyses to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis will include all randomized patients, with patients grouped according to the treatment assigned at randomization. For patients previously treated with prophylactic bypassing agents in Arm C and episodic *or prophylactic* bypassing agents in Arm D~~, (if opened),~~ the efficacy analyses will include all enrolled patients.

SECTION 6.5.1: Primary Efficacy Endpoint

The number of bleeds can also be annualized for each patient using the following formula: ABR = (Number of bleeds during the efficacy period/Total number of days during the efficacy period) × 365.25. If the NB model converges, an analysis of variance (ANOVA) to compare the mean ABR between the randomized arms will be provided only as a sensitivity analysis. However, if the convergence of the NB model is not achieved or is questionable, the primary efficacy analysis will be based on the ~~Wilcoxon Rank Sum~~*Van Elteren Test* of ABR.

SECTION 6.5.2: Secondary Efficacy Endpoints

The number of all bleeds (i.e., those treated and not treated with coagulation factors)*, spontaneous bleeds, joint bleeds, and target joint bleeds* over time in patients who receive prophylactic emicizumab compared with no prophylaxis will be *evaluated by the NB regression model,*~~assessed~~ as *specified for the primary*~~a secondary~~ efficacy endpoint. Also, the number of treated bleeds and all bleeds over time will be compared with patients' bleed rate prior to study entry. ~~Finally, the number of joint and target joint bleeds over time between the emicizumab prophylaxis and no prophylaxis arms will be evaluated.~~

SECTION 6.6: SAFETY ANALYSES

The iDMC (see Section 9.4.2) will evaluate safety at periodic safety reviews and recommend to the Sponsor whether the study should be *modified or* stopped early. All summaries and analyses will be prepared by the independent Data Coordinating Center (iDCC) and presented by treatment arm for the iDMC's review. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

[no notes on this page]

SECTION 7.3: ELECTRONIC PATIENT-REPORTED OUTCOME DATA

...The Sponsor will receive all data entered by patients on the electronic, handheld devices*, by sites via an emergency back-up data entry system with agreement from patients,* and all relevant study documentation.

SECTION 9.4: ADMINISTRATIVE STRUCTURE

This global study will enroll approximately 81–101 patients in Arms A, B, and C, as well as additional patients in Arm D. ~~if it is opened.~~

FIGURE 1: Study Schema

Figure 1 has been updated to reflect changes to the protocol.

TABLE 2: Guidelines for Management of Specific Adverse Events

Table 2 has been revised to reflect changes made to the protocol.

APPENDIX 1: Schedule of Assessments

Appendix 1 has been updated to reflect changes to the protocol.

APPENDIX 6: WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events

Appendix 6 has been updated.

INFORMED CONSENT AND ASSENT FORMS

The Informed Consent and Assent Forms have been updated to reflect changes to the protocol.

[no notes on this page]

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC EMICIZUMAB VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
PROTOCOL NUMBER:	BH29884
VERSION NUMBER:	3
EUDRACT NUMBER:	2015-002866-21
IND NUMBER:	122,954
TEST PRODUCT:	Emicizumab (RO5534262)
MEDICAL MONITOR:	[redacted], M.D., M.Phil.
SPONSORS:	F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of this form to your local study monitor.

[no notes on this page]

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC EMICIZUMAB VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
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EUDRACT NUMBER:	2015-002866-21
IND NUMBER:	122,954
TEST PRODUCT:	Emicizumab (RO5534262)
PHASE:	Phase III
INDICATION:	Hemophilia A with inhibitors
SPONSORS:	F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.

Objectives and Endpoints

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis in patients with hemophilia A with inhibitors (Arms A and B) on the basis of the following endpoint:

- Number of bleeds over time (i.e., bleed rate)

The primary definition of a bleed is a bleed for which coagulation factors are administered (*i.e., treated bleed;* see protocol).

Secondary Efficacy Objectives

The secondary efficacy objectives and endpoints for this study are as follows:

- Prophylactic emicizumab compared with no prophylaxis (Arms A and B):
  - To evaluate the efficacy in reducing the number of all bleeds (i.e., those treated and not treated with coagulation factors) over time
  - To evaluate the efficacy in reducing the number of *spontaneous* bleeds over time
  - To evaluate the efficacy in reducing the number of joint bleeds over time
  - To evaluate the efficacy in reducing the number of target joint bleeds over time
  - To evaluate the health-related quality of life (HRQoL) of patients according to Haem-A-QoL (aged ≥ 18) or Haemo-QoL-Short Form (ages 12–17) scores at 24 weeks
  - To evaluate the health status of patients according to EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) scores at 24 weeks
- *P*rophylactic emicizumab *compared with bleed rate prior to study entry (intra-patient comparison;* Arms *A* and *C*:
  - To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate *(both for treated bleeds and all bleeds)*

[no notes on this page]

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis on the basis of the following endpoints:

- To assess differences in number of days away from school/work
- To assess differences in number of days hospitalized

Safety Objective

The safety objective for this study is as follows:

- To evaluate the overall safety of prophylactic emicizumab compared with no prophylaxis in patients with hemophilia A with inhibitors on the basis of the following endpoints:

  Incidence and severity of adverse events

  Incidence and severity of thromboembolic events

  Changes in physical examination findings and vital signs

  Incidence of laboratory abnormalities

  Incidence and severity of injection-site reactions

  Incidence of adverse events leading to drug discontinuation

  Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events

  Incidence and severity of thrombotic microangiopathy

  Incidence and clinical significance of anti-emicizumab antibodies

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the exposure (C_{trough}) of emicizumab prior to drug administration on Day 1 at the following timepoints:

- Every week during Weeks 1–4 on emicizumab
- Every 2 weeks during Weeks 5–8 on emicizumab
- Every 4 weeks during Weeks 9–24 on emicizumab
- Every 8 weeks during Weeks 25–48 on emicizumab
- Every 12 weeks thereafter while on emicizumab, until the end of the study

Exploratory Biomarker Objectives

The exploratory biomarker objectives for this study are as follows:

- To assess potential pharmacodynamic (PD) biomarkers of emicizumab, including but not limited to aPTT, thrombin generation, and factor VIII (FVIII) activity, at timepoints throughout the study
- [redacted]

Study Design

Description of Study

This randomized, multicenter, open-label, Phase III clinical study will enroll patients aged 12 years or older with hemophilia A who have inhibitors against FVIII. Approximately 51 patients with inhibitors who received episodic treatment with bypassing agents prior to study entry will be enrolled globally and randomized in a 2:1 ratio (see protocol) to receive either prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously thereafter (Arm A), or to the control arm (Arm B), which will consist of no prophylaxis. Given the potential heterogeneity of bleed rates in the study patient population, randomized patients will be stratified according to the number of bleeds they experienced over the last 24 weeks prior to study entry (<9 or ≥ 9 bleeds) to ensure a balance of inhibitor patients with lower versus higher number of bleeds, respectively, at baseline across the two randomized arms of the proposed Phase III study. All patients will continue to receive

[no notes on this page]

episodic bypassing agent therapy to treat breakthrough bleeds, *preferably with rFVIIa at the lowest expected dose to achieve hemostasis*.

In addition, given that some patients with hemophilia A with inhibitors are also currently treated with bypassing agents on a prophylactic basis, approximately 30-50 patients with inhibitors on prophylactic bypassing agents will be enrolled in a separate therapeutic arm (Arm C) to receive prophylactic emicizumab at the same dose and schedule (see protocol). Enrollment into Arm C will continue for 24 weeks after Arms A and B have been closed to enrollment or until 50 patients have been enrolled, whichever occurs earlier, in order to collect additional safety and efficacy from patients previously on prophylactic bypassing agents.

Of note, all patients who participated in Study BH29768 (a non-interventional study; described at the end of this section) received priority to participate in a future emicizumab interventional study. A separate, therapeutic arm (Arm D) *has opened for* patients on episodic bypassing agents who participated in Study BH29768 but were unable to enroll in Arms A or B*, or for patients on prophylactic bypassing agents who were unable to enroll in Arm C,* before they closed to enrollment. Arm D will yield additional efficacy, safety, PK, and PD data and enable collection of plasma samples [redacted]

The primary efficacy analysis, defined as comparing the number of bleeds over time for patients randomized to receive prophylactic emicizumab versus no prophylaxis, will be conducted after all randomized patients have completed 24 weeks in the study or the last randomized patient who has not completed 24 weeks in the study discontinues study participation, whichever occurs first.

To obtain additional safety and efficacy data, prior episodic bypassing agent patients who had been randomized to not receive emicizumab (control arm, Arm B) will be offered treatment with prophylactic emicizumab at the same dose and schedule as patients who started Study BH29884 on emicizumab once they complete 24 weeks in the study. In addition, after at least 24 weeks on prophylactic emicizumab, all patients will be able to continue on their 1.5 mg/kg/week maintenance dose or may be provided the option to increase their dose to 3 mg/kg/week if they meet protocol-defined criteria of suboptimal response and receive approval from the Medical Monitor to do so (see protocol). Patients who continue to derive clinical benefit will be given the opportunity to continue receiving prophylactic emicizumab [redacted].

During the study, patients (or their legally authorized representative) will be asked to record their bleeds and medication use on an electronic, handheld device (see protocol). The bleed/medication questionnaire should be completed whenever a bleed or medication use occurs. In the event of no bleed or medication use, the patient should complete the questionnaire at least once a week to serve as confirmation that no bleed or medication use occurred. In addition, health status information will be collected whenever a bleed is reported. HRQoL, health status, patient safety, and days of school or work missed will be assessed every 4 weeks for approximately 24 weeks and every 4–12 weeks thereafter, as outlined in the schedule of assessments.

Physical examinations, vital sign assessments, ECG, and laboratory assessments will be collected as per the schedule of assessments and will be the same for all patients receiving emicizumab, regardless of whether they are enrolled in the randomized portion of the study or in the separate non-randomized arms. Adverse events will be captured on an ongoing basis, as they occur during the study.

All patients who receive emicizumab in the study will undergo PK assessment. As emicizumab is intended in this study for prophylactic use only (i.e., not to treat bleeds that have already occurred), neither activated prothrombin complex concentrate (aPCC) nor recombinant activated factor VIII (rFVIIa) interfere with emicizumab PK assessments, and some patients with hemophilia A with inhibitors require frequent dosing with bypassing agents due to having many bleeds or being on prophylaxis, a washout period is not required prior to enrollment so that new bleeds are minimized and treatment for any prior bleed is not interrupted.

Exploratory PD biomarkers (e.g., aPTT, FVIII activity, thrombin generation assay) will be collected as per the schedule of assessments. As values for these tests are normalized by even low plasma concentrations of emicizumab (see protocol), a variety of assay formats (one-stage, chromogenic) and modifications (predilution of patient plasma) will be investigated

1. **episodic bypassing agent therapy to treat breakthrough bleeds, preferably with rFVIIa at the lowes...**
Anchor Name: breakthrough bleed treatment *[Agency FCB Halesway Olga Kooi]*

for assessment of PD response at higher emicizumab plasma concentrations. [redacted] In addition, factor IX (FIX) and factor X (FX) antigen levels will be monitored.

Throughout the study, biomarkers related to thromboembolism (e.g., D-dimer, prothrombin 1.2 fragment) and emicizumab trough concentrations, will be collected as per the schedule of assessments. Immunologic biomarkers (i.e., anti-emicizumab antibodies) will also be measured as per the schedule of assessments (see protocol).

An independent Data Monitoring Committee (iDMC) composed of, at minimum, hemostasis/thrombosis experts and a statistician will be in place throughout the duration of the study and will monitor patient safety at pre-specified intervals and ad hoc as needed throughout the study.

Breakthrough bleeds *should preferably* be treated with *rFVIIa at the lowest expected dose* to *achieve hemostasis* and captured as they occur on the electronic, handheld device. Of note, the clinical experience in the ongoing Phase I/II clinical studies includes the treatment of over [redacted] breakthrough bleeds in patients receiving emicizumab with either FVIII or bypassing agents, without any related safety concerns reported. *However, in Study BH29884, 2 events of TMA and 2 thromboembolic events were observed in patients who concomitantly used repeated doses of aPCC for the treatment of breakthrough bleeds (see protocol). Therefore, it is recommended that breakthrough bleeds are treated with rFVIIa only, if possible, and that the use of aPCC or other bypassing agents should be avoided or limited (see protocol). Also, local and central laboratory assessments are required to monitor the risk for thromboembolic events or TMA as per the schedule of assessments (see protocol).* Investigators will be asked to contact the Medical Monitor in the event of suspected lack or loss of efficacy of emicizumab in order to discuss potential laboratory evaluations (e.g., anti-emicizumab antibodies, coagulation tests) to be performed as well as to re-evaluate the patient's benefit-risk of continued treatment. When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, category of bleed, time of each individual bleed (day, start time), symptoms of bleed, and treatment for bleed. Health status information will also be collected on the day a bleed occurs.

The reason for the use of coagulation products (e.g., aPCC or rFVIIa) will be documented (e.g., bleeding, prophylaxis). A thorough documentation of the treatments for bleeds will be requested, including agent, start time, dose, and reason for treatment. The number of infusions needed to treat the bleed will be derived from the medication log.

A non-interventional study (BH29768) has been initiated to document the number and types of bleeds and current treatment with episodic or prophylactic bypassing agents, as well as collect information on HRQoL, health status, and safety in patients with hemophilia A with FVIII inhibitors. The assessments in the non-interventional study will mitigate the risk of underreporting of bleeds that oftentimes occurs in the real world, and the resulting data will serve as a source of comparator information for some analyses conducted in the Phase III clinical study (Study BH29884). The non-interventional study will also allow an investigation of the feasibility of using an electronic, handheld device that has been developed to record data related to bleeds, hemophilia treatments, HRQoL, and health status. In addition, the non-interventional study will enable earlier identification and confirmation of patients who may qualify for the Phase III clinical study. It is anticipated that a significant number of patients participating in Study BH29768 will enroll in Study BH29884, as long as they meet the inclusion and exclusion criteria of the study and are able to enroll at a participating site while the study is open for enrollment.

Number of Patients

This global study will enroll approximately 81–101 patients in Arms A, B, and C, as well as additional patients in Arm D.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form

[no notes on this page]

- Able to comply with the study protocol, in the investigator's judgment
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of patient-reported outcomes questionnaires and bleed/medication questionnaire through the use of an electronic device
- Aged 12 years or older at the time of informed consent
- Body weight ≥ 40 kg at the time of screening
- Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (i.e., ≥ 5 Bethesda Units)
- Documentation of treatment with episodic or prophylactic bypassing agents for at least the last 24 weeks
- ≥ 6 bleeds in the last 24 weeks prior to screening (if on an episodic bypassing agent regimen) or ≥ 2 bleeds in the last 24 weeks prior to screening (if on a prophylactic bypassing agent regimen)
- Adequate hematologic function, defined as platelet count ≥ 100,000/μL and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin ≤ 1.5 × the upper limit of normal (ULN) (excluding Gilbert's syndrome) and AST and/or ALT ≤ 3 × ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine ≤ 2.5 × ULN and creatinine clearance by Cockcroft-Gault formula ≥ 30 mL/min
- For women who are not postmenopausal (≥ 48 weeks of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined highly effective contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of contraceptive methods with a failure rate of <1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a non-lipid-based spermicide.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Inherited or acquired bleeding disorder other than hemophilia A
- Ongoing (or plan to receive during the study) immune tolerance induction therapy or prophylaxis with FVIII with the exception of patients who have received a treatment regimen of FVIII prophylaxis with concurrent bypassing agent prophylaxis
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or current signs of thromboembolic disease
- Other conditions (e.g., certain autoimmune diseases) that may increase the risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Known HIV infection with CD4 count < 200 cells/μL within 24 weeks prior to screening

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- Use of systemic immunomodulators (e.g., interferon or rituximab) at enrollment or planned use during the study, with the exception of anti-retroviral therapy
- *Patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgment*
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study or that would, in the opinion of the investigator or Sponsor, preclude the patient's safe participation in and completion of the study or interpretation of the study results
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Receipt of
  - Emicizumab in a prior investigational study
  - An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration
  - A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter
  - An investigational drug concurrently
- Unwillingness to use highly effective contraception methods for the specified duration in the protocol (females only, unless required otherwise by the local health authority)
- Clinically significant abnormality on screening evaluations or laboratory tests that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient
- Pregnancy or lactation, or intent to become pregnant during the study
  - Women who are not postmenopausal (≥48 weeks of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

End of Study and Length of Study

The approximate length of the entire study from the first patient enrolled to the Last Patient Last Visit (LPLV; see below) is approximately 108 weeks.

The end of this study is defined as the date when the last remaining patient has completed the last visit (i.e., LPLV), as defined below:

- Has completed at least 24 weeks of emicizumab treatment and either transferred to [redacted] receive further emicizumab as per Roche Global Policy on Continued Access to Investigational Medicinal Products or to commercial product

  OR
- Completes the end of study safety follow-up visit 24 weeks after discontinuing emicizumab

  OR
- Has withdrawn consent

  OR
- Is lost to follow-up

Investigational Medicinal Products

Test Product (Investigational Drug)

Emicizumab 3 mg/kg/week subcutaneously for 4 weeks when initiating treatment, followed by 1.5 mg/kg/week subcutaneously for a minimum of 24 weeks total. There will be an option to increase the dose after at least 24 weeks of treatment to 3 mg/kg/week if a patient meets the criterion for insufficient control of bleeds on the 1.5 mg/kg/week emicizumab dose and with approval from the Medical Monitor.

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To support home administration of the drug, patients/caregivers will be required to complete in-person, instructional training on how to administer emicizumab as a subcutaneous (SC) injection. Patients/caregivers will be taught to perform the injections utilizing the Instructions for Use document. They will observe at least one SC injection performed by a healthcare provider (HCP) and will need to successfully administer at least one SC injection under an HCP's watch prior to starting home administration. The first five weekly treatments will be administered in a monitored setting, such as an infusion center, clinic, or hospital, in conjunction with emicizumab PK assessments. Patients will be observed for a minimum of 60 minutes after the first three doses. Patients/caregivers will be instructed on how to recognize signs/symptoms of hypersensitivity (including anaphylaxis) and obtain emergency care in the event of such reactions occurring. Each site will have the discretion to provide additional training or include additional observation (e.g., after the fourth and fifth doses), if deemed appropriate. If, despite additional training, the investigator determines that the patient/caregiver is unable to inject emicizumab, a trained and proficient caregiver or HCP should be identified to administer the SC injections. Patients/caregivers will be provided with contact information for the clinic in case they have questions related to self-administration between visits.

Compliance in the home setting is to be monitored by reviewing reported hemophilia medication use and recording collected used and unused vials at each site.

Statistical Methods

Efficacy Analyses

The primary and secondary efficacy analyses to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis will include all randomized patients, with patients grouped according to the treatment assigned at randomization. For patients previously treated with prophylactic bypassing agents in Arm C and episodic *or prophylactic* bypassing agents in Arm D, the efficacy analyses will include all enrolled patients.

Primary Efficacy Endpoint

The primary efficacy objective is to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis on the number of bleeds over time. The definition of a bleed is described in the protocol, with the primary endpoint comparing bleeds requiring treatment.

The primary efficacy analysis will be conducted after all randomized patients have completed 24 weeks in the study or the last randomized patient who has not completed 24 weeks in the study discontinues study participation, whichever occurs first, and using an intent-to-treat principle. The comparison of the number of bleeds over time between the randomized treatment arms will be performed using a negative binomial (NB) regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study included as an offset in the model. The model also includes the number of bleeds (<9 or ≥ 9) in the last 24 weeks prior to study entry as a stratification factor in the randomization. This analytic model estimates the rate ratio, λ_t/λ_c., which quantifies the risk of bleeding associated with prophylactic emicizumab (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level, and the estimated risk ratio is compared with 1, assuming the following statistical hypothesis:

H_0 (null hypothesis): Rate Ratio $= 1$ versus H_1 (alternative hypothesis): Rate Ratio $\neq 1$

The treatment effect therein is based on a contrast statement in the model with use of the SAS GENMOD procedure. Statistical significance at the pre-specified alpha level will be based on a Wald testing procedure. Bleed rates for prophylactic emicizumab and no prophylaxis and the rate ratio will be presented and include 95% confidence intervals.

The number of bleeds can also be annualized for each patient using the following formula: annualized bleed rate (ABR) = (Number of bleeds during the efficacy period/Total number of days during the efficacy period) $\times$ 365.25. If the NB model converges, an analysis of variance (ANOVA) to compare the mean ABR between the randomized arms will be provided only as a sensitivity analysis. However, if the convergence of the NB model is not achieved or is questionable, the primary efficacy analysis will be based on the *Van Elteren Test* of ABR.

Although this is an open-label study, Sponsor personnel will not have access to efficacy summaries by treatment arms prior to the formal reporting of the study results.

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A detailed description of the statistical methods that will be used for the primary and secondary efficacy analyses will be provided in the Statistical Analysis Plan (SAP).

Secondary Efficacy Endpoints

The number of all bleeds (i.e., those treated and not treated with coagulation factors), *spontaneous bleeds, joint bleeds, and target joint bleeds* over time in patients who receive prophylactic emicizumab compared with no prophylaxis will be *evaluated by the NB regression model,* as *specified for the primary* efficacy endpoint. Also, the number of treated bleeds and all bleeds over time will be compared with patients' bleed rate prior to study entry.

HRQoL (using the Haem-A-QoL or the Haemo-QoL-SF) and health status (using the EQ-5D-5L) will be assessed on a regular basis, as per the schedule of assessments (scheduled). Health status will also be assessed in the event of a bleed (unscheduled).

Adherence with the HRQoL and health status measures will be summarized.

Because different HRQoL measures (Haem-A-QoL and the Haemo-QoL-SF) are being used for the adult and adolescent patients, all calculations and analyses will be conducted separately for adults and adolescents. Scale scores for the Haem-A-QoL and Haemo-QoL-SF will be calculated and summarized descriptively. The HRQoL scale scores for all patients will be evaluated at 24 weeks in the study, a timepoint that is consistent with other recent registrational studies in hemophilia and analyses of such data. For each treatment arm, paired t-tests will be used to compare the 24-week with the baseline scale scores for each HRQoL measure. Within-subject and between-group changes from baseline on the different HRQoL scale scores will also be calculated at 24 weeks.

For the assessments of the EQ-5D-5L performed every 4 weeks, the number and percentage of patients in each of the five categories for each question for each group will be assessed. Changes in the EQ-5D-5L index utility score from baseline will also be compared between groups. In addition, summary statistics including mean, standard deviation, median, minimum and maximum will be displayed for the patients' health state using the EQ-VAS both within and between groups. The proportion of patients who report changes in each group exceeding the clinically meaningful threshold on the EQ-5D-5L index and EQ-VAS scores in each group will be reported at 24 weeks.

Separately, for each EQ-5D-5L completed in connection with a bleed, the level of pain associated with that episode, as well as the utility score and general health score will be reported.

Secondary endpoints used for labeling and those that are solely for scientific interest will be specified in the SAP. The method used for controlling the type 1 error rate will also be described.

Exploratory Efficacy Analysis

Summary statistics of the number of work/school days missed and days hospitalized will be presented by treatment arm.

Safety Analyses

The safety analyses population will be based on all enrolled patients grouped according to the actual treatment received. Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology, including complete blood count with differential), ECGs, vital signs, and antibodies to emicizumab.

To evaluate the overall safety of prophylactic emicizumab compared to no prophylaxis, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade for each treatment arm.

For clinical laboratory data, summary statistics will be presented by treatment arm. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

Data on the impact of immunogenicity (anti-emicizumab antibodies) on safety, efficacy, and/or clinical pharmacology and PK will be summarized using standard language/terminology.

Although this is an open-label study, Sponsor personnel will not have access to safety summaries by treatment arm prior to the formal reporting of the study results. HCPs at

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participating study sites, as well as the Sponsor's drug safety and medical monitoring staff, will have access to the treatment assignments of patients for safety monitoring purposes only.

The iDMC (see protocol) will evaluate safety at periodic safety reviews and recommend to the Sponsor whether the study should be *modified or* stopped early. All summaries and analyses will be prepared by the independent Data Coordinating Center (iDCC) and presented by treatment arm for the iDMC's review. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

Pharmacokinetic Analysis

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will be used to analyze the dose-concentration-time data of emicizumab following SC administration. Population PK parameters, such as clearance and volume of distribution, will be estimated, and the influence of various covariates, such as age, gender, and body weight, on these parameters will be investigated graphically. Secondary PK parameters, such as area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies. These analyses will be reported in a dedicated report.

Exploratory Biomarker Analyses

PD parameters (e.g., aPTT, parameters derived from thrombin generation, FVIII activity) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Determination of Sample Size

The sample size for this study is based on clinical rather than statistical considerations, taking into account the limited number of patients with hemophilia A with inhibitors available for participation in clinical studies and in an effort to collect sufficient data to assess the safety and efficacy of emicizumab.

The sample size calculation is based on the evaluation of the primary efficacy endpoint, defined as the number of bleeds over time (i.e., bleed rate) with emicizumab (treatment group, λ_t) versus no prophylaxis (control group, λ_c), which are said to follow a NB distribution with γ_t and γ_c described as shape parameters for treatment and control groups, respectively. With consideration of enrollment feasibility, a sample size of 45 patients, assuming an allocation ratio of 2:1 (30 patients in treatment group and 15 patients in control group), will achieve a power of more than 95% for λ_t and λ_c ranging from 1 to 4 and 18 to 30, respectively (see protocol). Here, the patients from the two groups are followed up to 0.5 units of time (i.e., 24 weeks). Of note, assuming $\lambda_c = 18$ and $\lambda_t = 4$ results in an expected ABR reduction of 78% in the treatment versus control groups. Sample size calculations were performed with East®, Version 6 (Cytel, Cambridge, MA), which allows specific shape parameters for both the treatment and control groups.

However, the above approach to sample size calculation assumes similar follow-up for each patient. Because this is unlikely to be seen in the study, power was also estimated by simulation to account for different follow-up times among patients. Conducting simulations on the basis of a NB regression model including an offset variable to account for variable follow-up times, with all other assumptions remaining the same as previously described, the sample size is projected to have greater than 95% power at the 2-sided 0.05 level of significance.

The analysis will include all enrolled patients, regardless of their length of follow-up. Therefore, to ensure the analysis is based on sufficient follow-up data and with 2:1 treatment to control randomization, approximately 34 patients in the randomized emicizumab treatment arm and 17 patients in the control arm (approximately 51 patients in total) will be enrolled.

During the study, a re-assessment of the initially specified sample size based on aggregated (not by treatment arm) data to date (and potentially from the non-interventional study [BH29768] findings) may be performed. This may result in an increase in sample size, if necessary, to maintain adequate power without affecting the type 1 error rate. Study integrity will be upheld, as access to information via aggregated analyses and their results will be minimized to limit operational bias.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	annualized bleeding rate
ADA	anti-drug antibody
aHUS	*atypical hemolytic uremic syndrome*
aPCC	activated prothrombin complex concentrate
AUC	area under the curve
BA	bioavailability
C_{max}	maximum plasma concentration
COX-2	cyclooxygenase-2
CVAD	central venous access device
[redacted]	[redacted]
[redacted]	[redacted]
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
FDA	U.S. Food and Drug Administration
FEIBA	Factor Eight Inhibitor Bypassing Activity
FIX	factor IX
FIX:Ag	factor IX antigen
FIXa	activated factor IX
FVIII	factor VIII
FVIIIa	*activated factor VIII*
FX	factor X
FX:Ag	factor X antigen
HCP	healthcare provider
[redacted]	[redacted]
[redacted]	[redacted]
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health-Related Quality of Life
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
ICH	International Conference on Harmonisation
IFU	Instructions For Use
IgG4	immunoglobulin G4
IMP	investigational medicinal product

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Abbreviation	Definition
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ITI	immune tolerance induction
IV	intravenous
IxRS	interactive voice or Web Response System
LPLV	last patient, last visit
MAD	multiple ascending dose
MN	mobile nursing
NB	negative binomial
[redacted]	[redacted]
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient-reported outcome
QTcF	QT interval corrected using Fridericia's formula
QOL	quality of life
RCR	Roche Clinical Repository
rFVIII	recombinant FVIII
rFVIIa	recombinant activated factor VII
SAD	single ascending dose
SAP	Statistical Analysis Plan
SC	subcutaneous
$t_{1/2}$	half-life
t_{max}	time to maximum plasma concentration
TMA	*thrombotic microangiopathy*
ULN	upper limit of normal
VAS	visual analog scale

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1. BACKGROUND

1.1 BACKGROUND ON HEMOPHILIA A WITH INHIBITORS

Hemophilia A is an X-linked recessive bleeding disorder that occurs in approximately 1 in 5000 live male births. Patients with hemophilia A have a deficiency or absence of blood coagulation factor VIII (FVIII), an essential component of the intrinsic pathway in the coagulation cascade (Mannucci and Tuddenham 2001; Franchini and Mannucci 2013).

Hemophilia A is most commonly caused by an inherited FVIII gene mutation within the Xq28 region of the X chromosome. It occurs almost exclusively in males having one defective copy of the relevant gene on their X chromosome. Because an affected male will transmit a normal Y chromosome to all his sons and an abnormal X chromosome to all his daughters, his sons will not be affected and all of his daughters will be carriers. For female carriers, with each birth there is a 50% chance to transmit the disorder to male infants and a 50% chance for female infants to be a carrier. Females who are carriers of hemophilia A may experience bleeding symptoms similar to those seen in men with mild hemophilia A, as approximately 10% of carriers have a FVIII activity that is less than 35% (Plug and Mauser-Bunschoten 2006). Rarely, women can have more severe bleeding symptoms requiring treatment and may develop FVIII inhibitors. Approximately 30% of patients with hemophilia A do not have a family history of the disorder; these cases arise from spontaneous FVIII gene mutations.

The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical signs of hemophilia A include easy bruising; prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial hemorrhage. The severity of the disease roughly correlates with the residual endogenous level of FVIII activity. Approximately 68% of people with hemophilia A have moderate (25%) or severe (43%) forms, characterized by FVIII activity levels $<5\%$ or $<1\%$, respectively, leading to frequent bleeding events with the sequelae of musculoskeletal complications, such as arthropathy, local functional deficits, hemorrhagic shock, neurocognitive defects, or even death (World Federation of Hemophilia 2013). These disease-related issues can have a significant impact on the health-related quality of life (HRQoL) of both adult and adolescent patients (Brown et al. 2009).

Prophylactic FVIII replacement therapy (i.e., administered on a scheduled basis with the intent to prevent bleeds) has been proven to minimize bleeding events and complications (Manco-Johnson et al. 2007). Since the 1990s, recombinant FVIII concentrates have been standard-of-care treatment options for patients with hemophilia A (Kingdon and Lundblad 2002). Treatment regimens to achieve optimal prevention of bleeding events vary individually; some patients tolerate nadir FVIII levels of 1%, whereas others require higher nadir FVIII levels to achieve the desired therapeutic outcome (Ahnstrom et al. 2004; Collins et al. 2010). Current standard prophylactic

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regimens commonly use infusion therapy administered three times weekly; other regimens require every other day administration, depending on the patient's needs (Shapiro 2013).

The required adherence to demanding therapeutic regimens that include frequent morning infusions to achieve adequate hemostatic coverage during periods of highest activity makes these regimens less effective and compromises their cost-benefit ratio (Thornburg 2010). Major issues with current regimens are the need for adequate venous access and patient/family compliance with regular prophylaxis, especially in the very young pediatric population, in whom central venous access devices (CVADs) have been used to overcome technical difficulties. Although CVADs make prophylaxis feasible in young children, CVADs are associated with complications, including mechanical failure, dehiscence of the skin over the reservoir, infection, and thrombosis (Ewenstein et al. 2004). In addition, significant healthcare provider efforts are required to manage optimal treatment solutions and to overcome identified issues (Schrijvers et al. 2013). Thus, both the disease and its treatment have the potential to affect HRQoL, the latter through limitations on daily activities that treatment may impose.

The development of inhibitory alloantibodies (inhibitors) occurs in approximately 20%–30% of patients with severe hemophilia A and in 3%–13% of those with moderate or mild disease (Franchini and Mannucci 2013). Inhibitors neutralize the activity of endogenous FVIII as well as of FVIII administered as replacement therapy. For patients with a history of a high-titer (≥5 BU/mL) inhibitor following a re-challenge with FVIII administration (high-responding inhibitor), the only hemostatic options currently available are pro-thrombotic coagulation factors that augment other parts of the coagulation cascade (i.e., "bypassing agents"). Bypassing products include Factor Eight Inhibitor Bypassing Activity (FEIBA), an activated prothrombin complex concentrate (aPCC; FEIBA will be referred to as aPCC throughout this document), and NovoSeven® (recombinant activated human FVIIa [rFVIIa]; NovoSeven® will be referred to as rFVIIa throughout this document) (Srivastava et al. 2013). Both have been used as prophylaxis to prevent bleeding in patients with inhibitors against FVIII ("inhibitor patients"); however, the only available product for this indication in most countries is the aPCC FEIBA. Of note, treatment of patients with congenital hemophilia A with any severity with high-titer inhibitors is similar, and their severity, as defined at diagnosis based on FVIII activity (mild, moderate, or severe), no longer is prognostic of their clinical phenotype and risk of bleeding.

APCCs may be associated with side effects, such as thromboembolic events, hypersensitivity reactions, myocardial infarction, and disseminated intravascular coagulation. Both aPCC and rFVIIa are administered intravenously, with aPCC prophylaxis requiring every other day dosing and rFVIIa requiring daily (or more frequent) dosing.

The development of effective prophylactic treatment options with decreased immunogenicity and less frequent dosing requirements is a high, unmet medical need in

the patient population of hemophilia A patients with FVIII inhibitors. Reducing the time and burden associated with frequent intravenous dosing and the impact of the disease on aspects of physical health and other areas of function, while promoting increased efficacy, may further improve HRQoL, as suggested by a study in which patients receiving a prophylactic treatment with FEIBA had improved HRQoL than those who received episodic therapy (i.e., administered following bleeds) with FEIBA (Gringeri et al. 2013). Therefore, despite major therapeutic advances in the treatment of hemophilia A, opportunities remain to optimize and transform therapy, in particular for patients with inhibitors.

1.2 BACKGROUND ON EMICIZUMAB

1.2.1 *Molecule and Preclinical Data*

Emicizumab (also known as ACE910 and RO5534262) is a recombinant, humanized, bispecific, immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX), mimicking the co-factor function of *activated* FVIII *(FVIIIa)*. In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors, as emicizumab shares no sequence homology with FVIII. In addition, emicizumab offers the possibility of subcutaneous (SC) administration, removing the need for venous access. Finally, because of the expected pharmacokinetic properties of this antibody, markedly extending the dosing interval to once weekly or even less frequently, this novel compound has the potential to dramatically change the treatment of patients with hemophilia A with and without FVIII inhibitors who are in need of effective, safe, and convenient prophylactic therapy.

Emicizumab binds with moderate affinity in the low μM range to FIXa and FX and mimics the co-factor activity of FVIIIa. This in turn, promotes the activation of FX by FIXa and downstream hemostasis for patients with hemophilia A who have hypofunctional levels of or entirely lack FVIII, irrespective of the presence of FVIII inhibitors. [redacted] Mechanistic in vitro studies were conducted in human and cynomolgus FVIII-neutralized plasma and in various coagulation factor-specific assay testing systems, which revealed that emicizumab shortened aPTT and promoted thrombin generation. [redacted]

In vivo pharmacology experiments in cynomolgus monkeys were conducted in a hemophilia A model where endogenous FVIII levels were neutralized by a FVIII specific monoclonal antibody. This model mimics essential characteristics of patients with hemophilia A and was used to test in vivo pharmacodynamics and efficacy under spontaneous or local trauma-induced bleeding conditions. In summary, emicizumab

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demonstrated the ability to significantly reduce bleeding tendency under both sets of conditions.

Potential prothrombotic risks associated with emicizumab-induced FVIII mimetic activity were further explored in [redacted]

Overall, the preclinical pharmacology program is considered to have fully characterized the nonclinical profile of emicizumab. The conducted in vitro and in vivo studies demonstrated the mode of action of emicizumab and provided supportive data on efficacious dose levels in a relevant hemophilia A disease model which were used for dose extrapolation to humans.

[redacted]

[redacted]

[redacted]

See the RO5534262 (Emicizumab) Investigator's Brochure for additional details on nonclinical studies with emicizumab.

1.2.2 *Clinical Experience*

Currently available experience with emicizumab in humans includes data from one Phase I study (ACE001JP) and its ongoing extension, a Phase I/II study (ACE002JP).

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ACE001JP was a single study conducted in 3 parts, including both healthy patients (Part A and Part B) and patients with hemophilia A (Part C). The objective of Parts A and B in healthy patients was to investigate the tolerability, safety, pharmacokinetic (PK), and pharmacodynamic (PD) response of SC administered emicizumab in adult Japanese and Caucasian males and to evaluate for racial differences, if any, in their PK and PD response. Healthy male volunteers aged 20–44 were eligible for enrollment. A total of 64 healthy volunteers were enrolled in Parts A and B from August 2012 to April 2013. In Part C, the objective was to investigate the tolerability, safety, PK, and PD response of SC administered emicizumab in patients with hemophilia A. Patients were eligible for enrollment if they were 12–59 years of age, >40 kg in weight, had a diagnosis of severe congenital hemophilia A, and had documentation of bleeds and treatment with coagulation factor in the last 6 months. For those with inhibitors, patients must have had ≥6 bleeds in the 6 months prior to enrollment, and for those without inhibitors, patients were required to have received ≥150 lifetime doses of FVIII replacement, including in the last 6 months. A total of 18 patients with hemophilia A were enrolled from May 2013 to June 2014.

In the single ascending dose (SAD) portion of the Study ACE001JP, healthy volunteers (Japanese [Part A] and Caucasian [Part B]) received a single SC injection of emicizumab (48 patients) or placebo (16 patients), at dose levels ranging from 0.001 to 1 mg/kg. Six patients received emicizumab and 2 patients received placebo at each dose level. In Part C (the multiple ascending dose [MAD] portion) of the Study ACE001JP, a total of 18 patients with hemophilia A were enrolled in three cohorts of 6 patients each for each dose level (1 mg/kg loading dose followed by weekly SC injections of 0.3 mg/kg [0.3 mg/kg/week group]; 3 mg/kg loading dose followed by weekly SC injections of 1 mg/kg [1 mg/kg/week group]; and 3 mg/kg weekly SC injections [3 mg/kg/week group]).

Study ACE002JP is an extension study that allows for continued treatment with emicizumab of patients enrolled in Part C of Study ACE001JP. [redacted]

Both Study ACE001JP and Study ACE002JP are currently in progress; data from the completed Parts A and B, as well as interim data from Part C of the Study ACE001JP and Study ACE002JP are presented here. The median age and body mass index (BMI) of the healthy volunteers across the dose groups in Part A ranged from 25.5–35.5 years and 20.28 to 21.44 kg/m^2, respectively. In Part B, the median age ranged from 28.5–30.5 years, and the median BMI ranged from 21.60–22.56 kg/m^2 across the dose groups. Among the 0.3, 1, and 3 mg/kg/week groups in Part C, the median age was 32, 30, and 33 years, respectively; the median BMI was 22.54, 22.87, and 22.31 kg/m^2,

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respectively. There were 5 adolescent patients (12–18 years): 1 patient (17 years old) in the 0.3 mg/kg/week group; 2 patients (12 years old and 18 years old) in the 1 mg/kg/week group; and 2 patients (12 years old and 18 years old) in the 3 mg/kg/week group. There were 11 patients with inhibitors: 4 patients in the 0.3 mg/kg/week group; 4 patients in the 1 mg/kg/week group; and 3 patients in the 3 mg/kg/week group. All patients in Part C of Study ACE001JP have completed the treatment period [redacted]. Study ACE001JP will be completed when the last patient completes the protocol-defined observation period of 28, 32, or 36 weeks if they were assigned to receive 0.3, 1, or 3 mg/kg/week of emicizumab, respectively. Study ACE002JP will enable patients from Study ACE001JP to continue receiving emicizumab [redacted].

The Phase I and I/II studies have shown promising results for emicizumab prophylaxis in reducing the annualized bleeding rate (ABR) in Japanese patients with hemophilia A with and without inhibitors against FVIII. Overall, three cohorts of 6 patients each were treated with 0.3 mg/kg (Cohort C-1), 1 mg/kg (Cohort C-2), or 3 mg/kg (Cohort C-3) emicizumab weekly. The number of patients with inhibitors against FVIII was 4 (Cohort C-1), 4 (Cohort C-2), and 3 (Cohort C-3). In 4 of 4 patients with inhibitors against FVIII, treatment with 0.3 mg/kg emicizumab weekly for 12 weeks resulted in a 64.7%–100% reduction in ABR compared with that reported for the previous 6 months, during which time patients received episodic treatment with bypassing agents. In 4 of 4 patients with inhibitors against FVIII, treatment with 1 mg/kg emicizumab weekly for 12 weeks resulted in an 88.9%–100% reduction in ABR compared with that reported for the previous 6 months, during which time patients' episodic treatment with bypassing agents. In 3 of 3 patients with inhibitors against FVIII, treatment with 3 mg/kg emicizumab weekly for 12 weeks resulted in a 100% reduction in ABR compared with that reported for the previous 6 months, during which time patients received prophylactic

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and episodic treatment with bypassing agents (Shima et al. 2014). For patients without inhibitors against FVIII (n=2 in Cohort C-1/Cohort C-2; n=3 in Cohort C-3), the reduction in ABR was 22.8%–100% when treated with 0.3 mg/kg emicizumab and 100% when treated with 1 mg/kg emicizumab weekly for 12 weeks. In Cohort C-3 (n=3), one patient had a reduction in ABR of 100%, another patient who previously had an ABR of 0 on FVIII prophylaxis continued to have an ABR of 0 on emicizumab prophylaxis, and a third patient had a reduction in ABR of 48% when treated with 3 mg/kg emicizumab weekly for 12 weeks. [redacted]

Emicizumab was safe and well-tolerated in these patients (see Investigator's Brochure). [redacted] There were no dose dependent increase in adverse events; and the majority of the adverse events were not considered related to emicizumab. One adverse event (injection-site erythema) in the 1 mg/kg weekly group resulted in discontinuation of treatment; the event was mild in intensity and resolved. [redacted] No thromboembolic adverse events have been reported when emicizumab has been administered alone or concomitantly with FVIII products or bypassing agents as episodic therapy.

In Study BH29884, as of November 2016, thrombotic microangiopathy (TMA; atypical hemolytic uremic syndrome [aHUS]) was observed in 2 patients receiving emicizumab and bypassing agents; and 2 cases of thromboembolic events were observed in 2 patients

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receiving emicizumab and bypassing agents. For more details refer to Sections 5.1.2.3 and 5.1.2.4.

In terms of PK, emicizumab exhibited linear PK after single SC administration. Following single SC injection, its mean elimination $t_{1/2}$ (4–5 weeks) [redacted]. Furthermore, comparison of PK profiles between Japanese and Caucasian patients did not reveal racial differences. In patients with hemophilia A, emicizumab trough plasma concentrations increased in a dose-dependent manner with weekly dosing to achieve a plateau (steady state) after approximately 12 weeks in the first two dosing groups, while they continued to increase in the highest dose group where no loading dose was administered and steady state was expected later.

In the Phase I/II Studies ACE001JP and ACE002JP, emicizumab has been administered to 48 healthy subjects and 18 patients with hemophilia A. [redacted]

Based on these compelling Phase I/II data, a clinical development program in adult and pediatric patients with hemophilia A (both with and without FVIII inhibitors) has been developed. See the RO5534262 (Emicizumab) Investigator's Brochure for additional details on clinical studies with emicizumab.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

For patients with hemophilia A who are diagnosed with inhibitors, permanent eradication of inhibitors is the ultimate goal. This can be achieved by means of intensive FVIII administration over many months with immune tolerance induction (ITI), which is successful in approximately 60%–80% of treated inhibitor patients (Hay and DiMichele 2012; Santagostino et al. 2009). However, hemostatic management may be challenging during the time interval required to achieve ITI success. Furthermore, ITI is not viewed as a viable option for inhibitor patients in many countries, owing to its high cost, the scarce local supply of FVIII concentrates, practical issues and potential complications associated with CVADs, and psychological stress on patients and their families for this highly demanding therapeutic endeavor. Finally, even with successful implementation, ITI will fail to eradicate inhibitors in approximately 20%–40% of treated patients (Mariani et al. 2003).

Therefore, for those inhibitor patients who are unable to eradicate their inhibitors or are not candidates for ITI, bypassing agents are required to treat or prevent bleeds.

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Unfortunately, the hemostatic effect of bypassing agents is unstable in comparison with that of FVIII concentrates. In addition, as opposed to the 8–12-hour half-life and 15–20-minute infusion time of FVIII, rFVIIa has a short half-life of only 2–3 hours, and aPCC requires 25–50 minutes to infuse (with a half-life of 4–7 hours), requiring frequent and extended IV infusions, respectively. In practice, some inhibitor patients will have bleeds that respond better to rFVIIa while others will respond better to aPCC. Several recent publications evaluating the efficacy of prophylactic therapy in adults and children with the bypassing agents rFVIIa (Konkle et al. 2007) and aPCC (Leissinger et al. 2007; Ettingshausen et al. 2010; Leissinger et al. 2011; Antunes et al. 2014) showed decreased bleeding rates compared to episodic treatment.

In the FEIBA prophylaxis pivotal study (PROOF study), inhibitor patients on episodic bypassing agents were eligible for participation if they had a minimum historical ABR of ≥12. On prophylactic aPCC, their median ABR (interquartile range) decreased from 28.7 (32.3) to 7.9 (8.1) (Antunes et al. 2014), suggesting that while this treatment was partially efficacious for some, there still exists suboptimal control of bleeds and unmet medical need in this population.

Given the hemostatic management challenges in adults and children with inhibitors, there is an urgent need for therapeutics that have more reliable efficacy, an extended half-life, and less treatment burden to prevent bleeding for patients with hemophilia A with inhibitors.

The nonclinical and clinical data related to emicizumab to date support a positive benefit-risk assessment. As described in Section 1.2, evaluation of in vivo pharmacodynamics and efficacy under spontaneous or local trauma-induced bleeding conditions in cynomolgus monkeys using a hemophilia A model demonstrated the ability of emicizumab to significantly reduce bleeding tendency under both sets of conditions. This was corroborated in the Phase I/II studies, where significant and stable ABR reductions [redacted] in the 1 and 3 mg/kg emicizumab weekly dose cohorts have been seen to date. [redacted] In the Phase I/II Studies *ACE001JP and ACE002JP*, no thromboembolic or systemic hypersensitivity adverse events were seen; *however, in Study BH29884, 2 cases of TMA (aHUS) and 2 thromboembolic events were observed in patients on emicizumab who received bypassing agents for the treatment of breakthrough bleeds. Three out of these 4 patients have fully recovered and the fourth patient's condition has improved (see Sections 5.1.2.3 and 5.1.2.4).*

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Given the significant unmet medical need among patients with hemophilia A with FVIII inhibitors and positive benefit-risk assessment, *the Sponsor believes that continuation* of *this* Phase III study is indicated.

2. OBJECTIVES AND ENDPOINTS

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis in patients with hemophilia A with inhibitors (Arms A and B) on the basis of the following endpoint:

- Number of bleeds over time (i.e., bleed rate)

The primary definition of a bleed is a bleed for which coagulation factors are administered (*i.e., treated bleed;* see Section 4.5.8).

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives and endpoints for this study are as follows:

- Prophylactic emicizumab compared with no prophylaxis (Arms A and B):

  To evaluate the efficacy in reducing the number of all bleeds (i.e., those treated and not treated with coagulation factors) over time

  To evaluate the efficacy in reducing the number of *spontaneous* bleeds over time

  To evaluate the efficacy in reducing the number of joint bleeds over time

  To evaluate the efficacy in reducing the number of target joint bleeds over time

  To evaluate the HRQoL of patients according to Haem-A-QoL (aged ≥ 18) or Haemo-QoL-Short Form (ages 12–17) scores at 24 weeks

  To evaluate the health status of patients according to EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) scores at 24 weeks

- *P*rophylactic emicizumab *compared with bleed rate prior to study entry (intra-patient comparison;* Arms *A* and *C*:

  To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate *(both for treated bleeds and all bleeds)*

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis on the basis of the following endpoints:

- To assess differences in number of days away from school/work
- To assess differences in number of days hospitalized

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2.2 SAFETY OBJECTIVE

The safety objective for this study is as follows:

- To evaluate the overall safety of prophylactic emicizumab compared with no prophylaxis in patients with hemophilia A with inhibitors on the basis of the following endpoints:

  Incidence and severity of adverse events

  Incidence and severity of thromboembolic events

  Changes in physical examination findings and vital signs

  Incidence of laboratory abnormalities

  Incidence and severity of injection-site reactions

  Incidence of adverse events leading to drug discontinuation

  Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events

  Incidence and severity of thrombotic microangiopathy

  Incidence and clinical significance of anti-emicizumab antibodies

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the exposure (C_{trough}) of emicizumab prior to drug administration on Day 1 at the following timepoints while on emicizumab:

- Every week during Weeks 1–4
- Every 2 weeks during Weeks 5–8
- Every 4 weeks during Weeks 9–24
- Every 8 weeks during Weeks 25–48
- Every 12 weeks thereafter, until the end of the study

2.4 EXPLORATORY BIOMARKER OBJECTIVES

The exploratory biomarker objectives for this study are as follows:

- To assess potential PD biomarkers of emicizumab, including but not limited to aPTT, thrombin generation, and FVIII activity, at timepoints throughout the study
- [redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This randomized, multicenter, open-label, Phase III clinical study will enroll patients aged 12 years or older with hemophilia A who have inhibitors against FVIII. Approximately 51 patients with inhibitors who received episodic treatment with bypassing agents prior to study entry will be enrolled globally and randomized in a 2:1 ratio (see Figure 1) to receive either prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks,

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followed by 1.5 mg/kg/week subcutaneously thereafter (Arm A), or to the control arm (Arm B), which will consist of no prophylaxis. Given the potential heterogeneity of bleed rates in the study patient population, randomized patients will be stratified according to the number of bleeds they experienced over the last 24 weeks prior to study entry (<9 or ≥ 9 bleeds) to ensure a balance of inhibitor patients with lower versus higher number of bleeds, respectively, at baseline across the two randomized arms of the proposed Phase III study. All patients will continue to receive episodic bypassing agent therapy to treat breakthrough bleeds, *preferably with rFVIIa at the lowest expected dose to achieve hemostasis*.

In addition, given that some patients with hemophilia A with inhibitors are also currently treated with bypassing agents on a prophylactic basis, approximately 30-50 patients with inhibitors on prophylactic bypassing agents will be enrolled in a separate therapeutic arm (Arm C) to receive prophylactic emicizumab at the same dose and schedule (see Figure 1). Enrollment into Arm C will continue for 24 weeks after Arms A and B have been closed to enrollment or until 50 patients have been enrolled, whichever occurs earlier, in order to collect additional safety and efficacy from patients previously on prophylactic bypassing agents.

Of note, all patients who participated in Study BH29768 (a non-interventional study; described at the end of this section) received priority to participate in a future emicizumab interventional study. A separate, therapeutic arm (Arm D) *has opened for* patients on episodic bypassing agents who participated in Study BH29768 but were unable to enroll in Arms A or B*, or for patients on prophylactic bypassing agents who were unable to enroll in Arm C,* before they closed to enrollment. Arm D will yield additional efficacy, safety, PK, and PD data and enable collection of plasma samples [redacted] (see Figure 1).

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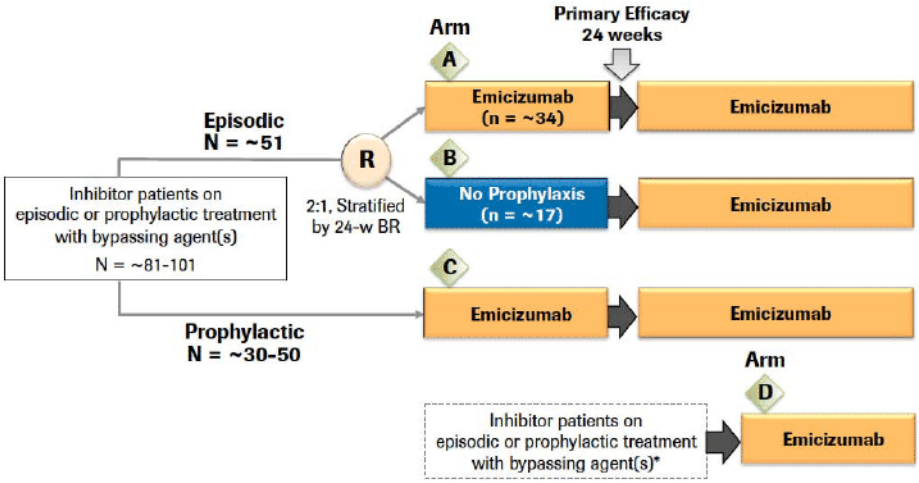
Figure 1 Study Schema



R = randomized, 24-w BR = 24-week bleed rate (prior to study entry)
*For episodic bypassing agent patients enrolled in Study BH29768 but were unable to enroll in Arms A or B, or for prophylactic bypassing agent patients who were unable to enroll in Arm C, before they closed to enrollment

The primary efficacy analysis, defined as comparing the number of bleeds over time for patients randomized to receive prophylactic emicizumab versus no prophylaxis, will be conducted after all randomized patients have completed 24 weeks in the study or the last randomized patient who has not completed 24 weeks in the study discontinues study participation, whichever occurs first.

To obtain additional safety and efficacy data, prior episodic bypassing agent patients who had been randomized to not receive emicizumab (control arm, Arm B) will be offered treatment with prophylactic emicizumab at the same dose and schedule as patients who started Study BH29884 on emicizumab once they complete 24 weeks in the study. In addition, after at least 24 weeks on prophylactic emicizumab, all patients will be able to continue on their 1.5 mg/kg/week maintenance dose or may be provided the option to increase their dose to 3 mg/kg/week if they meet protocol-defined criteria of suboptimal response and receive approval from the Medical Monitor to do so (see Section 4.3.1.2). Patients who continue to derive clinical benefit will be given the opportunity to continue receiving prophylactic emicizumab [redacted].

During the study, patients (or their legally authorized representative) will be asked to record their bleeds and medication use on an electronic, handheld device (see Section 7.3). The Bleed/Medication Questionnaire should be completed whenever a bleed or medication use occurs. In the event of no bleed or medication use, the patient should complete the questionnaire at least once a week to serve as confirmation that no

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bleed or medication use occurred. In addition, health status information will be collected whenever a bleed is reported. HRQoL, health status, patient safety, and days of school or work missed will be assessed every 4 weeks for approximately 24 weeks and every 4–12 weeks thereafter, as outlined in the schedule of assessments.

Physical examinations, vital sign assessments, ECG, and laboratory assessments will be collected as per the schedule of assessments and will be the same for all patients receiving emicizumab, regardless of whether they are enrolled in the randomized portion of the study or in the separate non-randomized arms. Adverse events will be captured on an ongoing basis, as they occur during the study.

All patients who receive emicizumab in the study will undergo PK assessment. As emicizumab is intended in this study for prophylactic use only (i.e., not to treat bleeds that have already occurred), neither aPCC nor rFVIIa interfere with emicizumab PK assessments, and some patients with hemophilia A with inhibitors require frequent dosing with bypassing agents due to having many bleeds or being on prophylaxis, a washout period is not required prior to enrollment so that new bleeds are minimized and treatment for any prior bleed is not interrupted.

Exploratory PD biomarkers (e.g., aPTT, FVIII activity, thrombin generation assay) will be collected as per the schedule of assessments. As values for these tests are normalized by even low plasma concentrations of emicizumab (see Section 1.3), a variety of assay formats (one-stage, chromogenic) and modifications (predilution of patient plasma) will be investigated for assessment of PD response at higher emicizumab plasma concentrations. [redacted] In addition, FIX and FX antigen levels will be monitored.

Throughout the study, biomarkers related to thromboembolism (e.g., D-dimer, prothrombin 1.2 fragment) and emicizumab trough concentrations, will be collected as per the schedule of assessments. Immunologic biomarkers (i.e., anti-emicizumab antibodies) will also be measured as per the schedule of assessments (see Appendix 1 and Appendix 2).

An independent Data Monitoring Committee (iDMC) composed of, at minimum, hemostasis/thrombosis experts and a statistician will be in place throughout the duration of the study and will monitor patient safety at pre-specified intervals and ad hoc as needed throughout the study.

Breakthrough bleeds *should preferably* be treated with *rFVIIa at the lowest expected dose* to *achieve hemostasis* and captured as they occur on the electronic, handheld device. Of note, the clinical experience in the ongoing Phase I/II clinical studies includes the treatment of over [redacted] breakthrough bleeds in patients receiving emicizumab with

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either FVIII or bypassing agents, without any related safety concerns reported. *However, in Study BH29884, 2 events of TMA and 2 thromboembolic events were observed in patients who concomitantly used repeated doses of aPCC for the treatment of breakthrough bleeds (see Sections 1.2, 1.3, 5.1.2.4, and 5.1.3). Therefore, it is recommended that breakthrough bleeds are treated with rFVIIa only, if possible, and that the use of aPCC or other bypassing agents should be avoided or limited (see Sections 3.1 and 3.3.3). Also, local and central laboratory assessments are required to monitor the risk for thromboembolic events or TMA as per the schedule of assessments (see Section 4.5.5 and Appendix 1).* Investigators will be asked to contact the Medical Monitor in the event of suspected lack or loss of efficacy of emicizumab in order to discuss potential laboratory evaluations (e.g., anti-emicizumab antibodies, coagulation tests) to be performed as well as to re-evaluate the patient's benefit-risk of continued treatment. When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, category of bleed, time of each individual bleed (day, start time), symptoms of bleed, and treatment for bleed. Health status information will also be collected on the day a bleed occurs.

The reason for the use of coagulation products (e.g., aPCC or rFVIIa) will be documented (e.g., bleeding, prophylaxis). A thorough documentation of the treatments for bleeds will be requested, including agent, start time, dose, and reason for treatment. The number of infusions needed to treat the bleed will be derived from the medication log.

A non-interventional study (BH29768) has been initiated to document the number and types of bleeds and current treatment with episodic or prophylactic bypassing agents, as well as collect information on HRQoL, health status, and safety in patients with hemophilia A with FVIII inhibitors. The assessments in the non-interventional study will mitigate the risk of underreporting of bleeds that oftentimes occurs in the real world, and the resulting data will serve as a source of comparator information for some analyses conducted in the Phase III clinical study (Study BH29884). The non-interventional study will also allow an investigation of the feasibility of using an electronic, handheld device that has been developed to record data related to bleeds, hemophilia treatments, HRQoL, and health status. In addition, the non-interventional study will enable earlier identification and confirmation of patients who may qualify for the Phase III clinical study. It is anticipated that a significant number of patients participating in Study BH29768 will enroll in Study BH29884, as long as they meet the inclusion and exclusion criteria of the study and are able to enroll at a participating site while the study is open for enrollment.

3.2 END OF STUDY AND LENGTH OF STUDY

LENGTH OF STUDY

The approximate length of the entire study from the first patient enrolled to the Last Patient Last Visit (LPLV, see below) is approximately 108 weeks.

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END OF STUDY

The end of this study is defined as the date when the last remaining patient has completed the last visit (i.e., LPLV), as defined below:

- Has completed at least 24 weeks of emicizumab treatment and either transferred to [redacted] receive further emicizumab as per Roche Global Policy on Continued Access to Investigational Medicinal Products or to commercial product

  OR

- Completes the end of study safety follow-up visit 24 weeks after discontinuing emicizumab

  OR

- Has withdrawn consent

  OR

- Is lost to follow-up

3.3 RATIONALE FOR STUDY DESIGN

Current standard-of-care treatment for patients with FVIII inhibitors involves treatment with bypassing agents (e.g., aPCC and rFVIIa). Despite European Union approval of prophylactic aPCC as early as 2007 in the United Kingdom and approval in the United States in 2013, the majority of adult and adolescent patients with hemophilia A with inhibitors worldwide are still treated with episodic bypassing agents (Carcao et al. 2015). Uptake of current prophylactic treatment may be limited by the occurrence of associated adverse events, including CVAD-related thrombosis and infection, perceived and actual problems with treatment adherence, and treatment cost (Leissinger et al. 2015a; 2015b).

In designing Study BH29884, the study designs of the pivotal studies for both aPCC (in inhibitor patients) and FVIII concentrates (in non-inhibitor patients) were extensively reviewed. The pivotal FEIBA study (Antunes et al. 2014) was conducted as a comparison of episodic versus prophylactic FEIBA. It may be argued that there was no prophylactic regimen available at the time this study was conducted that could have served as an alternative comparison. However, review of the prior approvals for FVIII concentrates, where FVIII prophylaxis is utilized in the majority of patients, revealed that the standard clinical study design for novel FVIII concentrates has been to compare episodic to prophylactic regimens (Valentino et al. 2012; Manco-Johnson et al. 2013; Mahlangu et al. 2014) rather than performing a comparison to a previously marketed FVIII prophylactic regimen. This precedent has likely been maintained even for more recent clinical study designs (e.g., long-acting FVIII products N8-GP and BAX855) due to operational feasibility concerns, design complexities such as the definition of the appropriate non-inferiority margin, and the large number of patients continuing to receive treatment with episodic regimens despite the availability of prophylactic ones.

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Therefore, given the high unmet need for patients with hemophilia A with inhibitors, the current patterns of utilization of bypassing agents, and the regulatory precedent, a study comparing prophylactic emicizumab to no prophylaxis in patients with hemophilia A with inhibitors who were treated with episodic bypassing agents prior to study entry is deemed to be appropriate for the first pivotal study and will provide clinical data that is clinically meaningful to the hemophilia community. If efficacy of emicizumab is demonstrated in the inhibitor population that has the highest unmet need (i.e., patients who are treated with episodic bypassing agents and experience upwards of 30 bleeds per year), this should translate to the smaller subset of the inhibitor population whose bleeds are better, albeit still not completely controlled (i.e., annual bleed rate of 8–10) on prophylactic bypassing agents.

Acknowledging that the treatment landscape may evolve in the future (e.g., more patients with hemophilia A with inhibitors may be treated with prophylactic bypassing agents), the proposed study will evaluate prophylactic emicizumab in patients previously treated with prophylactic bypassing agents in an additional, non-randomized arm.

In addition, a separate study arm (Arm D) *has* opened *for* patients on episodic bypassing agents who participated in Study BH29768 but were unable to enroll in Arms A or B*, or for patients on prophylactic bypassing agents who were unable to enroll in Arm C, prior to their closure*. The enrollment of these patients will provide additional data on the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab [redacted]

In conclusion, based on the current treatment landscape, regulatory precedent, operational considerations, and taking into account the desire not to delay access to a potentially efficacious therapy to the population of highest unmet need, the proposed design for Study BH29884 is considered to be the most appropriate.

3.3.1 Rationale for Emicizumab Dose and Schedule

Emicizumab prophylaxis has been administered subcutaneously in 18 Japanese patients with hemophilia A (with and without FVIII inhibitors) in Study ACE001JP[redacted]. Three dose groups (of 6 patients each) received the following treatment (administration period of at least 12 weeks):

- A loading dose of 1 mg/kg followed by weekly doses of 0.3 mg/kg
- A loading dose of 3 mg/kg followed by weekly doses of 1 mg/kg
- Weekly doses of 3 mg/kg

One patient, who was receiving weekly doses of 1 mg/kg, discontinued emicizumab during Study ACE001JP.

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Emicizumab was safe and well-tolerated in these patients (see Section 1.2 and the RO5534262 [emicizumab] Investigator's Brochure). [redacted]

A substantial reduction in bleeding events has been observed with prophylactic emicizumab treatment, [redacted]. ABR decreased in all patients, regardless of age or the presence of FVIII inhibitors.

Table 1 Mean Reduction (%) of Annualized Bleeding Rates in Inhibitor and Non-Inhibitor Patients Enrolled in Studies ACE001JP/ACE002JP

Emicizumab dose	0.3 mg/kg weekly	1 mg/kg weekly	3 mg/kg weekly
ABR reduction	[redacted]%	[redacted]%	[redacted]%

ABR = annualized bleeding rate.

[redacted]

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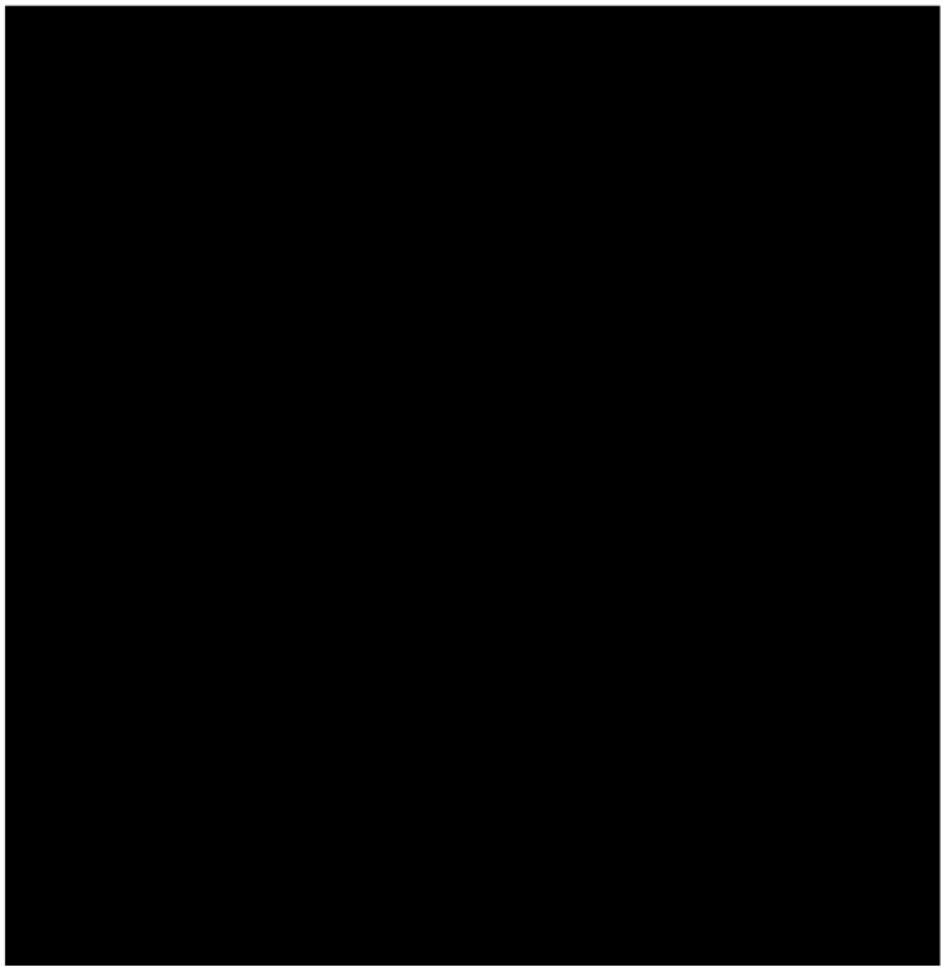
Figure 2 Individual Pharmacokinetic Profile with Corresponding Bleeding Event



The exposure-response relationship of emicizumab was quantitatively characterized and simulations suggested that a median ABR of 0 is achieved for emicizumab trough plasma concentration ≥ 45 μg/mL. On the basis of population PK modeling, a median trough plasma concentration of 45 μg/mL is predicted to be achieved after treatment with 4 weekly doses of 3 mg/kg and maintained, thereafter, with weekly doses of 1.5 mg/kg. The loading doses of 3 mg/kg weekly for 4 weeks were chosen in order to rapidly achieve the effective trough concentration of 45 μg/mL without exceeding the maximum dose of 3 mg/kg weekly investigated in the Phase I/II studies. Thereafter, a dose and schedule of 1.5 mg/kg weekly was chosen in order to reduce the peak-trough

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fluctuations and to maintain emicizumab plasma concentrations above 45 μg/mL over the entire dosing interval. This dosing regimen (i.e., 3 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly) will, therefore, be investigated in this study.

3.3.2 Rationale for Patient Population

As described in Section 3.3, patients with hemophilia A and inhibitors against FVIII who were treated with episodic bypassing agents prior to study entry will comprise the primary population for this Phase IIII study of prophylactic emicizumab compared with no prophylaxis in investigating the efficacy, safety, and PK of emicizumab.

Although the initial severity of a patient's hemophilia A may be directly related to his or her endogenous FVIII activity, the treatment of patients of any severity (mild, moderate, or severe) with high-titer inhibitors is similar (i.e., with bypassing agents). Because their initial severity of hemophilia A, which is defined at diagnosis on the basis of their FVIII activity, no longer is prognostic of their clinical phenotype and risk of bleeding, this will not be used to determine study eligibility.

Instead, inhibitor patients previously treated with episodic bypassing agents will be required to have at least 6 bleeds in the last 24 weeks prior to study entry to be eligible for enrollment in the randomized portion of Study BH29884. This is to select a group of patients with hemophilia A with inhibitors who have a high, unmet medical need and to enable detection of a clinically and statistically significant difference in bleed rates in this subset of an orphan disease population.

Inhibitor patients previously treated with episodic bypassing agents also comprised the control arm in prior prophylaxis studies involving inhibitor patients (Leissinger et al. 2011; Antunes et al. 2014). In both the PRO-FEIBA and PROOF studies, inhibitor patients ranging in age from 2–68 years old on episodic bypassing agents were eligible for participation if they had a minimum historical ABR of ≥12 (Leissinger et al. 2011; Antunes et al. 2014), which defines a group with high unmet medical need and is also an inclusion criterion for Study BH29884. Based on its mechanism of action (mimetic of FVIII's co-factor activity) and clinical study results to date, prophylactic emicizumab is expected to provide significant and clinically meaningful benefit to this inhibitor population that is in need of a reliably efficacious therapy to prevent bleeds.

Based on current treatment algorithms for patients with hemophilia A with inhibitors (Kempton and White 2009; Srivastava et al. 2013), it is anticipated that the majority of adults and adolescents treated with emicizumab will have previously undergone ITI without success or are not candidates for ITI, although prior ITI will not be required.

As clinical safety data related to the concomitant use of prophylactic emicizumab during ITI are not available at this time, patients currently receiving ITI will not be eligible for Study BH29884. Because the presence or amount of FVIII inhibitors in their plasma does not impact the efficacy of emicizumab, patients' inhibitor titers at the time of study

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entry will not influence their study eligibility. However, patients will be required to have a history of a high-titer inhibitor documented in the medical record in order to be eligible for the study.

Inhibitor patients previously treated with prophylactic bypassing agents are included in a separate arm (Arm C) in Study BH29884, as combining them with those previously treated with episodic bypassing agents would have introduced significant heterogeneity in baseline bleed rates. In order to collect additional safety and efficacy data on such patients, Arm C will remain open to enrollment for 24 weeks after Arms A and B close, or until 50 patients have enrolled, whichever occurs earlier. Also, *for* patients on episodic bypassing agents who participated in Study BH29768 (and accordingly received priority to participate in a future emicizumab interventional study*) but were unable to enroll in Arms A or B, and for patients on prophylactic bypassing agents who were unable to enroll in Arm C, before they closed,* a separate therapeutic arm (Arm D) *has opened*. In doing so, additional efficacy, safety, PK, and PD data will be collected, as well as blood samples [redacted].

3.3.3 Rationale for Control Group

There will be two types of control groups in this Phase III clinical study. The first will be a concurrent, no prophylaxis "usual care" arm, to which patients who were on episodic bypassing agents prior to study entry will be randomized (2:1 prophylactic emicizumab:no prophylaxis), which will enable an inter-patient comparison of the treatment and control groups. All patients, whether assigned to receive prophylactic emicizumab or no prophylaxis, will continue to receive bypassing agents on an episodic basis for the treatment of breakthrough bleeds during the study. Specific doses of bypassing agents will not be mandated in the study, but *patients receiving emicizumab must first receive approval from the investigator regarding what the appropriate dose and schedule of bypassing agents (preferably, rFVIIa)* should be *used* to *treat a bleed, using the lowest effective dose to control a given bleed for* each individual patient.

The second type of control group will be an individual patient's bleed rate prior to study entry. This will enable intra-patient analyses of bleed rates to be performed as well.

Both control groups are appropriate, as episodic bypassing agent therapy represents the regimen that the majority of patients with hemophilia A with FVIII inhibitors are currently receiving and because these control groups have been utilized in previous prophylaxis inhibitor studies (Leissinger et al. 2011; Antunes et al. 2014) (see Section 3.3).

3.3.4 Rationale for the Primary Efficacy Analysis

The objective of the primary efficacy analysis is to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis on the number of bleeds over time (i.e., bleed rate). As mentioned in Section 3.1, the primary efficacy analysis will occur after all randomized patients have completed 24 weeks in the study or the last randomized patient who has not completed 24 weeks in the study discontinues study

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participation, whichever occurs first. This timepoint in the study will lead to a range of observation periods from 24–48 weeks (estimated at n=28 patients) or longer (estimated at n=6 patients) in the prophylactic emicizumab arm and is deemed to be sufficient to reliably assess the effect of prophylactic emicizumab on bleed rate reduction. In the multiple ascending dose Phase I study involving Japanese patients with hemophilia A (Study ACE001JP), a statistically significant reduction in median ABR to 0 after 12 weeks of treatment (approximately 3 months) in the 1 and 3 mg/kg/week emicizumab dose cohorts was demonstrated. [redacted] consistent with evidence suggesting longer duration of prophylactic therapy in inhibitor patients is associated with maintenance of ABR reduction (Antunes et al. 2014). The duration of safety follow-up for all patients in the 1 and 3 mg/kg/week cohorts in Study ACE001JP/Study ACE002JP ranges from [redacted], respectively.

A recent publication of hemophilia B patients with FIX activity levels ≤ 2% who received episodic therapy showed no distinguishable trend in prospectively collected ABRs over approximately 59 weeks in the study (Shafer et al. 2014). As the number of bleeds over time is not expected to differ between patients with hemophilia A or B, it is reasonable to extrapolate this study's findings to the hemophilia A population.

In addition, because this will be a global study with enrollment from different continents occurring over time, all seasons will be represented in the bleed rate data.

3.3.5 Rationale for Patient-Reported Outcome Assessments

The study design utilizes the electronic capture of bleeds, HRQoL, and health status using an electronic, handheld device whose feasibility will already have been assessed in a previous study (Study BH29768). HRQoL is an important outcome in the care of patients with hemophilia (Brown et al. 2009). HRQoL in hemophilic patients is multifaceted and impacted by:

- Disease symptoms
  - Pain, arthropathy, disability, swelling, bleeding
- Outcome perception
  - Orthopedic outcomes, survival outcomes
- Treatment both prophylactic and on demand, as well as pain management
  - Painfulness, risk of infections, side effects, risk of complications
- Limitations on daily functioning
- Increased anxiety and depression
- Significant time spent in the hospital, emergency room, and receiving treatments to manage both diseases symptoms and treatment effects

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The goal of measuring HRQoL is to quantify the benefit of treatment from the patient perspective. Previous studies that have used the Haemo-QoL, a measure of different dimensions of HRQoL affected by hemophilia in children and adolescents, have reported improvements in physical health, feelings, view of self, family relations, friend relations, perceived support, relation with others, participation in sports, dealing with hemophilia, views of treatment, views of the future, and relationships (Santagostino et al. 2014). Improvements in physical health, feelings, view of self, and participation in work and school have also been observed on the adult version of the measure, the Haem-A-QoL (Stasyshyn et al. 2014).

The inclusion of HRQoL measures (see Section 4.5.7) in the current study will allow for the assessment of the impact of prophylactic treatment with emicizumab in adolescents and adults with hemophilia A and an evaluation of the changes in HRQoL in patients receiving prophylaxis with emicizumab compared with that of patients receiving only episodic treatment for breakthrough bleeds. It will also allow for an assessment of pain associated with bleeding episodes.

3.3.6 Rationale for Biomarker Assessments

*Some b*iomarkers to measure the PD effect of emicizumab on hemostasis have not been fully validated to date [redacted] *Refer to Section 5.1.4 for more information about the effects of emicizumab on existing laboratory assays*. Plasma samples will be collected for PD biomarker assessment in parallel with PK samples at all clinic visits to demonstrate evidence of biologic activity of emicizumab in patients and to support selection of a recommended dose. These PD biomarkers include but are not limited to coagulation assays such as aPTT, thrombin generation, and FVIII activity assays. All of these assays were previously shown in the Phase I/II study to exhibit a dose-response relationship to emicizumab concentration (for more information, see the RO5534262 [emicizumab] Investigator's Brochure). The aPTT assay will be run [redacted] to ensure that the assay range covers all levels of emicizumab exposure. [redacted]

Data from this extensive PD analysis of samples from patients in Arms A, B, and C will then be used [redacted] Plasma samples collected from patients in Arm D, as well as any residual samples from patients in Arms A, B, and C, will be used [redacted].

Exploratory plasma biomarkers will include factor IX antigen (FIX:Ag) and factor X antigen (FX:Ag) to assess whether drug treatment causes a change in the circulating levels of these coagulation factors, which are the binding targets of emicizumab, and may include measurement of other coagulation or hemophilia-related factors as well.

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4. MATERIALS AND METHODS

4.1 PATIENTS

The target population will be patients with hemophilia A with FVIII inhibitors who have been treated with bypassing agents to control or prevent bleeds with suboptimal success.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of patient-reported outcomes questionnaires and Bleed/Medication Questionnaire through the use of an electronic device
- Aged 12 years or older at the time of informed consent
- Body weight ≥40 kg at the time of screening
- Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (i.e., ≥5 Bethesda Units)
- Documentation of treatment with episodic or prophylactic bypassing agents for at least the last 24 weeks
- ≥ 6 bleeds in the last 24 weeks prior to screening (if on an episodic bypassing agent regimen) or ≥2 bleeds in the last 24 weeks prior to screening (if on a prophylactic bypassing agent regimen)
- Adequate hematologic function, defined as platelet count ≥100,000/μL and hemoglobin ≥8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin ≤1.5×the upper limit of normal (ULN) (excluding Gilbert's syndrome) and *both* AST and ALT ≤3×ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine ≤2.5×ULN and creatinine clearance by Cockcroft-Gault formula ≥30 mL/min

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- For women who are not postmenopausal (≥48 weeks of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined highly effective contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of contraceptive methods with a failure rate of <1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of <1% per year. Barrier methods must always be supplemented with the use of a non-lipid-based spermicide.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Inherited or acquired bleeding disorder other than hemophilia A
- Ongoing (or plan to receive during the study) immune tolerance induction therapy or prophylaxis with FVIII with the exception of patients who have received a treatment regimen of FVIII prophylaxis with concurrent bypassing agent prophylaxis
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or current signs of thromboembolic disease
- Other conditions (e.g., certain autoimmune diseases) that may increase the risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Known HIV infection with CD4 count <200 cells/μL within 24 weeks prior to screening
- Use of systemic immunomodulators (e.g., interferon or rituximab) at enrollment or planned use during the study, with the exception of anti-retroviral therapy
- *Patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgment*
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study or that would, in the opinion of the

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investigator or Sponsor, preclude the patient's safe participation in and completion of the study or interpretation of the study results

- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Receipt of

  Emicizumab in a prior investigational study

  An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration

  A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter

  An investigational drug concurrently
- Unwillingness to use highly effective contraception methods for the specified duration in the protocol (females only, unless required otherwise by the local health authority)
- Clinically significant abnormality on screening evaluations or laboratory tests that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient
- Pregnancy or lactation, or intent to become pregnant during the study

  Women who are not postmenopausal (≥48 weeks of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

4.2 METHOD OF TREATMENT ASSIGNMENT

Patients who received episodic treatment with bypassing agents prior to study entry will be randomized in a 2:1 ratio to receive either prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously, or to the control arm (no prophylaxis). A central randomization procedure will be used for all patients that fulfill the entry criteria at screening. A block-based randomization method will be used, stratified by the number of bleeds in the last 24 weeks (<9 or ≥ 9). The proposed randomization method is designed to balance treatment group assignment within the prognostic stratification factor.

Patients on prophylactic bypassing agents prior to study entry will be enrolled in a separate therapeutic arm (Arm C) to receive prophylactic emicizumab, at the same dose and schedule as described above. Patients on episodic bypassing agents prior to study entry, who participated in Study BH29768 but were unable to enroll in Arms A or B*, or patients on prophylactic bypassing agents who were unable to enroll in Arm C, before they closed*, will have an opportunity to enroll in an additional, separate therapeutic arm (Arm D) to also receive prophylactic emicizumab.

The time between screening and enrollment of eligible patients should be ≤4 weeks; otherwise, patients must be re-screened to determine if they continue to meet the

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inclusion and exclusion criteria. If a patient has previously been randomized or assigned to a treatment arm in Study BH29884, they cannot be re-screened.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Emicizumab

Emicizumab Drug Product will be supplied by the Sponsor as a sterile liquid for SC injection, contains no preservatives, and requires storage at 2–8° Celsius (do not freeze and protect from light). Each single-use vial contains [redacted] mg (nominal) of emicizumab at pH [redacted]. The Drug Product is formulated as [redacted] mg/mL emicizumab in [redacted] mmol/L [redacted], [redacted] mg/mL [redacted], [redacted] mmol/L [redacted] (pH [redacted]). For information on the formulation and handling of emicizumab, see the Investigator's Brochure.

4.3.1.2 Dosage, Dose Adjustment, and Administration

As discussed in Section 3.3.1, when each patient starts on prophylactic emicizumab, they will receive 3 mg/kg weekly for 4 weeks as loading doses, followed by 1.5 mg/kg weekly, as long as they continue to derive sufficient clinical benefit. After at least 24 weeks on prophylactic emicizumab, patients will have the opportunity to increase their emicizumab dose to 3 mg/kg weekly if they meet the following criteria **and** receive approval from the Medical Monitor:

- ≥2 spontaneous and clinically significant bleeds in the last 24 weeks on emicizumab, both of which occur after the end of the loading dose period
- At least one of the bleeds must be verified by a physician (e.g., with diagnostic imaging, photograph)

If the investigator believes that a specific patient warrants dose up-titration based on a different reason (e.g., traumatic bleed out of proportion to the degree of injury), they must discuss the case with the Medical Monitor for consideration and potential approval.

If a patient has a systemic hypersensitivity reaction or severe adverse reaction that may be attributable to emicizumab, subsequent doses should be held until the situation is discussed with the Medical Monitor and approval to resume dosing is given. Should certain, unanticipated events occur during the study that require treatment with multiple daily administrations of bypassing agents or FVIII concentrates for multiple days, such as non-elective surgery or severe/life-threatening bleeds, the investigator should contact the Medical Monitor immediately to discuss such cases and the management of future emicizumab doses. Any other emicizumab dose adjustment request will require discussion of the clinical case with and approval from the Medical Monitor.

Study site healthcare providers (HCPs) will be trained on how to properly prepare the study medication and administer the correct calculated dose subcutaneously as described in the “Instructions for Use” (IFU) document. Patients will in turn be trained by

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an HCP on study medication preparation and self-administration *at the recommended sites of injection, as detailed in* the IFU. In the event that a caregiver will ultimately administer study drug to the patient in the home setting, the caregiver is to be trained. The HCP is to inform the patient/caregiver of the volumetric dose to be administered and dosing frequency.

Details on the devices to be used for study medication withdrawal and SC injection are provided in the Pharmacy Manual.

Emicizumab will be administered as a SC injection in the home setting, with one dose every week, after a period of in-clinic administration and training. The first five drug administrations must be performed in a monitored setting, such as an infusion center, clinic, or hospital, with a 60-minute observation period following each of the first three doses. The observation period for the fourth and fifth doses will be at the investigator's discretion. For patients with a previous history of a clinically significant hypersensitivity reaction, additional precautions as described in Section 5.1.2.2 should be considered. The patient/caregiver will also have the opportunity to ask any questions to the HCP before the scheduled start of home administration. The patient/caregiver will observe at least one SC injection performed by the HCP and successfully administer at least one SC injection while being observed by the HCP prior to starting home administration. Each site will have the discretion to provide additional training if deemed appropriate. If, despite additional training, the investigator determines that the patient/caregiver is unable to inject emicizumab, then arrangements may be made to identify a trained caregiver or HCP to administer the SC injections. At applicable sites, study drug may be administered by a trained mobile nursing (MN) professional at the patient's home or another suitable location, if the patient has given written informed consent to participate in MN visits.

Patients/caregivers will be provided with the clinic contact information to use in case they have questions related to self-administration between visits.

Medication administration errors during training will be documented in the eCRF. If necessary, patients or their HCP may choose to continue administration of study drug in the clinic. Compliance in the home setting is to be monitored by reviewing reported emicizumab use and recording collected used and unused vials at each visit.

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If the patient forgets or cannot administer study medication on the scheduled dosing day, study medication should be administered as soon as possible within a window of 3 days from the scheduled dosing date. If more than 3 days has passed, the missed dose should be skipped, and the patient should take their next dose at the next scheduled time (with the study medication dosing resumed in accordance with the original dosing schedule). All dosing should be clearly documented on the electronic, handheld device.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Patients and/or the caregiver will be provided with alert cards, which they will be requested to carry at all times. These will include guidance on recognizing signs/symptoms of thromboembolic events or allergic/anaphylactic/anaphylactoid reactions and how to obtain emergency care. *In addition, alert cards are designed to notify non-study HCPs that emicizumab will interfere with certain coagulation laboratory tests (see the RO5543262 [Emicizumab] Investigator's Brochure for more information) and that the investigator should be contacted for assistance in interpreting the test results.*

Guidelines for dosage modification are discussed in Section 3.1, and those for treatment interruption or discontinuation are provided in Section 4.6.

4.3.2 Investigational Medicinal Product Accountability

Emicizumab, the only investigational medicinal product (IMP) in Study BH29884, is required for completion of this study and will be provided by the Sponsor, and accountability for each vial is required throughout the study. The study site will acknowledge receipt of IMPs using the interactive voice or Web response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

Used and unused IMP vials will be returned by study patients to the study site and appropriately accounted for. Used vials will then be disposed of at the study site according to the study site's institutional standard operating procedure. Instructions regarding how to handle unused vials should be obtained from the Sponsor. If the investigator prefers to destroy the IMP at his or her site, the site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

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4.3.3 Post-Study Access to Emicizumab

The Sponsor will offer post-study access to the study drug (emicizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for hemophilia A with FVIII inhibitors
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for hemophilia A with FVIII inhibitors
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:
http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT AND RESCUE THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Concomitant use of the following drugs and therapies will be permitted:

- Drugs intended to control *or prevent* bleeds, including bypassing agents*, should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase patients' coagulation potential, the doses required to*

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achieve hemostasis may be lower than the bypassing agent doses used prior to starting the study.

Caution should be taken for patients who are using rFVIIa (e.g., consideration of using no more than 90 µg/kg of rFVIIa as an initial dose).

Use of aPCC in combination with emicizumab should be avoided completely in patients who have the option of using other bypassing agents to treat bleeds. In the event that aPCC is the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than 50 units/kg of aPCC to be administered as an initial dose.

Other bypassing agents (e.g., Byclot®) should be avoided. In cases where such agents are the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than the lowest dose described in the prescribing information to be administered as an initial dose (e.g., no more than 60 µg/kg of Byclot®).

- *Exact dose and schedule of bypassing agents should be discussed with patients at the beginning and throughout the study. Repeated dosing of rFVIIa, aPCC, or other bypassing agents should be performed only under medical supervision, which includes laboratory monitoring by additional local and central laboratory assessments (see Appendix 1), and consideration should be given to verifying bleeds prior to repeated dosing.*
- Drugs and therapies to treat adverse events and use of topical antiseptics, anesthetics, eye drops, etc., that are not considered to result in systemic exposure
- *Caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients receiving emicizumab.*

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 4 weeks prior to initiation of study treatment:

- Use of drugs that would affect hemostasis (e.g., aspirin, non-steroidal anti-inflammatory drugs that are not selective or preferential cyclooxygenase-2 [COX-2] inhibitors, or anticoagulants [other than to flush, dwell, or de-clot a CVAD]) but excluding drugs intended to control bleeding episodes or used in the context of minor surgery (e.g., tooth extraction) or injuries (e.g., concussion) to prevent deterioration
- Use of systemic immunomodulators (e.g., rituximab, interferon) other than anti-retroviral therapy
- Elective surgery (excluding minor procedures such as tooth extraction*, CVAD removal,* or incision and drainage as well as emergency surgeries)
- Use of other investigational drugs
- *Use of aPCC for short-term prophylaxis*
- Use of a concomitant prophylactic regimen with FVIII *or rFVIIa*

  Intermittent, prophylactic doses *or short-term prophylaxis* (e.g., around the time of surgery), however, are permitted

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- *Use of anti-fibrinolytics in conjunction with aPCC or Byclot®*

If prohibited therapy is administered for any reason, it should be recorded on the eCRF. If prohibited treatment is prescribed or considered medically necessary, the medical monitor should be consulted to discuss any changes in the benefit/risk and determine whether the patient should continue on the study.

4.5 STUDY ASSESSMENTS

See Appendix 1 for the schedule of assessments performed during the study.

At applicable sites, certain study assessments may be performed by an MN professional at the patient's home or another suitable location, such as their school or office, to improve access and convenience for patients participating in the study. The Sponsor may select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of assessments (see Appendix 1) specifies the assessments that may be performed by an MN professional.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not enrolled will be maintained at the study site. For adolescents (i.e., 12–17 years of age), an Informed Assent Form will be completed instead. Parents or *legally authorized representative* of adolescents will also complete an Informed Consent Form.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization or assignment into a treatment arm. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes hemophilia-related history, clinically significant diseases, procedures, use of alcohol and drugs of abuse within the past year, and medication allergies. In particular, sites should record whether the patient has any history of prior immune tolerance induction, anaphylaxis, or known thrombophilia. It should also include all medication taken in the 4 weeks prior to screening (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies).

Demographic data will include age, sex, and self-reported race and ethnicity.

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4.5.3 Physical Examinations

A complete physical examination should include but not necessarily be limited to the evaluation of head, eye, ear, nose, and throat and include cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified during screening should be recorded on the General Medical History and Baseline Conditions eCRF. Subsequently, a targeted (i.e., musculoskeletal, dermatological) and/or symptom-driven examination should be conducted as noted in the schedule of assessments or as clinically indicated. New or worsened abnormalities from screening should be recorded as adverse events, if appropriate.

4.5.4 Vital Signs

Vital signs will include measurement of heart and respiratory rate, temperature, systolic and diastolic blood pressure, height, and weight and should be recorded before study drug administration. Frequency of vital sign assessments should follow the schedule of assessments but may also be taken anytime as unscheduled assessments as judged by the investigator.

4.5.5 Laboratory, Biomarker, and Other Biological Samples

Local laboratory assessments will be performed as indicated on the schedule of assessments. On days of study drug administration, laboratory samples should be drawn before the administration of study drug. Laboratory assessments will include the following:

- Hematology (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells], mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width)
- Serum chemistries (sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, and uric acid)
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and again within 7 days prior to the first dose of emicizumab, if applicable.

  Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.
- *In patients who receive bypassing agents, the following local laboratory tests will be performed within 24–48 hours of initial bypassing agent use so the investigator may monitor for potential thromboembolic events and thrombotic microangiopathy:*

  Platelet count

  Serum creatinine

  LDH

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Peripheral blood smear analysis to evaluate for schistocytes

A plasma sample should also be provided for local (first aliquot) and central (second aliquot) laboratory monitoring of:

Prothrombin fragment 1+2

Fibrinogen

D-dimer

If the test for prothrombin fragment 1+2 is not available at the site, the sample should be sent to the local reference laboratory, if available and if the results from the local reference laboratory can be obtained within a reasonable timeframe to allow for decision-making.

For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents administered to treat a given bleed.

If applicable, laboratory results should be recorded in the unscheduled visit eCRFs.

The following samples will be sent to the Sponsor or a designee for centralized analysis:

- Plasma samples for PK analysis
- Plasma samples for immunogenicity assessment
- Samples to detect anti-emicizumab antibodies will be collected prior to emicizumab administration, as indicated in the schedule of assessments (see Appendix 1), but only samples from the following visits will be analyzed:

  Arms A, C, and D

  Immediately prior to the injection *on Week* 1*, Week 5, Week 13, Week 21, Week 33, Week 41, Week* 49

  Every 12 weeks starting from Week 61

  At the 24-week, post-emicizumab safety follow-up visit

  Arm B

  Immediately prior to the injection every 8 weeks from Weeks 25–73

  Every 12 weeks starting from Week 85

  At study termination

  At the 24-week, post-emicizumab safety follow-up visit following initiation of emicizumab

  If any of these samples are positive and/or if there is suboptimal clinical response or low PK exposure, the remaining collected samples may be analyzed for anti-emicizumab antibodies. Anti-emicizumab antibodies may also be drawn at the time of hypersensitivity events.
- Plasma samples for FVIII inhibitor assessments

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- Plasma for PD and exploratory PD biomarker assessments (aPTT, PT, FVIII activity, thrombin generation, FIX:Ag, FX:Ag, and others as listed in Appendix 2)

  PD biomarker samples will be collected at every visit (including at Screening and Week 1), as indicated in the schedule of assessments (see Appendix 1).

In certain instances, blood draws may be performed by an MN professional.

4.5.6 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of assessments (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The following parameters will be obtained (and reported by the instrument): QT, RR, HR, QTcB, QTcF, PR and QRS, and T- and U-wave morphology. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should ideally not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

Any ECG changes that are associated with symptoms or lead to a change in study treatment or concomitant treatment, or discontinuation from study treatment, must be reported as an adverse event on the adverse event eCRF. The investigator or designee must review, sign, and date all ECG tracings. The ECG may be repeated if investigator deems it appropriate. Paper copies will be kept as part of the patient's permanent study file at the site.

4.5.7 Patient-Reported Outcomes

To capture bleed and hemophilia medication use data, as well as HRQoL*, health status, and* data *related to the number of missed days of school or work* during study treatment, patients will complete the questionnaires on an electronic, handheld device that will be provided to them during their Week 1 visit at the site. The electronic, handheld device and instructions for completing the questionnaires will be provided by the investigator staff. After bleed, medication, health status, or HRQoL entries have been saved, the data will be transmitted automatically from the device to a centralized, vendor database. Bleed and medication use data since the patient's previous clinic visit will be reviewed at subsequent clinic visits, as per the schedule of assessments, for completeness and accuracy. *In extenuating circumstances where patients/caregivers are unable to enter these data into the electronic, handheld device, sites may utilize an emergency back-up*

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data entry system to record bleed and medication use on their behalf. However, this may only occur after first confirming the data's veracity with patients/caregivers.

HRQoL:

The Haem-A-QoL and the Haemo-QoL-SF will be used to measure HRQoL in adults and adolescents, respectively (see Appendix 3 and Appendix 4).

The Haem-A-QoL was designed for adult patients with hemophilia. It consists of 46 items comprising 10 dimensions (physical health, feelings, view, sport and leisure time, work and school, dealing, treatment, future, family planning, and relationships/partners) and a scale representing total score. Items are rated along 5 response options, although for some items there is also a 'not applicable' option (von Mackensen and Gringeri 2005; 2010).

The Haemo-QoL has been developed in a series of age-related questionnaires to measure HRQoL in children and adolescents with hemophilia (Bullinger et al. 2002; von Mackensen and Bullinger 2004; Pollak et al. 2006). These versions include a 77-item long form, a 35-item short form, and an 8-item index form. The short version of the Haemo-QoL was also developed: long versions for three age groups contain 21–77 items and cover 8–12 dimensions of quality of life (QOL). Furthermore, two age-specific short form measures containing 16 and 35 items were developed. The short version for older children (8–16 years) containing 35 items was selected for this study. This version contains 35 items, which cover nine dimensions considered relevant for the children's HRQoL (physical health, feelings, view of yourself, family, friends, other people, sports and school, dealing with hemophilia and treatment). Items are rated with five respective response options: never, seldom, sometimes, often, and always.

Health Status:

The EQ-5D-5L (see Appendix 5) is a generic, preference-based health utility measure that assesses health status and is used to inform pharmacoeconomic evaluations. The EQ-5D-5L consists of two parts. The first part, health state classification, contains five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman et al. 2011; Janssen et al. 2013). Published weights are available that allow for the creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The second part is a 0 to 100-point visual analog scale (VAS), which assesses current health status; higher scores are reflective of better health.

Missed Days of School or Work:

Patients will also be asked to document the number of days of school or work missed in the previous 4 weeks at the timepoints outlined in the schedule of assessments (see Appendix 1).

[no notes on this page]

4.5.8 Bleed Definitions

DEFINITION OF A BLEED

For the purposes of the efficacy analyses, a standardized definition of bleed, adapted from standard criteria defined by the Subcommittee on Standards and Criteria, FVIII/FIX subcommittee of the International Society of Thrombosis and Hemostasis and similar to that used in a recent clinical study, will be utilized in this study (Blanchette et al. 2014; Mahlangu et al. 2014).

- An event is considered a bleed if coagulation factors are administered to treat signs or symptoms of bleeding (e.g., pain, swelling, etc.).
- Bleeds starting from the first sign of bleed and ending 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections are ≤72 hours apart, are considered the same bleed.
- Any injection to treat the bleed, taken >72 hours after the preceding injection, is considered the first injection to treat a new bleed at the same location.
- Any bleed at a different location is considered a separate bleed regardless of time from last injection.

An additional definition of all bleeds (i.e., both treated and not treated with coagulation factors) will be applied for certain secondary efficacy analyses.

DEFINITION OF A TARGET JOINT

- A major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (frequency of ≥3 bleeds into the same joint over the last 24 weeks prior to study entry)

BLEED SITES

- Joint bleeds, which are defined as having an unusual sensation (“aura”) in the joint in combination with any of the following:

  Increasing swelling or warmth of the skin over the joint

  Increasing pain

  Progressive loss of range of motion or difficulty in using the limb as compared with baseline
- Muscle bleeds (sites as per the Bleed/Medication Questionnaire)
- Other bleeds (sites as per the Bleed/Medication Questionnaire)

[no notes on this page]

DEFINITIONS OF BLEED TYPES

In addition, the assessment of a bleed will be separated into spontaneous bleeds, traumatic bleeds and bleeds related to procedure/surgery. Both spontaneous bleeds (i.e., the occurrence of hemorrhage where neither the patient nor a caregiver can identify a reason) and traumatic bleeds (i.e., hemorrhage occurring secondary to an event such as trauma, "strenuous" activity, or "overuse") will be collected.

- Spontaneous bleeds: Bleeds will be classified as spontaneous if a patient records a bleed when there is no known contributing factor such as definite trauma, antecedent "strenuous" activity, "overuse," or procedure/surgery. The determination of what constitutes "strenuous" or "overuse" will be at the discretion of the patient. For example, light jogging may be considered "non-strenuous" while sprinting may be considered "strenuous," lifting of weights for a short period of time may be considered "moderate use" while repetitive weightlifting may be considered "overuse."
- Traumatic bleeds: Bleeds should be classified as traumatic if a patient records a bleed when there is a known or believed reason for the bleed. For example, if a patient were to exercise "strenuously" and then have a bleed in the absence of any obvious injury, the bleed would be recorded as a traumatic bleed because, although no injury occurred, there was antecedent "strenuous" activity. Bleeds with preceding injuries would certainly be classified as traumatic.
- Bleeds related to procedure/surgery: such as hematomas resulting from any surgeries or invasive procedures (e.g., tooth extractions, venipuncture, or SC drug administrations) or invasive diagnostic procedures (e.g., lumbar puncture, arterial blood gas determination, or any endoscopy with biopsy, etc.) would not be counted as bleeds but will be collected on the Bleed/Medication Questionnaire. Bleeds related to procedure/surgery are not associated with any trauma except procedure/surgery-induced trauma.

Patients (or patient's legally authorized representative) will complete the Bleed/Medication Questionnaire when bleeds or medication use occur and also on at least a weekly basis to confirm whether or not they had a bleed or used any medications to treat their hemophilia, including emicizumab. If they have had a bleed, they are to answer questions on the above topics as well as medication they took to treat the bleed.

4.5.9 Samples for Roche Clinical Repository

4.5.9.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

[no notes on this page]

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (see Section 4.5.9) will not be applicable at that site.

4.5.9.3 Sample Collection

The following sample will be collected for research purposes, including but not limited to research on genetic (inherited) biomarkers related to emicizumab, hemophilia A, or other coagulation disorders:

- Whole blood for DNA extraction (at Week 1, 2, or any other visit)

For this sample, the date of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.9.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, the whole blood sample is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of

[no notes on this page]

these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.9.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient or patient guardian the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.9.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical

Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. A patient's withdrawal from Study BH29884 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study BH29884.

4.5.9.7 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient's inability or unwillingness to comply with protocol requirements
- Non-compliance despite appropriate education measures taken by the clinical site

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn.

4.6.2 Study Treatment Discontinuation

Patients must stop study treatment if they experience the following:

- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be

replaced. Patients who become pregnant should immediately stop treatment and be managed as per local guidelines.

If the patient discontinues study treatment, bleed, hemophilia medication, health-related quality of life, health status, and missed days of school or work should be recorded by the patient on the electronic, handheld device until the safety follow-up visit (i.e., 24 weeks after the last study drug administration).

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

- Incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence (e.g., Bleed/Medication Questionnaire data not checked by investigator/co-investigator for >8 weeks)
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Emicizumab is not approved and is currently in clinical development. Thus, the complete safety profile is not known at this time. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

5.1.1 Patient Selection

The inclusion and exclusion criteria in this study are designed to select patients who are not at increased risk based on the current understanding of the investigational medication. See Section 4.1.1, Section 4.1.2 for full inclusion and exclusion criteria, respectively.

[no notes on this page]

5.1.2 Risks Associated with Emicizumab

5.1.2.1 Injection-Site Reactions

In the completed and ongoing Japanese studies, injection-site reactions have been observed in some patients with hemophilia A. These local injection-site reactions included injection-site erythema, injection-site hematoma, injection-site rash, injection-site discomfort, *injection-site pain,* and injection-site pruritus. All local injection-site reactions were of mild intensity. Further details of the observed injection-site reactions are available in the Investigator's Brochure.

Directions for emicizumab administration should be followed, as outlined in Section 3.3.1, Section 4.3.1.2, and in the IFU. *This includes alternating the site of injection, from one injection to the next, in the recommended injection-site locations listed in the IFU.*

5.1.2.2 Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid Reaction

Because emicizumab is a biological product, acute, systemic hypersensitivity reactions, including anaphylaxis and anaphylactic reactions, may occur. In completed and ongoing clinical studies of emicizumab, no severe hypersensitivity reactions have been reported. These events should be reported as Serious Adverse Events or Adverse Events of Special Interest as described in Section 5.2.3.

HCPs administering the study medication in the clinic must be trained in the appropriate administration procedures, be able to recognize the signs and symptoms associated with potential hypersensitivity, anaphylactic, and anaphylactoid reactions, and should be familiar with Sampson's criteria for defining anaphylaxis (Sampson et al. 2006; see Appendix 7). HCPs should also instruct patients how to recognize the signs and symptoms of hypersensitivity, anaphylactic, and anaphylactoid reactions and to contact an HCP or seek emergency care in case of any such occurrence. Patients/caregivers will also receive two alert cards to remind them of this information and these instructions should any of these reactions occur.

For patients with a previous history of a clinically significant hypersensitivity reaction, after each of the first three doses, the site will call the patient 24 hours after each dose to assess the status of the patient. Additional precautions following each of these doses may also be considered including having an extended observation period or IV access prior to dosing, etc. The investigator may include these or other precautions, as deemed appropriate.

5.1.2.3 Hypercoagulation and Thromboembolic Events

As of November 2016, there have *been 2 thromboembolic events reported* in *2 patients with hemophilia A with inhibitors while receiving emicizumab in Study BH29884.* [redacted]

[no notes on this page]

[redacted]

These events should be reported as Serious Adverse Events or Adverse Events of Special Interest as described in Section 5.2.3. HCPs should educate patients/caregivers to recognize signs and symptoms of potential thromboembolism (i.e., dyspnea, chest pain, leg pain or swelling*; or if in the head, headache, numbness in the face, eye pain or swelling, or vision impairment)* and ensure that they understand the importance of seeking appropriate medical attention. Patients/caregivers will also receive two alert cards to remind them of this information and these instructions should thromboembolism be suspected.

5.1.2.4 *Thrombotic Microangiopathy*

Thrombotic microangiopathy is used to describe a group of disorders with clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage that can include the kidneys, gastrointestinal system, or central nervous system, etc. As of November 2016, 2 cases of TMA, diagnosed as aHUS, were observed in Study BH29884 involving patients receiving emicizumab. [redacted]

[redacted] *Any TMA event should be reported as an adverse event of special interest and also as a serious adverse event, if it meets criteria for such (see Sections 5.2.2 and 5.2.3).*

[no notes on this page]

5.1.3 Management of Specific Adverse Events

Table 2 Guidelines for Management of Specific Adverse Events

Event	Actions to Be Taken
Injection-Site Reaction	• Injection-site reactions should be treated as clinically indicated. • Emicizumab should not be injected into areas where the skin is red, bruised, tender, or hard or into areas where there are moles or scars. • In the clinic setting, patients will be monitored for signs of injection-site reactions in the period immediately following injections. Patients will be given guidance on reporting injection-site reactions when administering drug at home or after they leave the clinic.
Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid Reaction	• Suspected cases should be fully evaluated and treated as clinically indicated. • Medicinal products for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, and glucocorticoids) and resuscitation equipment must be available for immediate use during the initial administrations in the infusion center, clinic, or hospital. • If a patient has symptoms of anaphylaxis or severe hypersensitivity, administration of study drug must be immediately stopped and treatment of the reaction be initiated. • The investigator should contact the Medical Monitor to assess if the clinical benefit clearly outweighs the risk to determine if and when the patient should resume taking emicizumab and discuss the patient's continued study participation. If patient continues in the study, the next two scheduled doses must be in a monitored setting with at least a 60-minute observation period and resuscitation treatment immediately available. After each of these two doses in the clinic, the site will call the patient 24 hours after each dose to assess status of the patient. • Investigators may order any pertinent laboratory tests, including an unscheduled anti-drug antibody, in the event any of these reactions occur.
Hypercoagulation and Thromboembolic Events	• *Please see Sections 3.1 and 3.3.3 for guidance on management of breakthrough bleeds, including required laboratory monitoring.* • HCPs should be vigilant for patients who exhibit signs/symptoms consistent with thromboembolic events and immediately begin work-up and treatment, as per local guidelines. • If a patient has a thromboembolic event, administration of study drug should be *interrupted. The decision to resume emicizumab after a thromboembolic event must be discussed with and approved by the Medical Monitor.*

HCP = healthcare provider; *TMA = thrombotic microangiopathy.*

[no notes on this page]

Table 2 Guidelines for Management of Specific Adverse Events (cont.)

Event	Actions to Be Taken
Thrombotic microangiopathy	• *Please see Sections 3.1 and 3.3.3 for guidance on management of breakthrough bleeds, including required laboratory monitoring.* • *HCPs should be vigilant for patients who exhibit signs/symptoms consistent with TMA and immediately begin work-up and treatment, as per local guidelines.* • *If a patient has a TMA event, further administration of study drug should be interrupted. The decision to resume emicizumab after an event of TMA must be discussed with and approved by the Medical Monitor.*
Coagulation Disorder and Risk of Bleeding	• HCPs should be vigilant for abnormal or unusual bleeding tendencies. Coagulation tests or other work-up may be indicated if judged to be appropriate by the investigator. If bleeding is observed, appropriate action as per local guidelines must be taken immediately.

HCP = healthcare provider; *TMA = thrombotic microangiopathy.*

5.1.4 *Interpretation of Coagulation Assays for Patients Receiving Emicizumab*

Emicizumab interacts with standard laboratory assays used in the management of patients with hemophilia A. In one-stage assays, emicizumab is associated with a supra-physiologically short time to clot formation and thus normalization of aPTT at subtherapeutic levels and an overestimation of true FVIII activity. Emicizumab is not recognized or neutralized by FVIII inhibitors and, therefore, cannot be detected by a functional test such as Bethesda or Nijmegen-Bethesda assays, which use a one-stage clotting-based readout. Emicizumab activity cannot be detected by chromogenic assays using purified bovine coagulation proteins and can only be detected using an assay composed of human proteins. See the RO5543262 [Emicizumab] Investigator's Brochure for additional details on which tests can be used and how the test results can be interpreted.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

[no notes on this page]

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

Bleeds considered as serious adverse events should be reported *on the appropriate* adverse event eCRF *page, regardless of whether* the *bleeds are consistent with patients' pre-study disease state (the* bleed *will remain recorded as well on the Bleed*/Medication Questionnaire). New, non-serious bleeds consistent with patients' pre-study disease state will not be considered adverse events and will not be recorded on the eCRF but *will* be captured on the Bleed/Medication Questionnaire.

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug

[no notes on this page]

- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as Grade 1–4, according to the World Health Organization [WHO] Toxicity Grading Scale for Determining The Severity of Adverse Events criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). *These may include suspected or confirmed cases.* Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Systemic hypersensitivity reactions and anaphylactic and anaphylactoid reactions (see Sampson's Criteria in Appendix 7)
- Thromboembolic events
- *Microangiopathic hemolytic anemia or thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura, hemolytic uremic syndrome)*

[no notes on this page]

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to randomization (randomized arms) or initiation of study drug (non-randomized arms)**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After randomization (randomized arms) or initiation of study drug (non-randomized arms), all adverse events will be reported until the patient completes his or her last study visit. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The WHO toxicity grading scale (see Appendix 6) will be used for assessing adverse event severity (WHO 2003). Table 3 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

[no notes on this page]

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (<48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Notes: Developed by the Division of Microbiology and Infectious Diseases.
Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection-Site Reactions

*Local a*dverse events that occur within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as an "injection-*site* reaction" on the Adverse Event eCRF. Associated signs and symptoms (e.g., injection-site erythema or injection-site rash) should be recorded on the dedicated Injection-Site Reaction eCRF. *If a patient experiences both a local and systemic reaction to the same administration of study drug, each reaction should* be recorded separately on the Adverse Event eCRF. *Only for local injection-site reactions should t*he dedicated Injection-Site Reaction eCRF be used to capture the individual signs/symptoms.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events, other than injection-site reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should

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be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$baseline value) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event *of special interest* the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ULN (of which $\geq$35% is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice *in the absence of cholestasis or other causes of hyperbilirubinemia*

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of

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the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of hemophilia.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of hemophilia, "hemophilia progression" should be recorded on the Adverse Event eCRF.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Hemophilic Bleeds

Medical occurrences or symptoms of deterioration that are anticipated as part of hemophilia should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in terms of severity (e.g., increased number of doses of bypassing agents to stop bleeds with emicizumab, in the absence of neutralizing anti-emicizumab antibodies, compared with before study entry), frequency of bleeds, or nature of hemophilia at any time during the study. Should any of these occur (according to the investigator's clinical assessment), they should be documented as an adverse

event on the Adverse Event eCRF, conveying that the underlying condition has changed by including applicable descriptors (e.g., "increased clinical severity of hemophilia").

Events that are clearly consistent with the *anticipated* pattern of the underlying disease *and do not indicate an unexpected worsening in severity or frequency* should not be recorded as adverse events. These data will be reflected in efficacy assessment data only.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for drug administration)
- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing or drug administration error of emicizumab are available, as no such instances have been observed to date. To minimize the risk of errors associated with future home administration of emicizumab, data related to

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medication errors with observed patient/caregiver administration of emicizumab during the first 5 weeks at the site by the investigator and/or clinical staff will be recorded and corrected at the time of occurrence. In addition, the recording of medication and handling errors associated with home administration, as well as drug compliance, will be collected at each clinic visit.

5.3.5.13 Patient-Reported Outcome Data

The patient-reported outcome measurements are described in Section 4.5.7. The methods for collecting and analyzing such data are different from those for the ascertainment of observed or volunteered adverse events. However, if any patient-reported responses suggestive of a possible adverse event are identified during site review of the patient-reported data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF. The patient-reported data will be presented in separate tables, figures, and data listings from the adverse event data, and will be included in the appropriate section of the final study report.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

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5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D., M.Phil. (primary)

Telephone No.: [redacted]

Medical Monitor: [redacted], M.D. (secondary)

Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Randomization or Study Drug Initiation

After informed consent has been obtained but prior to randomization (randomized arms) or initiation of study drug (non-randomized arms), only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators.

5.4.2.2 Events That Occur after Randomization or Study Drug Initiation

After randomization (randomized arms) or initiation of study drug (non-randomized arms), serious adverse events and non-serious adverse events of special interest will be reported until the last scheduled study visit (see Section 5.6). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

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5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 24 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Although embryo-fetal development studies are not available, condom use will not be required in male patients enrolled in the study because the margin between the minimal anticipated biological effect level (MABEL) plasma concentration (7 ng/mL) and the estimated maternal C_{max} (at both 1.5 and 3 mg/kg/week dosing regimens) is greater than 10-fold (Banholzer et al. 2012). At this time, very little emicizumab is thought to transfer into semen, and there are no known reproductive risks to female partners of male patients treated with emicizumab. Therefore, contraception use by male patients and proactive collection of pregnancy information for female partners of male patients treated with emicizumab will not be required during the study.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

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5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. *At the time of pregnancy outcome, reporting instructions provided in Section 5.4.3.1 should be followed.*

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 24 weeks after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and e-mailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or e-mail address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest (see Section 5.2.3) against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

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To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- RO5534262 (Emicizumab) Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

The sample size for this study is based on clinical rather than statistical considerations, taking into account the limited number of patients with hemophilia A with inhibitors available for participation in clinical studies and in an effort to collect sufficient data to assess the safety and efficacy of emicizumab.

The sample size calculation is based on the evaluation of the primary efficacy endpoint, defined as the number of bleeds over time (i.e., bleed rate) with emicizumab (treatment group, λ_t) versus no prophylaxis (control group, λ_c), which are said to follow a negative binomial (NB) distribution with γ_t and γ_c described as shape parameters for treatment and control groups, respectively. With consideration of enrollment feasibility, a sample size of 45 patients, assuming an allocation ratio of 2:1 (30 patients in treatment group and 15 patients in control group), will achieve a power of more than 95% for λ_t and λ_c ranging from 1 to 4 and 18 to 30, respectively (see Table 4). Here, the patients from the two groups are followed up to 0.5 units of time (i.e., 24 weeks). Of note, assuming $\lambda_c = 18$ and $\lambda_t = 4$ results in an expected ABR reduction of 78% in the treatment versus control groups. Sample size calculations were performed with East®, Version 6 (Cytel, Cambridge, MA), which allows specific shape parameters for both the treatment and control groups.

However, the above approach to sample size calculation assumes similar follow-up for each patient. Because this is unlikely to be seen in the study, power was also estimated by simulation to account for different follow-up times among patients. Conducting simulations on the basis of a NB regression model including an offset variable to account for variable follow-up times, with all other assumptions remaining the same as previously described, the sample size is projected to have greater than 95% power at the 2-sided 0.05 level of significance.

The analysis will include all enrolled patients, regardless of their length of follow-up. Therefore, to ensure the analysis is based on sufficient follow-up data and with 2:1 treatment to control randomization, approximately 34 patients in the randomized

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emicizumab treatment arm and 17 patients in the control arm (approximately 51 patients in total) will be enrolled.

During the study, a re-assessment of the initially specified sample size based on aggregated (not by treatment arm) data to date (and potentially from the non-interventional study [Study BH29768] findings) may be performed. This may result in an increase in sample size, if necessary, to maintain adequate power without affecting the type 1 error rate. Study integrity will be upheld, as access to information via aggregated analyses and their results will be minimized to limit operational bias.

Table 4 Power Calculations

Rate for Control Treatment Arm (λ_c, $n_c=15$)	**Rate for Experimental Treatment Arm** (λ_t, $n_t=30$)			
	1 ($\gamma_t=0.11$)	2 ($\gamma_t=0.22$)	3 ($\gamma_t=0.33$)	4 ($\gamma_t=0.44$)
18 ($\gamma_c=2$)	**1** ($\lambda_t / \lambda_c=0.056$)	**0.999** ($\lambda_t / \lambda_c=0.111$)	**0.99** ($\lambda_t / \lambda_c=0.167$)	**0.952** ($\lambda_t / \lambda_c=0.222$)
25 ($\gamma_c=2.78$)	**1** ($\lambda_t / \lambda_c=0.04$)	**1** ($\lambda_t / \lambda_c=0.08$)	**0.994** ($\lambda_t / \lambda_c=0.12$)	**0.973** ($\lambda_t / \lambda_c=0.16$)
30 ($\gamma_c=.33$)	**1** ($\lambda_t / \lambda_c=0.033$)	**0.999** ($\lambda_t / \lambda_c=0.067$)	**0.995** ($\lambda_t / \lambda_c=0.1$)	**0.978** ($\lambda_t / \lambda_c=0.133$)

6.2 GENERAL

This section provides a general overview of the methods. If any of the items require a unique approach that differs from the general overview, then it will be noted in the appropriate section.

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum, and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

All summary tables will be structured with a column for each treatment arm and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

Analyses will follow the principle of intention-to-treat (i.e., based on randomized population).

6.3 SUMMARIES OF CONDUCT OF STUDY

Flow of patients through the study will be displayed in a 'CONSORT' diagram. A clear account of all patients who entered the study, who were enrolled and randomized, and who entered and completed each phase of the study will be displayed. In addition,

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reasons for premature discontinuations from study treatment and reasons for withdrawing from the study (e.g., during follow-up) will be described.

Variables from the eCRF used to establish how many patients reached the various stages of the study, how many dropped out and for what reasons will be described in the Statistical Analysis Plan (SAP).

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Comparisons between the treatment arms of demographic data and baseline characteristics will be conducted to establish if any observed differences between the treatment arms are not due to imbalances in patient characteristics at baseline. Only descriptive analyses are planned, and no formal statistical tests will be applied.

6.5 EFFICACY ANALYSES

The primary and secondary efficacy analyses to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis will include all randomized patients, with patients grouped according to the treatment assigned at randomization. For patients previously treated with prophylactic bypassing agents in Arm C and episodic *or prophylactic* bypassing agents in Arm D, the efficacy analyses will include all enrolled patients.

6.5.1 Primary Efficacy Endpoint

The primary efficacy objective is to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis on the number of bleeds over time. The definition of a bleed is described in Section 4.5.8, with the primary endpoint comparing bleeds requiring treatment.

The primary efficacy analysis will be conducted after all randomized patients have completed 24 weeks in the study or the last randomized patient who has not completed 24 weeks in the study discontinues study participation, whichever occurs first, and using an intent-to-treat principle. The comparison of the number of bleeds over time between the randomized treatment arms will be performed using a NB regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study included as an offset in the model. The model also includes the number of bleeds (<9 or ≥ 9) in the last 24 weeks prior to study entry as a stratification factor in the randomization. This analytic model estimates the rate ratio, λ_t/λ_c., which quantifies the risk of bleeding associated with prophylactic emicizumab (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level, and the estimated risk ratio is compared with 1, assuming the following statistical hypothesis:

H_0 (null hypothesis): Rate Ratio $= 1$ versus H_1 (alternative hypothesis): Rate Ratio $\neq 1$.

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The treatment effect therein is based on a contrast statement in the model with use of the SAS GENMOD procedure. Statistical significance at the pre-specified alpha level will be based on a Wald testing procedure. Bleed rates for prophylactic emicizumab and no prophylaxis and the rate ratio will be presented and include 95% confidence intervals.

The number of bleeds can also be annualized for each patient using the following formula: ABR = (Number of bleeds during the efficacy period/Total number of days during the efficacy period) × 365.25. If the NB model converges, an analysis of variance (ANOVA) to compare the mean ABR between the randomized arms will be provided only as a sensitivity analysis. However, if the convergence of the NB model is not achieved or is questionable, the primary efficacy analysis will be based on the *Van Elteren Test* of ABR.

Although this is an open-label study, Sponsor personnel will not have access to efficacy summaries by treatment arms prior to the formal reporting of the study results.

A detailed description of the statistical methods that will be used for the primary and secondary efficacy analyses will be provided in the SAP.

6.5.2 Secondary Efficacy Endpoints

The number of all bleeds (i.e., those treated and not treated with coagulation factors), *spontaneous bleeds, joint bleeds, and target joint bleeds* over time in patients who receive prophylactic emicizumab compared with no prophylaxis will be *evaluated by the NB regression model,* as *specified for the primary* efficacy endpoint. Also, the number of treated bleeds and all bleeds over time will be compared with patients' bleed rate prior to study entry.

HRQoL (using the Haem-A-QoL or the Haemo-QoL-SF) and health status (using the EQ-5D-5L) will be assessed on a regular basis, as per the schedule of assessments (scheduled). Health status will also be assessed in the event of a bleed (unscheduled).

Adherence with the HRQoL and health status measures will be summarized.

Because different HRQoL measures (Haem-A-QoL and the Haemo-QoL-SF) are being used for the adult and adolescent patients, all calculations and analyses will be conducted separately for adults and adolescents. Scale scores for the Haem-A-QoL and Haemo-QoL-SF will be calculated and summarized descriptively. The HRQoL scale scores for all patients will be evaluated at 24 weeks in the study, a timepoint that is consistent with other recent registrational studies in hemophilia (Lentz et al. 2013; Powell et al. 2013; Mahlangu et al. 2014) and analyses of such data (Santagostino et al. 2014; Wyrwich et al. 2015). For each treatment arm, paired t-tests will be used to compare the 24-week with the baseline scale scores for each HRQoL measure. Within-subject and between-group changes from baseline on the different HRQoL scale scores will also be calculated at 24 weeks.

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For the assessments of the EQ-5D-5L performed every 4 weeks, the number and percentage of patients in each of the five categories for each question for each group will be assessed. Changes in the EQ-5D-5L index utility score from baseline will also be compared between groups. In addition, summary statistics including mean, standard deviation, median, minimum and maximum will be displayed for the patients' health state using the EQ-VAS both within and between groups. The proportion of patients who report changes in each group exceeding the clinically meaningful threshold on the EQ-5D-5L index and EQ-VAS scores in each group will be reported at 24 weeks.

Separately, for each EQ-5D-5L completed in connection with a bleed, the level of pain associated with that episode, as well as the utility score and general health score will be reported.

Secondary endpoints used for labeling and those that are solely for scientific interest will be specified in the SAP. The method used for controlling the type 1 error rate will also be described.

6.5.3 Exploratory Efficacy Analysis

Summary statistics of the number of work/school days missed and days hospitalized will be presented by treatment arm.

6.6 SAFETY ANALYSES

The safety analyses population will be based on all enrolled patients grouped according to the actual treatment received. Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology, including complete blood count with differential), ECGs, vital signs, and antibodies to emicizumab.

To evaluate the overall safety of prophylactic emicizumab compared with no prophylaxis, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade for each treatment arm.

For clinical laboratory data, summary statistics will be presented by treatment arm. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

Data on the impact of immunogenicity (anti-emicizumab antibodies) on safety, efficacy, and/or clinical pharmacology and PK will be summarized using standard language/terminology (Shankar et al. 2014).

Although this is an open-label study, Sponsor personnel will not have access to safety summaries by treatment arm prior to the formal reporting of the study results. HCPs at participating study sites, as well as the Sponsor's drug safety and medical monitoring

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staff, will have access to the treatment assignments of patients for safety monitoring purposes only.

The iDMC (see Section 9.4.2) will evaluate safety at periodic safety reviews and recommend to the Sponsor whether the study should be *modified or* stopped early. All summaries and analyses will be prepared by the independent Data Coordinating Center (iDCC) and presented by treatment arm for the iDMC's review. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

6.7 PHARMACOKINETIC ANALYSES

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will be used to analyze the dose-concentration-time data of emicizumab following SC administration. Population PK parameters, such as clearance and volume of distribution, will be estimated, and the influence of various covariates, such as age, gender, and body weight, on these parameters will be investigated graphically. Secondary PK parameters, such as area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies. These analyses will be reported in a dedicated report.

6.8 EXPLORATORY BIOMARKER ANALYSES

PD parameters (e.g., aPTT, parameters derived from thrombin generation, FVIII activity) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patient-reported data will be collected with use of electronic, handheld devices provided by a vendor. In case the electronic, handheld device is not available, paper questionnaires may be used. The electronic, handheld device is designed for entry of data in a way that is attributable, secure, and accurate and in compliance with FDA regulations for electronic records (21 Code of Federal Regulations, Part 11). The data will be transmitted electronically in real-time to a centralized database. The data from the bleed/medication, HRQoL, and health status questionnaires are available for view access only via secure access to a Web portal provided by the vendor. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. Regular data transfers will occur from the centralized database at the vendor to the database at the Sponsor. The Sponsor will receive all data entered by patients on the electronic, handheld devices*, by sites via an emergency back-up data entry system with agreement from patients,* and all relevant study documentation.

Once the study is complete, the data, audit trail, and study and system documentation will be archived. The investigator will receive data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

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Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic patient-reported outcome data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and additional local regulatory requirements.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Adolescent's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

Patients who are declared legally incompetent or who are physically or mentally incapable of providing informed consent but otherwise meet the qualifications for participation in Study BH29884 will be included, as emicizumab prophylaxis may directly benefit this population with high unmet medical need. In such cases, investigators will obtain informed consent from a guardian or legally authorized representative of the patient in accordance with applicable law. In addition, the investigator must also obtain the assent of the patient when they are able to give assent to decisions made on their behalf. Any indication on the part of the patient that they are not willing to participate in the study will be honored.

In cases where there is reason to question the competence of a patient who has not been declared incompetent (e.g., a patient in the early stages of Alzheimer's disease), a patient advocate will be involved in the consent process and throughout the duration of the patient's participation in the study.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal

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Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This global study will enroll approximately 81–101 patients in Arms A, B, and C, as well as additional patients in Arm D.

Randomization and drug assignment will be performed by an IxRS, which will also manage emicizumab inventory for all sites globally.

Patient-reported outcomes will be captured electronically using a device provided by a third-party vendor for all patients globally.

Central laboratories will be used for a subset of laboratory assessments specified in Section 4.5.5.

9.4.1 Steering Committee

A Steering Committee, consisting of medical experts in the field of bleeding disorders who collectively have the scientific, medical, and clinical study management experience to evaluate and provide guidance on the conduct of clinical studies, will monitor and supervise the progress of the study towards meeting its objectives (e.g., provide input on scientific decisions, propose solutions for overcoming operational challenges, and consider modifications to the protocol). The policies and procedures will be detailed in a separate Steering Committee Charter document.

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9.4.2 Independent Data Monitoring Committee and Independent Data Coordinating Center

An iDMC will be assembled to review the safety and efficacy data collected during the study. The iDMC members will consist of, at minimum, independent hemostasis/thrombosis experts and a statistician, none of whom will be otherwise involved in the conduct of study. All analyses for review by the iDMC will be prepared by an iDCC that is independent of the Sponsor. At the beginning of the study, intensive monitoring and analysis of all significant safety events will be performed. Analyses of safety events will be conducted after the first 9 randomized patients have completed 8 weeks in the study and again after the first 18 randomized patients have completed 12 weeks in the study. Thereafter, the iDMC will meet at a frequency determined by the iDMC and the Sponsor according to the emerging safety profile.

An iDCC will perform unblinded analyses and provide tables and listings to support the iDMC reviews of safety data. The safety data will include demographic data, adverse events, serious adverse events, and laboratory abnormalities (coagulation, hematology, and chemistry). Further information will be given on request.

Following each meeting, the iDMC will recommend to the Sponsor whether the study should continue according to the protocol or may suggest changes to the protocol based on the outcome of the data review. In exceptional cases, the iDMC may recommend stopping the study or closing a treatment arm for safety reasons. The iDMC will monitor the incidence of the anticipated adverse events, as well as the overall safety of patients, during the study.

The meeting schedule and all other iDMC-related activities will be specified in a separate iDMC charter. All results will be confidential and will not be divulged to non-members of the iDMC, including the Sponsor. All closed meetings will be summarized in written minutes available only to iDMC members and the iDCC statistician and kept by the iDCC statistician until the end of the study. The recommendations can be communicated to the Sponsor verbally but have to be confirmed in writing according to a pre-defined timeframe. Strict confidentiality rules will be applied to avoid any dissemination of either safety or efficacy interim results outside the iDMC.

The final decision of acting upon the iDMC's recommendations will rest with the Sponsor. The policies and procedures will be detailed in a separate iDMC Charter document.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the final analysis of the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer

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to the Roche Global Policy on Sharing of Clinical Trials Data at the following Website:
http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical study results within 6 months after the availability of the respective clinical study report. In addition, for all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

Schedule of Assessments–Arms A, C, and D																		
	Screen-ing	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Every 8 Weeks from Wk 33	Wk 49	Every 12 Weeks from Wk 61	At Least Weekly[a]	Study Com-pletion/ ET	Safety F/U Visit [b]
Informed consent [c]	x																	
Inclusion/exclusion criteria	x																	
Medical history and demographics [d]	x																	
Physical examination [e]	x	x				x						x		x			x	x
Vital signs [f]	x	x [f]	x	x	x	x	x	x	x	x	x	x [f]	x	x [f]	x		x [f]	x [f]
Concomitant medications [g]		x				x		x	x	x	x	x	x	x	x		x	x
ECG [h]	x	x [h]				x						x	x [h]				x	
Safety laboratory assessments [i]	x [i]	x	x	x	x	x		x	x	x	x	x	x	x	x		x	x
Anti-FVIII antibodies [j]	x	x					x					x		x	x [j]			x
Anti-emicizumab antibodies [k]		x [k]				x	x	x [k]	x	x [k]	x	x [k]	x [k]	x [k]	x [k]		x	x [k]
Bleed/medication questionnaire [l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Bleed/medication data review [m]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Adverse events [n]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
IMP management [o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
HRQoL [p]		x				x		x	x	x	x	x	x	x	x		x	
Health status (EQ-5D-5L) [q]		x				x		x	x	x	x	x	x	x	x		x	
PK assessment [r]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
PD biomarkers assessment [s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x

[no notes on this page]

Appendix 1
Schedule of Assessments (cont.)

Schedule of Assessments–Arms A, C, and D																		
	Screen-ing	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Every 8 Weeks from Wk 33	Wk 49	Every 12 Weeks from Wk 61	At Least Weekly[a]	Study Com-pletion/ ET	Safety F/U Visit [b]
RCR whole blood DNA sample [t]			x															
Following treatment with bypassing agents [u]		*Monitoring for thromboembolic events and thrombotic microangiopathy.* [u]																

Schedule of Assessments–Arm B									
	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Every 4 Weeks from Wk 9 Until Switch to Emicizumab at Wk 25	At Least Weekly [a]
Informed consent [c]	x								
Inclusion/exclusion criteria	x								
Medical history and demographics [d]	x								
Physical examination [e]	x	x							
Vital signs [f]	x	x [f]				x		x	
Concomitant medications [g]		x				x		x	
ECG [h]	x	x [h]							
Safety laboratory assessments [i]	x [i]	x							
Anti-FVIII antibodies [j]	x								
Bleed/medication questionnaire [l]	x	x	x	x	x	x	x	x	x

[no notes on this page]

Appendix 1
Schedule of Assessments (cont.)

Schedule of Assessments–Arm B									
	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Every 4 Weeks from Wk 9 Until Switch to Emicizumab at Wk 25	At Least Weekly [a]
Bleed/medication data review [m]		x				x		x	
Adverse events [n]		x				x		x	
HRQoL [p]		x				x		x	
Health status (EQ-5D-5L) [q]		x				x		x	
PD biomarkers assessment [s]	x	x							
RCR whole blood DNA sample [t]		x							
Targeted physical examination [e]	x				x				
Vital signs [f]	x [f]	x	x	x	x	x	x	x	x
Concomitant medications [g]	x				x		x	x	x
ECG [h]	x				x				
Safety laboratory assessments [i]	x	x	x	x	x		x	x	x
Anti-FVIII antibodies [j]	x [j]					x			
Anti-emicizumab antibodies [k]	x [k]				x	x	x [k]	x	x [k]
Bleed/medication questionnaire [l]									
Bleed/medication data review [m]	x	*x*	*x*	*x*	x	*x*	x	x	x
Adverse events [n]	x	x	x	x	x	x	x	x	x
IMP management [o]	x	x	x	x	x	x	x	x	x
HRQoL [p]	x				x		x	x	x

[no notes on this page]

Appendix 1
Schedule of Assessments (cont.)

Schedule of Assessments–Arm B																	
	Wk 25	Wk 26	Wk 27	Wk 28	Wk 29	Wk 31	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	Every 8 Weeks from Wk 57	Wk 73	Every 12 Weeks from Wk 85	At Least Weekly[a]	Study Com-pletion/ ET	Safety F/U Visit [b]
Health status (EQ-5D-5L) [q]	x				x		x	x	x	x	x	x	x	x		x	
PK assessment [r]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
PD biomarkers assessment[s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Following treatment with bypassing agents [u]	*Monitoring for thromboembolic events and thrombotic microangiopathy.* [u]																

eCRF = electronic Case Report Form; EQ-5D-5L = EuroQoL Five-Dimension-Five Levels Questionnaire; ET = early termination; F/U = follow-up; FVIII = factor VIII; HRQoL = health-related Quality of Life; IMP = investigational medicinal product, PD = pharmacodynamics; PK = pharmacokinetic; RCR = Roche Clinical Repository; Wk = Week.

Notes: The maximum allowable time between Screening and enrollment is 4 weeks; if the elapsed time between Screening and enrollment is more than 4 weeks, Screening must be repeated. All assessments should be performed within ± 2 days of the scheduled visit for the first 12 weeks, then ± 7 days thereafter; for Arm B patients, emicizumab should be offered at Week 25, after which all assessments should be performed within ± 2 days of the scheduled visit for the first 12 weeks on emicizumab, then ± 7 days thereafter. Except for the Bleed/Medication Questionnaire, HRQoL, and health status, all other patient data will be collected during office visits. On treatment days, pre-injection blood collection should be made 0–120 minutes before the injection.

[a] Patients will complete the Bleed/Medication Questionnaire when they have bleeds or hemophilia medication use, including emicizumab, or at minimum every week.

[b] A safety follow-up visit will occur 24 weeks after discontinuing emicizumab.

[c] Obtain written informed consent (or patient assent and parent written informed consent if patient is an adolescent) before distribution of an electronic, handheld device and collection of any data. Randomization and enrollment form will be completed after informed consent and/or assent is obtained.

[d] Collected from patient medical records and documented in the eCRF, including information on target joint(s).

[e] A complete physical examination will be performed at Screening and targeted physical examinations at visits indicated. Targeted physical examination of joints (for bleeds, evidence of arthropathy) and skin (for bruises, hematomas, and injection-site reactions), in addition to other organ systems should be performed as clinically indicated. If Screening and Week 1 occur on the same date, the physical examination entry may be entered once for the Week 1 visit.

[no notes on this page]

Appendix 1
Schedule of Assessments (cont.)

[f] Body temperature (oral, rectal, axillary, or tympanic), blood pressure, pulse, respiratory rate, and weight will be measured and recorded in the eCRF at each clinic visit prior to any injections (if applicable). Height will be measured and recorded only at Screening and at Weeks 25 and 49 after starting emicizumab. At the investigator's discretion, vital signs may be taken to help monitor for hypersensitivity reactions during or after injections, but they should not be entered into the eCRF. If Screening and Week 1 occur on the same date, the vital signs entry may be entered once for the Week 1 visit.

[g] Concomitant medications (e.g., extra pain medication with bleed) will be asked about at each clinic visit, excluding treatments for bleeds (i.e., bypassing agents and other medications to treat bleeds), which will be collected on the bleed questionnaire. Hemostatic medications to treat or prevent bleeds in the week prior to starting emicizumab will also be collected.

[h] If screening ECG is abnormal, repeat at Week 1 (or Week 2, if Screening and Week 1 occur on the same date). ECGs will also be performed 4–8 and 24 weeks after starting emicizumab or dose up-titration, as well as at study completion/early termination.

[i] Laboratory data (performed locally) include: complete blood count with differential and serum chemistries. Female patients with childbearing potential will be required to have a negative serum pregnancy test result at screening (and again within 7 days prior to the first dose of emicizumab, if applicable) and urine pregnancy tests performed at every clinic visit, with the exception of Weeks 2–4 and 7. If patients undergo up-titration of their dose after ≥ 24 weeks on emicizumab, an additional blood draw for safety laboratory assessments should be performed within the first 4 weeks after up-titration. If Screening and Week 1 occur on the same date, sufficient blood should be drawn to cover the required laboratory tests for both visits (and one entry recorded in the eCRF under Week 1). Safety laboratory assessments completed at Screening visit do not have to be repeated at Week 1 if the period between Screening and Week 1 is ≤5 days and there has been no change in the patient's health status as assessed by the investigator; however, PD biomarker samples should be collected at both visits if Screening and Week 1 occur on different dates.

[j] Anti-FVIII antibodies will be analyzed at Screening; pre-dose after starting emicizumab at Weeks 1, 7, 25, 49, and 73; and at the safety follow-up visit (i.e., 24 weeks after discontinuing emicizumab) at a central laboratory.

[k] Samples to detect anti-emicizumab antibodies will be collected prior to emicizumab administration. Anti-emicizumab antibodies may also be drawn at the time of hypersensitivity events.

[l] Reported by the patient; includes start date and time, reason, type, location, and associated symptoms of any bleed, as well as start date and time, reason, type, and dose of any hemophilia medication use.

[m] At the Week 1 visit, patients will be trained on how to use and be provided their own electronic, handheld device to record their bleeds and hemophilia medication use. Investigator review of patient-reported Bleed/Medication Questionnaire information with the patient/caregiver for completeness and accuracy will occur at visits indicated. Information regarding all traumatic events, even if they do not result in a bleed, is required to be collected in the eCRF.

[n] Injection-site reaction adverse events will be collected on a separate form from the adverse event form. See Section 5.3.5.10 for how to record "increased clinical severity of hemophilia" as an adverse event.

[o] Drug accountability will not be performed at the first visit of emicizumab receipt. Drug dispensation will not occur at the study completion/early termination visit.

[no notes on this page]

[p] Haem-A-QoL questionnaire (age ≥ 18) and Haemo-QoL-Short Form (ages 12–17).

[q] On days that patients report having a new bleed and every 4 weeks, they will be prompted to also complete the EQ-5D-5L questionnaire on the electronic, handheld device.

[r] Emicizumab concentration. Plasma samples for this assessment should be taken prior to injection of study drug.

[s] See Appendix 2 for detailed explanation of PD biomarker assessments (Sets 1 and 2). Blood samples may also be drawn to conduct biomarker assays at the central laboratory on an unscheduled basis (at the clinical judgment of the investigator) at any time. If Screening and Week 1 occur on the same date, sufficient blood should be drawn to cover the required laboratory tests for both visits (and one entry recorded in the eCRF under Week 1); however, baseline PD samples prior to administration of emicizumab (if applicable) must be drawn.

[t] Sample for the RCR is optional and requires an additional signature. This may be collected at Weeks 1 or 2 or at any other visit.

[u] *Following bypassing agent treatment, patients should provide a sample for local laboratory monitoring of thromboembolic events and thrombotic microangiopathy for platelet count, serum creatinine, LDH, and peripheral blood smear analysis for schistocytes within 24–48 hours of initial bypassing agent use. A plasma sample should also be provided for local (first aliquot) and central (second aliquot) laboratory monitoring of fibrinogen, prothrombin fragment 1+2, and D-dimer. If the prothrombin fragment 1+2 test cannot be done at the site, the sample should be sent to the local reference laboratory, if available and if the results from the local reference laboratory can be obtained within a reasonable timeframe to allow for decision making. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents administered to treat a given bleed. If applicable, laboratory results should be recorded in the unscheduled visit eCRFs.*

[no notes on this page]

Appendix 2
Schedule of Pharmacodynamic Assessments

Sample	Visit [a]	Biomarker assays [b]
PD Set 1	**Starting on emicizumab [c]:** Screening Every week during Weeks 1–4 Every 2 weeks during Weeks 5–8 Every 4 weeks during Weeks 9–24 Every 8 weeks during Weeks 25–48 Every 12 weeks thereafter, while on emicizumab Study Completion/Early Termination Safety Follow-up Visit Unscheduled visit (at the discretion of the investigator), while on emicizumab [d] **Starting on episodic bypassing agents, switch to emicizumab after 24 weeks**: Screening Week 1 Every week during Weeks 25–28 Every 2 weeks during Weeks 29–32 Every 4 weeks during Weeks 33–48 Every 8 weeks during Weeks 49–84 Every 12 weeks thereafter, while on emicizumab Study Completion / Early Termination Safety Follow-up Visit Unscheduled visit (at the discretion of the investigator), while on emicizumab [d]	Standard aPTT Modified aPTT PT FVIII activity Thrombin generation FIX antigen FX antigen D-dimer Prothrombin fragment 1+2
PD Set 2	**Starting on emicizumab [c]:** Screening Week 1 Week 25 Study Completion/Early Termination Safety Follow-up Visit **Starting on episodic bypassing agents, switch to emicizumab after 24 weeks**: Screening Week 1 Week 25 Week 49 Study Completion/Early Termination Safety Follow-up Visit	FXIII activity VWF antigen Fibrinogen Bone turnover markers

[redacted] FIX=factor IX; FVIII=factor VIII; FX=factor X; FXIII=factor XIII; PD=pharmacodynamics; VWF=von Willebrand factor.

[a] All samples are to be collected on Day 1 of the indicated week, prior to emicizumab injection (if applicable). All PD samples will be citrate or EDTA plasma. Refer to Appendix 1 for exact study visits.

[b] Biomarker assays will include, but are not limited to, those listed. [redacted]

[no notes on this page]

Appendix 2
Schedule of Pharmacodynamic Assessments (cont.)

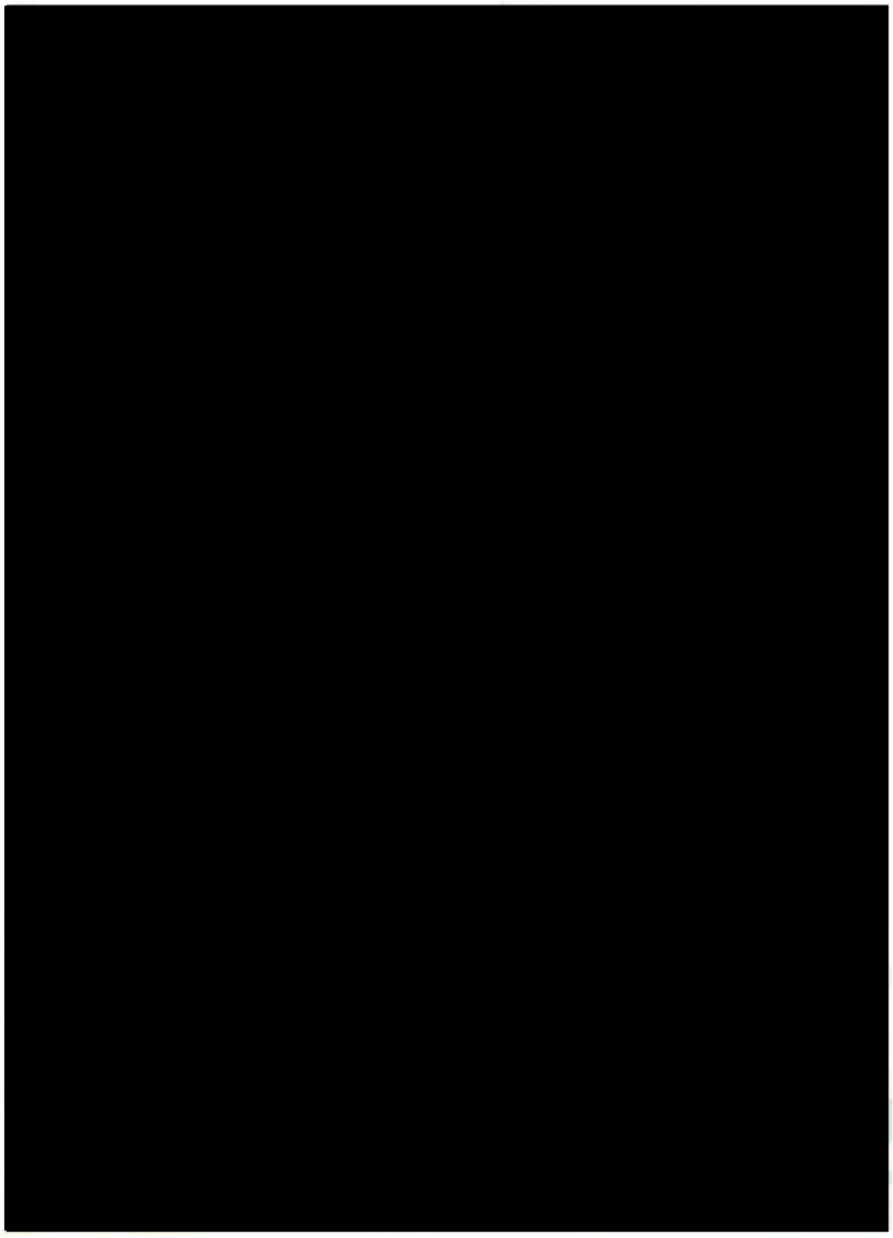
Blood volumes and processing procedures will be specified in the Laboratory Manual.

[c] Patients enrolled in Arm D will have a reduced panel of PD biomarkers run at each visit.

[d] Reasons for unscheduled visits may include evaluation or treatment for bleeds or hypersensitivity reactions.

[no notes on this page]

Appendix 3
Haemo-QoL-SF (United States/English)



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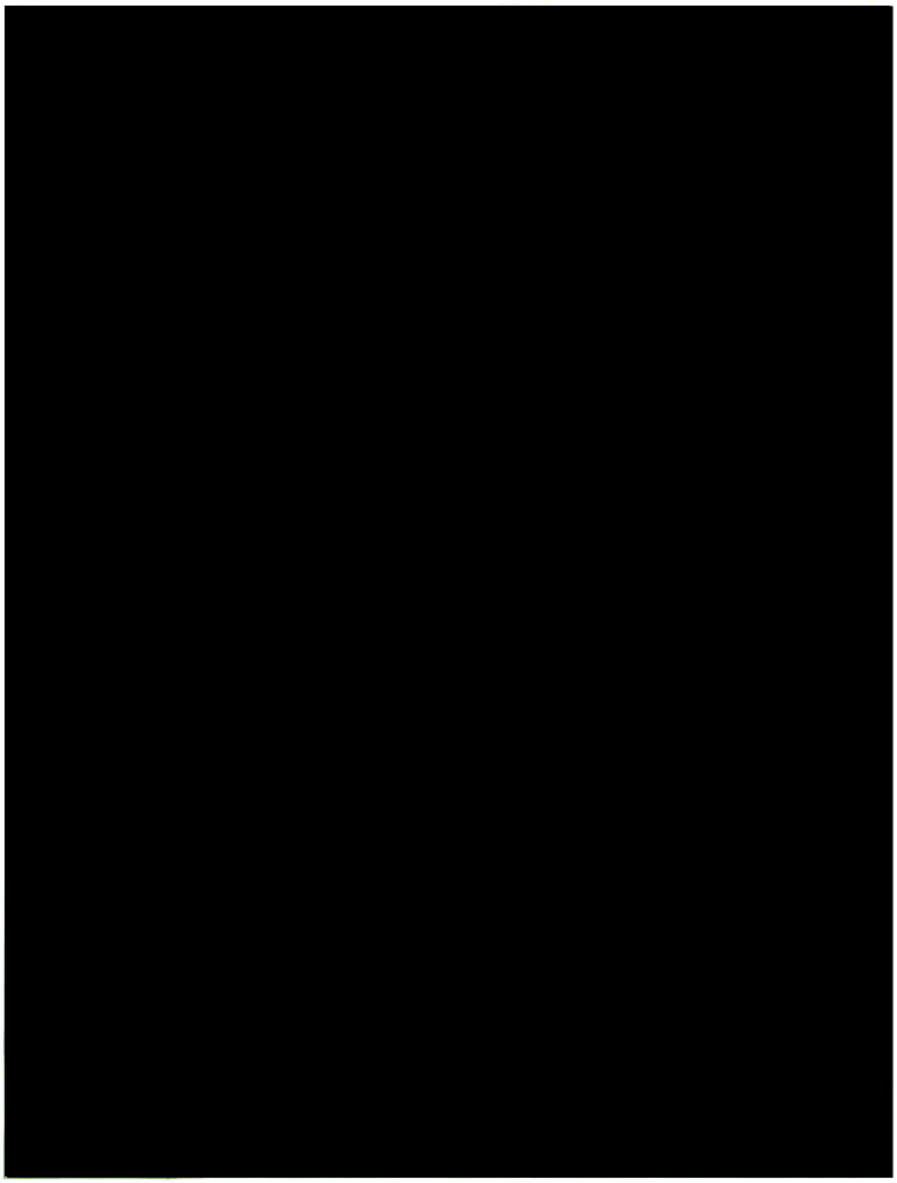
Appendix 3
Haemo-QoL-SF (United States/English) (cont.)



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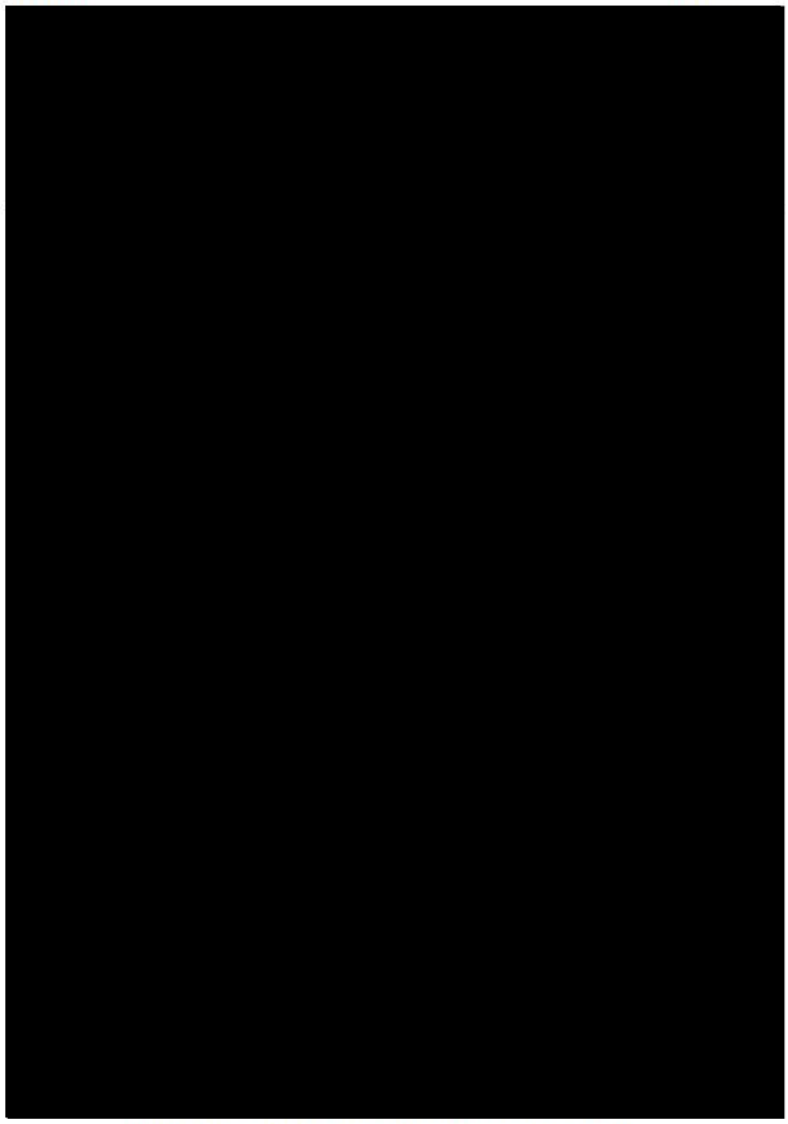
Appendix 4
Haem-A-QoL (United States/English)



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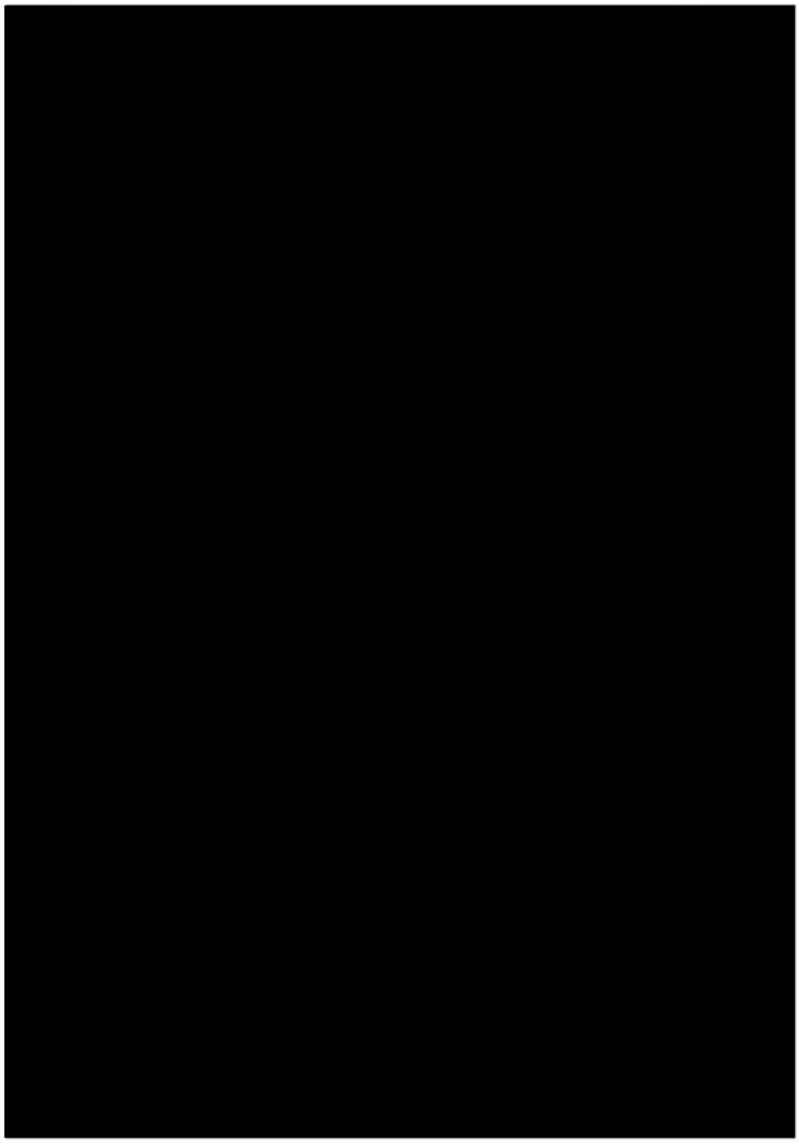
Appendix 4
Haem-A-QoL (United States/English) (cont.)



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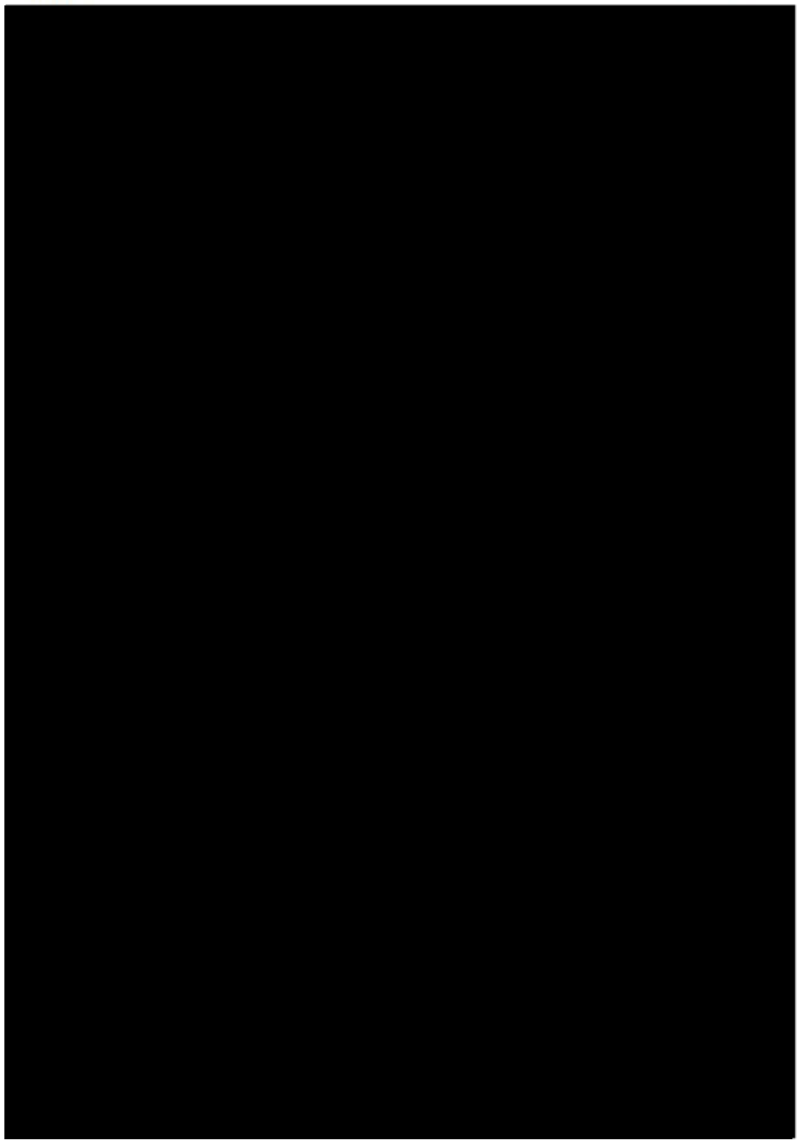
Appendix 4
Haem-A-QoL (United States/English) (cont.)



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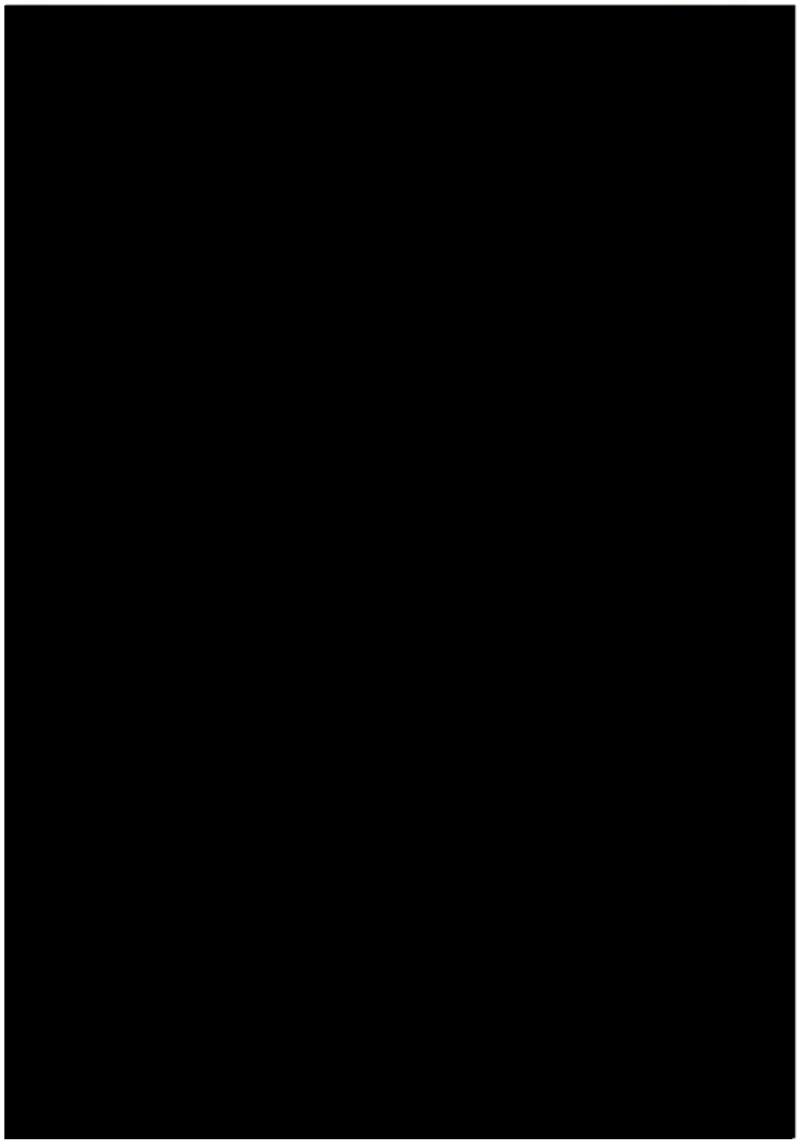
Appendix 4
Haem-A-QoL (United States/English) (cont.)



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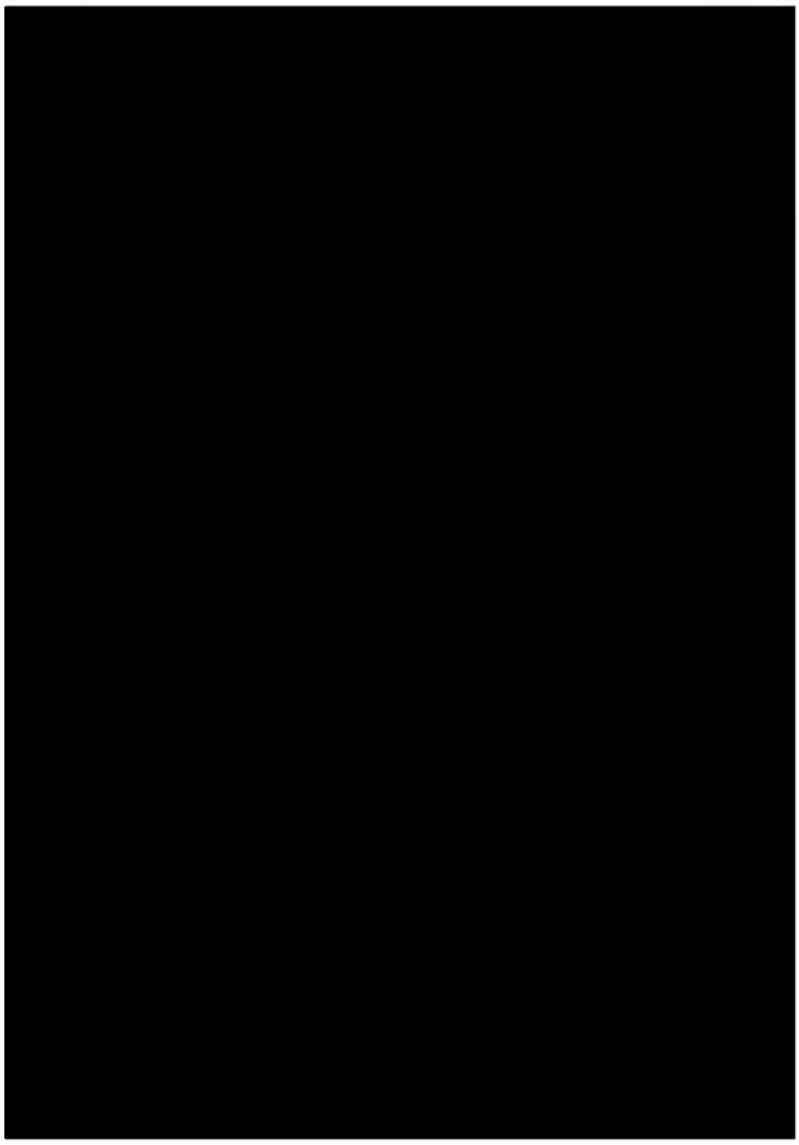
Appendix 4
Haem-A-QoL (United States/English) (cont.)



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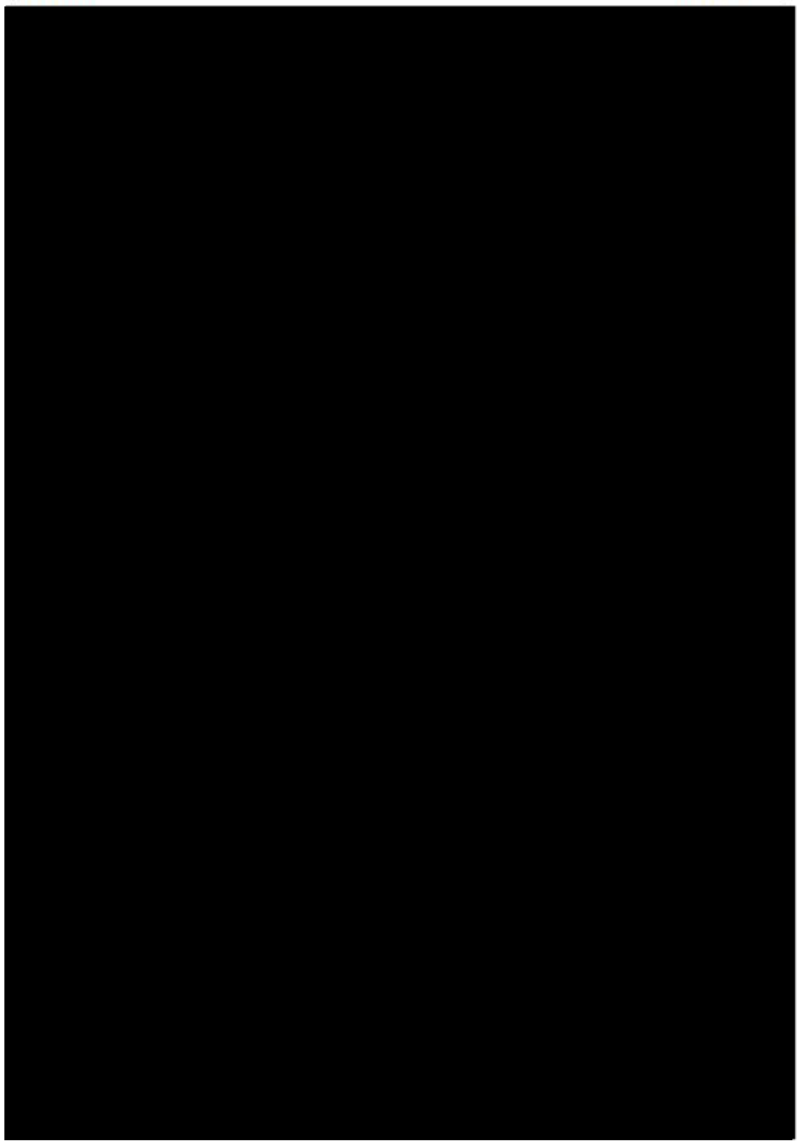
Appendix 4
Haem-A-QoL (United States/English) (cont.)



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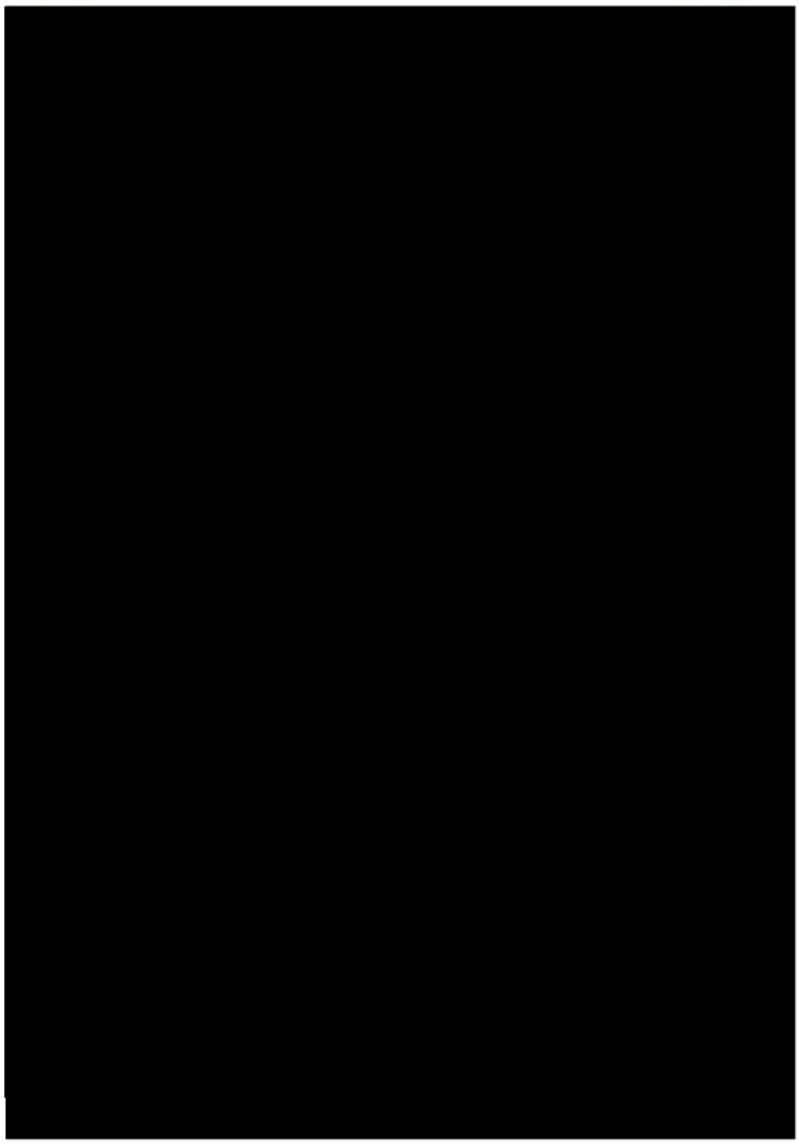
Appendix 4
Haem-A-QoL (United States/English) (cont.)



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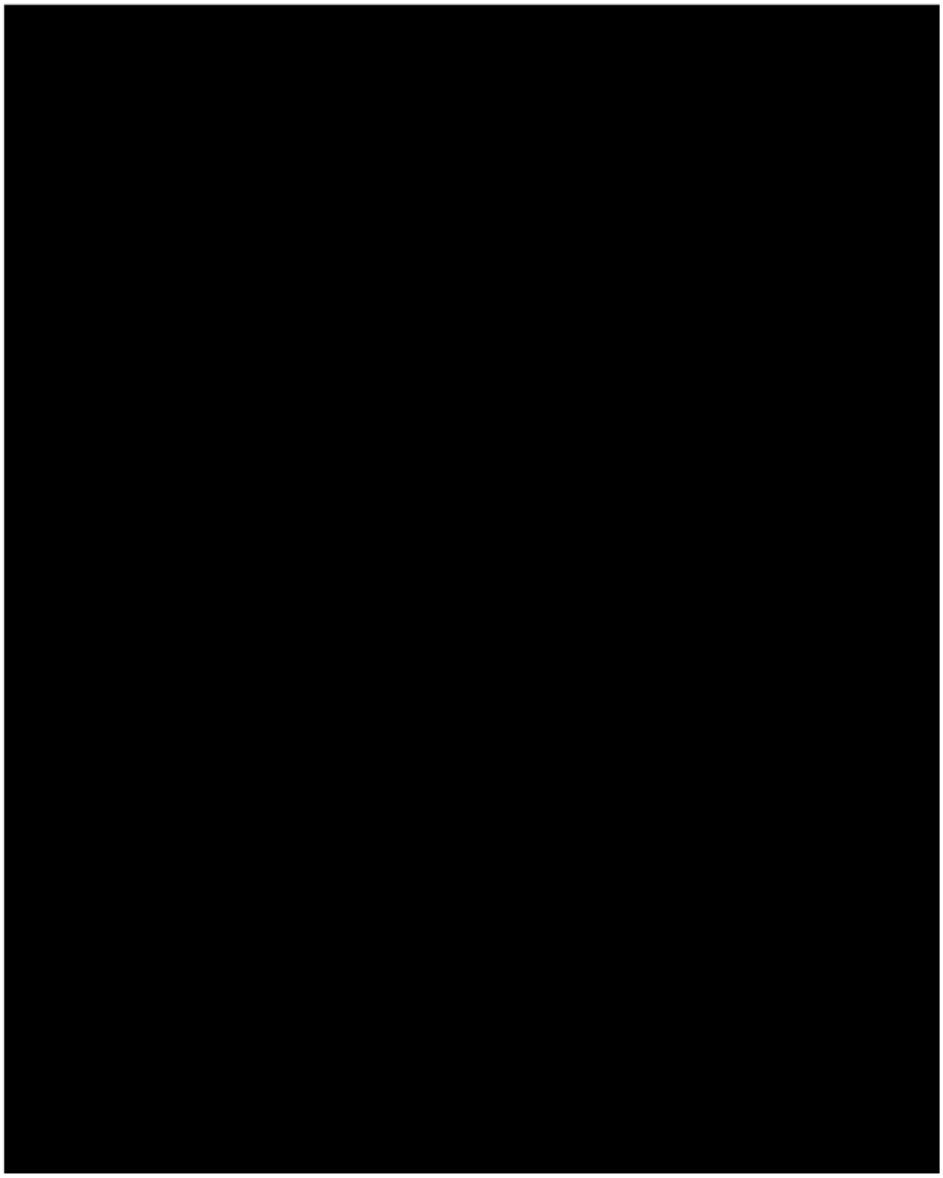
Appendix 5
EQ-5D-5L (United Kingdom/English)



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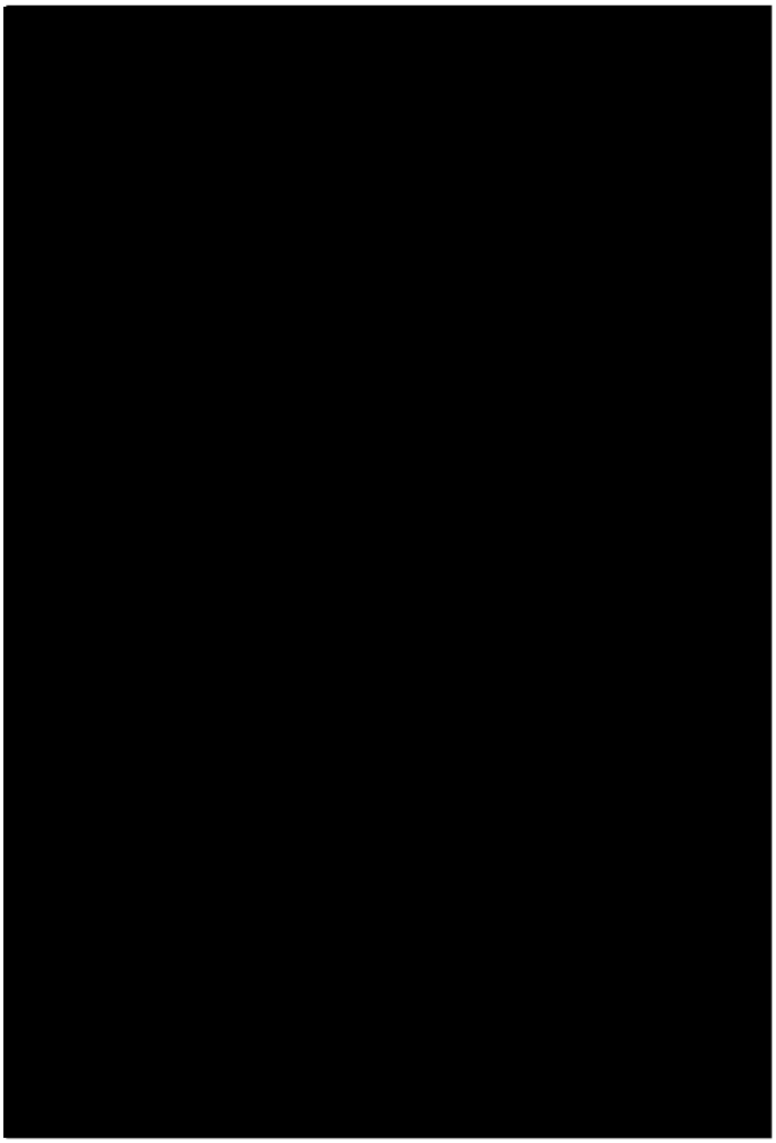
Appendix 5
EQ-5D-5L (United Kingdom/English) (cont.)



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Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
HEMATOLOGY				
Hemoglobin	9.5–10.5 g/dL	8.0–9.4 g/dL	6.5–7.9 g/dL	<6.5 g/dL
Absolute neutrophil count	1000–1500/mm^3	750–999/mm^3	500–749/mm^3	<500/mm^3
Platelets	75000–99999/mm^3	50000–74999/mm^3	20000–49999/mm^3	<20000/mm^3
Prothrombin time (PT)	1.01–1.25×ULN	1.26–1.5×ULN	1.51–3.0×ULN	>3×ULN
Activated partial thromboplastin (APTT)	1.01–1.66×ULN	1.67–2.33×ULN	2.34–3×ULN	>3×ULN
Fibrinogen	0.75–0.99×LLN	0.50–0.74×LLN	0.25 - 0.49×LLN	<0.25 x LLN
Fibrin split product	20–40 mcg/mL	41–50 mcg/mL	51–60 mcg/mL	>60 mcg/mL
Methemoglobin	5–9.9%	10.0–14.9%	15.0–19.9%	>20 %
LIVER ENZYMES				
AST (SGOT)	1.25–2.5×ULN	2.6–5×ULN	5.1–10×ULN	>10×ULN
ALT (SGPT)	1.25–2.5×ULN	2.6–5×ULN	5.1–10×ULN	>10×ULN
GGT	1.25–2.5×ULN	2.6–5×ULN	5.1–10×ULN	>10×ULN
Alkaline phosphatase	1.25–2.5×ULN	2.6–5×ULN	5.1–10×ULN	>10×ULN
Amylase	1.1–1.5×ULN	1.6–2.0×ULN	2.1–5.0×ULN	>5.0×ULN

[no notes on this page]

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CHEMISTRIES				
Hyponatremia	130–135 mEq/L	123–129 mEq/L	116–122 mEq/L	<116 or mental status changes or seizures
Hypernatremia	146–150 mEq/L	151–157 mEq/L	158–165 mEq/L	>165 mEq/L or mental status changes or seizures
Hypokalemia	3.0–3.4 mEq/L	2.5–2.9 mEq/L	2.0–2.4 mEq/L or intensive replacement Rx required or hospitalization required.	<2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6–6.0 mEq/L	6.1–6.5 mEq/L	6.6–7.0 mEq/L	>7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55–64 mg/dL	40–54 mg/dL	30–39 mg/dL	<30 mg/dL or mental status changes or coma
Hyperglycemia (note if fasting)	116–160 mg/dL	161–250 mg/dL	251–500 mg/dL	>500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4–7.8 mg/dL	7.7–7.0 mg/dL	6.9–6.1 mg/dL	<6.1 mg/dL or life-threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6–11.5 mg/dL	11.6–12.5 mg/dL	12.6–13.5 mg/dL	>13.5 mg/dL life-threatening arrhythmia

[no notes on this page]

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CHEMISTRIES continued				
Hypomagnesemia	1.4–1.2 mEq/L	1.1–0.9 mEq/L	0.8–0.6 mEq/L	<0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0–2.4 mg/dL	1.5–1.9 mg/dL or replacement Rx required	1.0–1.4 mg/dL intensive Rx or hospitalization required	<1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	1.1–1.5×ULN	1.6–2.5×ULN	2.6–5×ULN	>5×ULN
BUN	1.25–2.5×ULN	2.6–5×ULN	5.1–10×ULN	>10×ULN
Creatinine	1.1–1.5×ULN	1.6–3.0×ULN	3.1–6×ULN	>6×ULN or required dialysis
URINALYSIS				
Proteinuria	1+or <0.3% or <3g/L or 200 mg–1 g loss/day	2–3+or 0.3–1.0% or 3–10 g/L 1–2 g loss/day	4+or >1.0% or >10 g/L 2–3.5 g loss/day	nephrotic syndrome or >3.5 g loss/day
Hematuria	microscopic only	gross, no clots	gross+clots	obstructive or required transfusion
CARDIAC DYSFUNCTION				
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; no Rx required	requires treatment
Hypertension	transient inc. >20 mm; no Rx	recurrent, chronic, >20 mm, Rx required	requires acute Rx; no hospitalization	requires hospitalization

[no notes on this page]

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CARDIAC DYSFUNCTION continued				
Hypotension	transient orthostatic hypotension, no Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1–2 units transfused	massive blood loss; >3 units transfused
RESPIRATORY				
Cough	transient; no Rx	treatment-associated cough local Rx	uncontrolled	
Bronchospasm, Acute	transient; no Rx <70%–79% FEV_1 (or peak flow)	requires Rx normalizes with bronchodilator; FEV_1 50%–69% (or peak Flow)	no normalization with bronchodilator; FEV_1 25%–49% (or peak flow retractions)	cyanosis: FEV_1 <25% (or peak flow) or intubated
GASTROINTESTINAL				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids

[no notes on this page]

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
GASTROINTESTINAL continued				
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	severe discomfort; no significant intake; activities limited	minimal fluid intake
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3–4 loose stools/day	5-7 loose stools/day	orthostatic hypotension or >7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required
NEURO AND NEUROMUSCULAR				
Neuro-cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and therapy required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization

[no notes on this page]

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
NEURO AND NEUROMUSCULAR continued				
Neuro control (ADL = activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/agitation some limitation of ADL; minimal Rx	severe confusion/agitation needs assistance for ADL; therapy required	toxic psychosis; hospitalization
Muscle strength	subjective weakness no objective symptoms/signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
OTHER PARAMETERS				
Fever: oral, >12 hours	37.7–38.5 C or 99.9–101.3 F	38.6–39.5 C or 101.4–103.1 F	39.6–40.5 C or 103.2–104.9 F	>40.5 C or >104.9 F
Headache	mild, no Rx therapy	transient, moderate; Rx required	severe; responds to initial narcotic therapy	intractable; required repeated narcotic therapy
Fatigue	no decrease in ADL	normal activity decreased 25–50%	normal activity decreased >50% can't work	unable to care for self
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Local Reaction	tenderness or erythema	induration <10 cm or phlebitis or inflammation	Induration ≥10 cm or ulceration	necrosis

[no notes on this page]

Appendix 6
WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
OTHER PARAMETERS continued				
Mucocutaneous	erythema; pruritus	diffuse, maculo-papular rash, dry desquamation	vesiculation, moist desquamation, or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery

NOTE: For coding purposes, the following toxicity grades may be used interchangeably: 1 =mild; 2 =moderate; 3 =severe; 4 =life threatening.

[no notes on this page]

Appendix 7
Clinical Criteria for Diagnosing Anaphylaxis

These criteria are taken from a summary report from the second symposium on the definition and management of anaphylaxis, conducted by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network.[1] Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue/uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
   - Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure[2]
   - Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

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[1] Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–7.

[2] Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

[no notes on this page]

HAVEN 1 (BH29884) Summary of changes to protocol

A summary of the changes to each new version of protocol BH29884 is provided below.

Within the protocol documents, information was redacted based on Roche's policy to redact all protected personal data and commercially confidential information; additional information was redacted if it involved:

1. Unpublished data that may be published in the future

2. Discussion of future studies/activities that may be conducted in the future

3. Copyrighted material held by external, non-Roche parties

SUMMARY OF CHANGES TO PROTOCOL BH29884_Amendment version 2
To modify the study design or analyses
Increase the potential number of hemophilia A patients with inhibitors who were previously treated with prophylactic bypassing agents (Arm C) from approximately 10−20 to 30−50 (Section 3.1).
Add an emicizumab treatment arm (Arm D), which will open if there remain patients on episodic bypassing agents who had participated in the non-interventional study, BH29768, (and received priority to participate in a future emicizumab interventional study) but were unable to enroll in time to either Arm A or B. (Sections 3.1, 3.3, 3.3.2, 3.3.6, 4.2, 6.5, and 9.4).
Clarify and make minor changes to the inclusion and exclusion criteria, including the clarification that the exclusion of ongoing (or future) immune tolerance induction or FVIII prophylaxis was intended to exclude patients for which this was the primary regimen prior to study entry, not patients who have previously received FVIII prophylaxis with concurrent bypassing agent prophylaxis. The latter will be permitted to enroll in Arm C as long as they still meet the minimum bleed rate requirement and all other criteria. (Sections 4.1.1 and 4.1.2).
Add a secondary endpoint to compare all bleeds (i.e., both treated and not treated with coagulation factors) (Section 6.5.2).
Remove the interim analysis (Section 6.9).
To further define and/or clarify
Remove the requirement for data collected over 24 weeks prior to study entry for analyses involving historical bleed rate (Sections 2.1.2, 3.3.3, 6.5.2).
Clarify that patients are instructed to complete the bleed/medication questionnaire when bleeds or hemophilia medication use occur and at least once a week (Sections 3.1, 4.5.8).
Clarify that no predefined stopping rules have been included in the iDMC Charter, given the limited sample size of Study BH29884 and the lack of clearly identified, significant adverse events in the Phase I/II Study ACE001JP/002JP. It was decided and agreed upon by the iDMC that recommendations to stop the study would be based on their independent assessment of the Study BH29884 safety data in its totality, which will occur at pre-specified iDMC meetings (i.e., after the first 9 randomized patients have completed 8 weeks in the study and after the first 18 randomized patients have completed 12 weeks in the study). Thereafter, the iDMC will meet at a frequency determined by the iDMC and the Sponsor (Sections 3.1, 6.6, and 9.4.2).
Clarify the specific data points being collected in the electronic, handheld device, (Section 3.1).

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Remove language that states that the Sponsor, with the exception of the bioanalytical manager, bioanalytic laboratory, biomarker laboratory, and pharmacometrician, will remain blinded to the randomization assignments throughout the conduct of the study (Section 4.2).
Modify dose up-titration criteria (Section 4.3.1.1).
Provide the option for patients who are approved to up-titrate their dose to potentially combine emicizumab volumes from more than 1 vial into 1 syringe (Section 4.3.1.1).
Remove the requirement for proactive collection of pregnancy information for female partners of male patients treated with emicizumab (Section 5.4.3.2).
Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics (see protocol for details).
Global changes: RO5534262 has been replaced with the recently approved international non-proprietary name for this drug, emicizumab, throughout the protocol. Home nursing has been changed to mobile nursing throughout the protocol.
Changes to the protocol synopsis have been made to reflect above changes to protocol.

SUMMARY OF CHANGES TO PROTOCOL BH29884_ Amendment version 3
To modify the study design or analyses
Recent information on safety findings of thromboembolic events and thrombotic microangiopathy (TMA) observed in Study BH29884 has been added, including requirements for laboratory monitoring of coagulation status following bypassing agent use. The section for risks associated with emicizumab was updated accordingly and microangiopathic hemolytic anemia/TMA is newly classified as an adverse event of special interest. An exclusion criterion to exclude patients at high risk to experience TMA has been added (Sections 1.2, 1.3, 3.1, 4.1.2, 5.1.2.3, 5.1.2.4, 5.1.3, Table 2, Appendix 1).
A new efficacy objective to evaluate the clinical effect of prophylactic emicizumab on the number of spontaneous bleeds over time (spontaneous bleed rate) was added (Section 2.1.2). Note that this new objective was already previously specified in the Statistical Analysis Plan.
Arm D has been modified to also allow prophylactic bypassing agent patients who were unable to enroll in Arm C before it closed to enroll in Study BH29884 (Sections 3.1, 3.3, 3.3.2, 3.3.6, 4.2, 6.5, and 9.4). The efficacy of patients in Arm D will be reflected only in analyses involving all patients treated with emicizumab (Section 2.1.2).
The permitted treatment for breakthrough bleeds has been specified with guidance regarding the use of concomitant bypassing agents in patients being treated with emicizumab (Sections 3.1 and 3.3.3).
To further define and/or clarify
The use of short-term prophylaxis with activated prothrombin complex concentrate concomitantly with emicizumab is prohibited (Section 4.4.2).
Background information regarding the interference of some coagulation assays by emicizumab has been added (Section 5.1.4).
Removal of the requirement for proactive collection of pregnancy information for female partners of male patients treated with emicizumab (Section 5.4.3.4).
Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics (see protocol for details).
See pages 4–15 for changes to the protocol synopsis.

[no notes on this page]

STATISTICAL ANALYSIS PLAN

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC EMICIZUMAB VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
PROTOCOL NUMBER:	BH29884
STUDY DRUG:	Emicizumab (RO5534262)
VERSION NUMBER:	1
IND NUMBER:	122954
EUDRACT NUMBER:	2015-002866-21
SPONSOR:	F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.*
PLAN PREPARED BY:	[redacted]
DATE FINAL:	See electronic date stamp below.

STATISTICAL ANALYSIS PLAN APPROVAL

Name	Reason for Signing	Date and Time (UTC)
[redacted]	Company Signatory	04-Jul-2016 07:49:25

*Chugai will act as the Sponsor only in South Korea, Taiwan, and Japan. The specific details of the legal/regulatory entity within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and the Clinical Trial Application with the Competent Authority.

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1. BACKGROUND

Hemophilia A is an X-linked recessive bleeding disorder that occurs in approximately 1 in 5000 live male births. Patients with hemophilia A have a deficiency or absence of blood coagulation factor VIII (FVIII), an essential component of the intrinsic pathway in the coagulation cascade (Mannucci and Tuddenham 2001; Franchini and Mannucci 2013).

The development of inhibitory alloantibodies (inhibitors) occurs in approximately 20%–30% of patients with severe hemophilia A and in 3%–13% of those with moderate or mild disease (Franchini and Mannucci 2013). Inhibitors neutralize the activity of endogenous FVIII as well as of FVIII administered as replacement therapy. For patients with a history of a high-titer (≥5 BU/mL) inhibitor following a re-challenge with FVIII administration (high-responding inhibitor), the only hemostatic options currently available are pro-thrombotic coagulation factors that augment other parts of the coagulation cascade (i.e., “bypassing agents”).

Current standard prophylactic regimens commonly use infusion therapy administered three times weekly; other regimens require daily or every other day administration, depending on the patient’s needs (Shapiro 2013). Major issues with current regimens are the need for adequate venous access and patient/family compliance with regular prophylaxis, especially in the very young pediatric population, in whom central venous access devices (CVADs) have been used to overcome technical difficulties. Thus, both the disease and its treatment have the potential to affect health-related quality of life (HRQoL), the latter through limitations on daily activities that treatment may impose.

The development of effective prophylactic treatment options with decreased immunogenicity and less frequent dosing requirements is a high, unmet medical need in the population of hemophilia A patients with FVIII inhibitors.

Emicizumab is a recombinant, humanized, bispecific, immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX), mimicking the co-factor function of FVIIIa. In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors, as emicizumab shares no sequence homology with FVIII. In addition, emicizumab offers the possibility of subcutaneous (SC) administration, removing the need for venous access. Finally, because of the pharmacokinetic properties of this antibody, markedly extending the dosing interval to once weekly or even less frequently, this novel compound has the potential to dramatically change the treatment of patients with hemophilia A with and without FVIII inhibitors who are in need of effective, safe, and convenient prophylactic therapy.

Currently available experience with emicizumab in humans includes data from one Phase I study (ACE001JP) and its ongoing extension, a Phase I/II study (ACE002JP).

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See Section 1.2 of the protocol for a detailed description of the study results. The results have also been published (Uchida et al. 2015; Shima et al. 2016). Based on these compelling Phase I/II data, a clinical development program in adult and pediatric patients with hemophilia A (both with and without FVIII inhibitors) has been initiated.

[redacted] meetings have been held with [redacted] to discuss the emicizumab development program and Study BH29884. In [redacted], the Sponsor initiated early dialogue with [redacted] and [redacted] through the [redacted] procedure for scientific advice. This procedure was initiated to agree on requirements to support the registration of emicizumab for the prevention of bleeding episodes in adults and adolescents (≥ 12 years of age) with hemophilia A and FVIII inhibitors. At these meetings, the study design and objectives were discussed. In particular, the methodology for the primary endpoint has been agreed upon [redacted].

2. STUDY DESIGN

This randomized, multicenter, open-label, Phase III clinical study is enrolling patients aged 12 years or older with hemophilia A who have inhibitors against FVIII. Approximately 51 inhibitor patients who received episodic treatment with bypassing agents prior to study entry will be randomized in a 2:1 ratio (see Figure 1). Patients will be randomized either to receive prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously (Arm A), or to the control arm (Arm B), which will consist of no prophylaxis. Given the potential heterogeneity of bleed rates in the study patient population, randomized patients will be stratified according to the number of bleeds they experienced over the last 24 weeks prior to study entry (<9 or ≥ 9 bleeds) to ensure a balance of inhibitor patients with lower versus higher number of bleeds, respectively, at baseline across the two randomized arms of the Phase III study.

In addition, given that hemophilia A patients with inhibitors are currently treated with bypassing agents on both a prophylactic and episodic basis, approximately 30–50 patients with inhibitors previously treated with prophylactic bypassing agents will be enrolled in a separate therapeutic arm (Arm C) to receive prophylactic emicizumab at the same dose and schedule (see Figure 1). Enrollment into Arm C will continue for 24 weeks after Arms A and B have been closed to enrollment or until 50 patients have been enrolled, whichever occurs earlier, in order to collect additional safety and efficacy from patients previously on prophylactic bypassing agents.

Of note, all patients who participated in Study BH29768 (a non-interventional study [NIS]) received priority to participate in a future emicizumab interventional study. A separate, therapeutic arm (Arm D) will open at a future timepoint if there remain patients on episodic bypassing agents who participated in NIS BH29768 but were unable to

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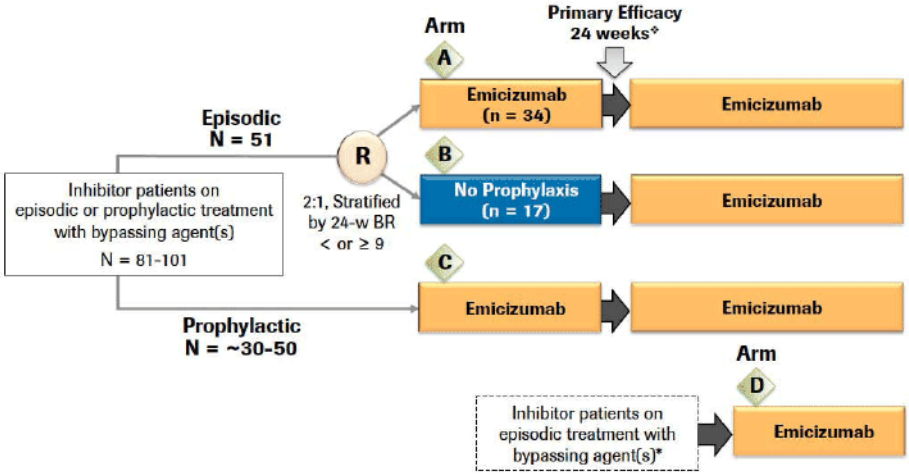
enroll in Arms A or B before they closed to enrollment. Arm D will yield additional efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) data and enable collection of plasma samples [redacted] (see Figure 1).

Figure 1 Study Schema



R = randomized, 24-w BR = 24-week bleed rate (prior to study entry)
*Primary efficacy analysis: after all randomized patients have completed 24 weeks in the study or the last randomized patient who has not completed 24 weeks in the study discontinues study participation, whichever occurs first; Arms A and B will close when the last randomized patient has been enrolled; after this time point, Arm C will remain open for 24 additional weeks; potential to up-titrate dose in emicizumab arms if suboptimal response and opportunity to switch from no prophylaxis to emicizumab in control arm after participating in this study for at least 24 weeks
*If episodic patients from Study BH29768 are unable to enroll in Arms A or B before they close, Arm D will open only for such patients at a future timepoint after the last randomized patient has been enrolled

The primary efficacy analysis will be conducted at the earliest timepoint when all randomized patients have either completed 24 weeks of treatment or the last randomized patient who has not completed 24 weeks in the study discontinues from the study. To obtain additional safety and efficacy data on emicizumab, each patient who had been randomized to no prophylaxis (control arm, Arm B) will be provided the opportunity to switch to receive prophylactic emicizumab (at the same dose and schedule as patients who started Study BH29884 on emicizumab) once they complete 24 weeks in the study. In addition, those who had previously been enrolled to receive prophylactic emicizumab (Arms A, C, and D) and who are deriving clinical benefit will be given the opportunity to continue on their 1.5 mg/kg/week maintenance dose [redacted]. After receiving prophylactic emicizumab at a dose of 1.5 mg/kg/week for at least 24 weeks, all patients will be provided the option

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to increase their dose to 3 mg/kg/week, if they meet protocol-defined criteria of suboptimal response.

Summary of treatments arms is provided below in a tabular format.

Table 1 Treatment Arms

	Treatment Regimen [a]	Randomized (Yes/No)	Previous Bypassing Agent Regimen
Arm A	Prophylactic emicizumab at 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week SC	Yes	Episodic
Arm B Control Arm	No prophylaxis	Yes	Episodic
Arm B After Switch to Emicizumab	Prophylactic emicizumab at 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week SC	Yes Patients in Arm B are allowed to switch to emicizumab after 24 weeks	Episodic
Arm C	Prophylactic emicizumab at 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week SC	No	Prophylaxis
Arm D	Prophylactic emicizumab at 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week SC	No	Episodic

SC = subcutaneous

[a] Opportunity for dose up-titration to 3 mg/kg after 24 weeks on emicizumab for all patients in all arms.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1.

2.2 COLLECTION OF BLEED AND MEDICATION DATA

Bleed and medication data are collected through a bleed and medication questionnaire (BMQ), which was developed by the Sponsor given that no standard questionnaire for collection of this data was available.

The BMQ was developed as a patient-reported measure of bleeding episodes (including cause, type, location, and symptoms of bleeds) and hemophilia-related medication use. The draft questions were developed following review of the hemophilia A literature and discussions with medical professionals regarding what information related bleeds was most important to capture. Prior to use in this study, qualitative interviews with patients

with hemophilia A were conducted in order to evaluate the measure's content validity and to test the understanding and usability of the BMQ on an electronic, handheld device. Cognitive interviews were conducted in person with a total of 20 patients aged 12 years and older with hemophilia A; the results demonstrated that the BMQ was comprehensive and relevant to patients' experiences with bleeds and treatments. Recommendations for some minor wording changes based on patient feedback were incorporated in order to improve the content validity of the final BMQ used in this study.

The BMQ is completed by the patient or a caregiver using an electronic, handheld device. Patients are instructed to enter all bleeds and hemophilia-related medications, including emicizumab administrations, as they occur. In case a patient did not experience any bleeds or administer any treatments for a week, the patient is asked to log in to the device and fill in the questionnaire to confirm this. These weekly entries, in addition to the bleeds and medication entries, can be also used to assess compliance. Of note, the patient is able to enter bleeds and medications for the past 8 days, including the day the entries are made. This retrospective data entry window was considered acceptable in terms of recall bias and was added in order to optimize the completeness of data collection.

The patient is able to edit and delete bleeds and medications immediately after they are entered. However, if the data have already been submitted to the vendor's database (i.e., after responses have been confirmed by the patient), the patient is no longer able to edit or delete the data. Furthermore, the investigator and patient are instructed to review the data together at every clinic visit. If the patient has been unable to enter data for any reason, the investigator is able to do so using a Web-based site data entry system (not subject to the previous 8-day data entry window). Note, the symptoms of joint and muscle bleeds are not collected in this case because the patient may not be able to reliably remember them. In addition, the investigator is able to request a change be made to the vendor's database by submitting a data clarification request (DCR).

Furthermore, the Sponsor's data manager and Medical Monitor review the patient-entered data for clear inconsistencies against data collected on the electronic Case Report Form (eCRF) or to identify obvious data points to be clarified (e.g., missing entry of the weekly emicizumab injection). These requests are sent to the investigator, who reviews them with the patient, and may enter the data via the site data entry system or request a change to be made in the vendor's database, via a DCR, if necessary.

The Haem-A-QoL, Haemo-QoL-SF, and EQ-5D-5L questionnaires and data regarding days away from school/work are filled in by the patients using the same electronic, handheld device. However, for this type of data, there is no possibility for retrospective data entry, entries through the site data entry system, data clarification requests, or corrections to data in the vendor's database.

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Of note, an earlier version of the same BMQ and a comparable method of data collection were used in the NIS BH29768. For patients enrolled in both Studies BH29678 and BH29884, this consistency allows data from the two studies to be compared for the secondary endpoint of intra-patient comparison.

2.3 ENDPOINTS

2.3.1 Primary Efficacy Endpoint

Bleed rate is defined as the number of bleeds over the efficacy period. A bleed is included in the primary analysis if it was treated with coagulation factors and fulfills the adapted International Society on Thrombosis and Haemostasis (ISTH; Blanchette 2014) criteria ("treated bleed"), as described in the protocol. More specifically, the following rules are applied.

2.3.1.1 Efficacy Period

The start of the efficacy period for each individual patient is defined as the first day the patient had the potential to enter a bleed or a hemophilia medication on the electronic, handheld device. For patients on emicizumab (Arms A, C, and D and Arm B after treatment switch), this should coincide with the Week 1 visit and/or the day of the first emicizumab dose. For the patients who do not start the study on emicizumab (Arm B), this should coincide with the Week 1 visit.

For patients on emicizumab, the end of the efficacy period is defined as the date of the clinical cutoff or the date of withdrawal from the initial study period (i.e., treatment phase according to eCRF), whichever is earlier. For patients randomized to no prophylaxis (Arm B) the end of the efficacy period is defined as the day before the first emicizumab dose was administered for patients who switch to receive emicizumab after 24 weeks or the date of withdrawal from the initial study period (i.e., treatment phase according to eCRF). For patients whose dose is up-titrated, the efficacy period ends 1 day prior to the first day on the up-titrated dose.

For patients who withdraw from the study before reaching the Week 1 visit, the duration of efficacy period is set to 1 day, and it starts and ends on the day of randomization/enrollment.

For patients whose dose is up-titrated, the bleeds on the up-titrated dose are analyzed separately. The efficacy period on a given up-titrated dose starts with the first day on this dose and ends on the day of the clinical cutoff or the date of withdrawal.

2.3.1.2 Treated Bleed

A bleed is considered to be a "treated bleed" if it is directly followed (i.e., there is not an intervening bleed) by a hemophilia medication reported to be a "treatment for bleed," irrespective of the time between the treatment and the preceding bleed. A bleed and the first treatment thereafter are considered to be pairs (i.e., one treatment belongs to one

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bleed only), with the following exception: if multiple bleeds occur on the same calendar day, the subsequent treatment is considered to apply for each of these multiple bleeds.

Bleeds due to surgery/procedure are not included in the primary analysis. Only treatments that were recorded as "treatment for bleed" are included in the determination of a treated bleed.

72-Hour Rule:

Two bleeds of the same type (e.g., "joint," "muscle," or "other") and at the same anatomical location are considered to be one bleed if the second occurs within 72 hours from the last treatment for the first bleed. The last treatment is defined as the last treatment before a new bleed occurs, either in the same or in a different location. This is in-line with the above definition that bleeds and treatments are considered to be pairs.

2.3.2 Secondary Efficacy Endpoints

The same definition of efficacy period for the primary endpoint is used for all bleeds related to the secondary endpoints (see Section 2.3.1.1).

2.3.2.1 All Bleeds

"All bleeds" comprise both treated and non-treated bleeds. In this definition, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded as for the primary analysis.

The endpoint of all bleeds fulfills the adapted ISTH criteria, as described in the protocol for the primary endpoint and the 72-hour rule, in particular. For treated bleeds, it is implemented exactly as defined for the primary endpoint (see Section 2.3). For non-treated bleeds (not followed by any treatments with coagulation factors before the recording of a subsequent bleed), it is implemented by calculating a treatment-free period of 72 hours from the bleed itself.

2.3.2.2 Joint Bleeds

In the analysis of joint bleeds, only treated bleeds that fulfill the 72-hour rule are included. Bleeds due to procedure/surgery are, again, excluded.

Joint bleeds are defined as bleeds where the bleed type is "joint" and at least one of the following symptoms has been experienced: unusual sensation (e.g., tingling), swelling or warmth, pain or decreased range of motion, or difficulty moving the joint compared with usual.

2.3.2.3 Target Joint Bleeds

Target joints are major joints into which repeated bleeds occur (i.e., ≥ 3 bleeds into the same joint over the last 24 weeks prior to study entry). The target joints prior to study entry are identified through the eCRF. The bleeds in target joints during the efficacy period are defined by first selecting the bleeds that fulfill the definition of a joint bleed (see Section 2.3.2.2) and then counting how many of these occurred in a target joint

prior to study entry. The locations to be taken into account are: shoulder, elbow, wrist, fingers/thumb, hip, knee, ankle, sole/heel, and toes. Left and right side of the same joint type are considered to be separate joints.

2.3.2.4 Spontaneous Bleeds

In the analysis of spontaneous bleeds, only treated bleeds that fulfill the 72-hour rule are included.

Bleeds are classified as “spontaneous” if there is no other known contributing factor such as trauma or procedure/surgery.

2.3.2.5 Intra-Patient Comparison

In the intra-patient comparison, only patients who participated in the NIS BH29768 are included. This is because it is possible to apply the detailed definition only if the data are collected with the same granularity for both time periods. Of note, for some patients who participated in NIS BH29768, the total time in that study prior to enrollment in Study BH29884 may be less than 24 weeks.

The efficacy period in NIS BH29768 is defined as the time from the first entry on the electronic, handheld device or site data entry system to the day before the patient is enrolled in Study BH29884. Usually, the date of the first entry is the date the Training Module on the electronic, handheld device is completed.

2.3.2.6 EQ-5D-5L at 24 Weeks

The EQ-5D-5L index utility score using the UK value set and visual analog scale (VAS) will be evaluated at 24 weeks in the study.

2.3.2.7 Haem-A-QoL/Haemo-QoL-SF at 24 Weeks

Because different measures, Haem-A-QoL and Haemo-QoL-SF, are used for the adult and adolescent patients, respectively, all calculations and analyses will be conducted separately for these two measures. Total score and physical health sub-scale for the Haem-A-QoL and Haemo-QoL-SF will be evaluated at 24 weeks in the study.

2.3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

- Number of days away from school/work
- Number of days hospitalized
- EQ-5D-5L at the time of a bleed and at scheduled intervals not related to bleeding

2.3.4 Pharmacokinetic Endpoints

The pharmacokinetic (PK) endpoint for this study is the exposure (C_{trough}) of emicizumab prior to drug administration at the following timepoints:

- Every week during Weeks 1–4 on emicizumab

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- Every 2 weeks during Weeks 5–8 on emicizumab
- Every 4 weeks during Weeks 9–24 on emicizumab
- Every 8 weeks during Weeks 25–48 on emicizumab
- Every 12 weeks, thereafter, while on emicizumab, until the end of the study

2.3.5 Safety Endpoints

Safety parameters to be measured include exposure, adverse events (including serious adverse events, adverse events of special interest, adverse events leading to drug discontinuation, and deaths), clinical laboratory results (hematology, chemistry, and anti-emicizumab antibodies), vital signs, ECG, and concomitant medication use.

2.3.6 Biomarker Endpoints

Biomarker endpoints include activated partial thromboplastin time, D-Dimer, peak height thrombin generation, factor IX antigen, factor XIII activity, factor VIII inhibitor, factor VIII activity, factor X antigen and vWF antigen, fibrinogen, prothrombin international normalized ratio and prothrombin fragment 1 + 2.

2.4 DETERMINATION OF SAMPLE SIZE

The sample size for this study is based on both clinical and statistical considerations, taking into account the limited number of patients with hemophilia A with inhibitors available for participation in clinical studies and the goal of collecting sufficient data to assess the safety and efficacy of emicizumab. Nonetheless, a sample size calculation was conducted to assess its adequacy.

The sample size calculation is based on the evaluation of the primary efficacy endpoint, defined as the number of bleeds over time (i.e., bleed rate) with emicizumab (treatment group, λ_t) versus no prophylaxis (control group, λ_c), which are said to follow a negative binomial (NB) distribution with γ_t and γ_c described as shape parameters for treatment and control groups, respectively. With consideration of enrollment feasibility, a sample size of 45 patients, assuming an allocation ratio of 2:1 (30 patients in treatment group and 15 patients in control group), will achieve a power of more than 95% for λ_t and λ_c ranging from 1 to 4 and 18 to 30, respectively (see Table 2). Here, the patients from the two groups are followed up for 0.5 units of time (i.e., 24 weeks). Of note, assuming $\lambda_c = 18$ and $\lambda_t = 4$ results in an expected annualized bleeding rate (ABR) reduction of 78% in the treatment versus control groups. Sample size calculations were performed with East®, Version 6 (Cytel, Cambridge, MA), which allows specific shape parameters for both the treatment and control groups.

However, the above approach to sample size calculation assumes similar follow-up for each patient. Because this is unlikely to be seen in the study, power was also estimated by simulation to account for different follow-up times among patients. Conducting simulations on the basis of a NB regression model including an offset variable to account for unequal follow-up times, with all other assumptions remaining the same as previously

[no notes on this page]

described, the sample size is projected to have greater than 95% power at the 2-sided 0.05 level of significance.

The analysis will include all randomized patients, regardless of their length of follow-up. Therefore, to ensure the analysis is based on sufficient follow-up data and with 2:1 treatment to control randomization, approximately 34 patients in the randomized emicizumab treatment arm and 17 patients in the control arm (approximately 51 patients in total) will be randomized.

Table 2 Power Calculations for Arm A versus Arm B

Rate for Control Treatment Arm B (λ_c, n_c=15)	**Rate for Experimental Treatment Arm A** (λ_t, n_t=30)			
	1 (γ_t=0.11)	2 (γ_t=0.22)	3 (γ_t=0.33)	4 (γ_t=0.44)
18 (γ_c=2)	**1** (λ_t / λ_c=0.056)	**0.999** (λ_t / λ_c=0.111)	**0.99** (λ_t / λ_c=0.167)	**0.952** (λ_t / λ_c=0.222)
25 (γ_c=2.78)	**1** (λ_t / λ_c=0.04)	**1** (λ_t / λ_c=0.08)	**0.994** (λ_t / λ_c=0.12)	**0.973** (λ_t / λ_c=0.16)
30 (γ_c=.33)	**1** (λ_t / λ_c=0.033)	**0.999** (λ_t / λ_c=0.067)	**0.995** (λ_t / λ_c=0.1)	**0.978** (λ_t / λ_c=0.133)

2.5 ANALYSIS TIMING

The primary analysis takes place at the earliest time when all randomized patients reach 24 weeks in the study or have withdrawn. The primary comparison consists of Arms A and B. At this time, not all patients in Arms C and D will have been in the study for 24 weeks; however, all available data from these patients will be analyzed at this timepoint as well. Note, the results for Arms C and D need to be interpreted with caution due to the short follow-up for some patients.

The final analysis will occur at the end of the study as defined in the protocol. Additional updates may be performed between the primary and final analysis, as requested by Health Authorities or deemed necessary by the Sponsor.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Patients who received episodic treatment with bypassing agents prior to study entry will be randomized in a 2:1 ratio to receive either prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously, or to the control arm (no prophylaxis). A central randomization procedure will be used for all patients who fulfill the entry criteria at screening. A block-based randomization method will be used, stratified by the number of bleeds in the last 24 weeks (<9 or ≥ 9). The

proposed randomization method is designed to balance treatment group assignment within the prognostic stratification factor.

Patients on prophylactic bypassing agents prior to study entry will be enrolled in a separate therapeutic arm (Arm C) to receive prophylactic emicizumab, at the same dose and schedule as described above. Patients on episodic bypassing agents prior to study entry who participated in the NIS BH29768 but were too late to be randomized due to enrollment of these arms being full, will have an opportunity to enroll in an additional, separate therapeutic arm (Arm D) to also receive prophylactic emicizumab.

3.2 DATA MONITORING

An independent Data Monitoring Committee (iDMC) has been assembled to review the safety data collected during the study. The iDMC consists of, at minimum, two independent hemostasis/thrombosis experts and a statistician, none of whom are otherwise involved in the conduct of study. All analyses for review by the iDMC will be prepared by an independent Data Coordinating Center (iDCC) that is independent of the Sponsor. Analyses of safety events will be conducted after the first 9 randomized patients have completed 8 weeks in the study and again after the first 18 randomized patients have completed 12 weeks in the study. Thereafter, the iDMC will meet at a frequency determined by the iDMC and the Sponsor according to the emerging safety profile.

An iDCC will perform unblinded analyses and provide tables and listings to support the iDMC reviews of safety data. The safety data under review will include demographic data, adverse events, serious adverse events, and laboratory abnormalities (coagulation, hematology, and chemistry). Further information will be given by the iDCC to the iDMC on request.

Following each meeting, the iDMC will recommend to the Sponsor whether the study should continue according to the protocol or may suggest changes to the protocol based on the outcome of the data review. In exceptional cases, the iDMC may recommend stopping the study or closing a treatment arm for safety reasons. The iDMC will monitor the incidence of the adverse events, as well as the overall safety of patients, during the study.

Further details are specified in a separate iDMC charter.

4. STATISTICAL METHODS

4.1 OUTPUT LAYOUTS

The key output layouts are designed to address the study objectives in a flexible manner and provide an overall view of the efficacy and safety of emicizumab. In particular, patients in Arm B are allowed to switch to receive emicizumab after the first 24 weeks in the study, yielding two “study periods” (i.e., when they receive no prophylaxis for the first

24 weeks [no prophylaxis period] and emicizumab prophylaxis thereafter [emicizumab period]). These two periods are analyzed separately, and either period can be displayed on outputs together with the other treatment arms.

The four key output layouts are:

- **Randomized patients**: comparison of emicizumab (Arm A) versus no prophylaxis (control arm [Arm B prior to switch to emicizumab]); these outputs form the core set of the efficacy comparisons and will be supported by a corresponding safety analysis
- **All patients**: these outputs will be used to describe the baseline characteristics and study conduct
- **All emicizumab patients**: these outputs will provide an overall view of all data collected under emicizumab prophylaxis (including control arm patients after switch) and will include analyses of safety and descriptive efficacy.
- **Intra-patient comparison**: each treatment arm is displayed separately with its own historical control; for evaluations of the secondary endpoint with intra-patient comparison, only patients who participated in the NIS BH29768 are included

Patients may be allowed to up-titrate their emicizumab dose after at least 24 weeks under prophylactic emicizumab if they meet the prespecified criteria as described in the protocol. The data under the new, higher dose is analyzed and reported separately. Additional summaries will be produced for key safety and exposure on all data (i.e., data before and after up-titration). Note, with longer follow-up or in case up-titration occurs more frequently than expected, outputs on all data may form the core analysis and additional summaries will be produced by dose.

4.2 ANALYSIS POPULATIONS

4.2.1 Randomized Population (ITT)

The primary analysis population for efficacy is the ITT population, defined as all randomized patients (i.e., patients randomized to emicizumab will be counted in this arm even if they received no treatment). Note this population includes only patients in Arms A and B.

4.2.2 All Patients

All Patients includes all patients in their originally assigned treatment arms, according to the interactive voice or Web Response System (IxRS).

4.2.3 All Emicizumab Patients

All Emicizumab Patients is exactly the same for Arms A, C, and D, but for Arm B, it includes only the patients who switched to receive emicizumab.

4.2.4 Pharmacokinetic-Evaluable Population

The PK population includes all patients who have received at least one dose of emicizumab and have at least one post-dose emicizumab concentration result.

4.2.5 Safety Populations

Safety Population 1 includes for Arms A, C, and D, all patients who received at least one dose of emicizumab, and for Arm B, all patients who started the study period (defined as having had the Week 1 visit). Safety Population 2 is exactly the same for Arms A, C, and D, but for Arm B it includes only the patients who received at least one dose of emicizumab.

4.2.6 Non-Interventional Study Population

This population includes patients who participated in NIS BH29768 prior enrollment to this study.

4.2.7 Up-Titrated Population

This population includes patients whose dose was up-titrated to 3 mg/kg.

4.3 ANALYSIS OF STUDY CONDUCT

The flow of patients through the study will be displayed in a “CONSORT” diagram. A clear account of all patients who entered the study, were enrolled and randomized, and entered and completed each period of the study will be displayed. In addition, reasons for premature discontinuation from study treatment and reasons for withdrawing from the study will be described.

Major protocol deviations will be summarized.

Observation time and duration of follow-up, as well as adherence to planned scheduled assessments and compliance with data entry into the electronic, handheld device, will also be evaluated.

4.4 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic characteristics (e.g., age, sex, race/ethnicity, weight, and height) and baseline disease characteristics (including number of bleeds in the past 24 weeks, hemophilia severity, previous hemophilia treatments, number of target joints) will be summarized by treatment group for all patients and for all randomized patients (i.e., the ITT population), in particular.

Note that unavoidable imbalances between the treatment groups may occur due to the small size of the study and inherent differences between patients on previous episodic and prophylactic bypassing agent treatment.

[no notes on this page]

4.5 EFFICACY ANALYSIS

Formal hypothesis testing is conducted only for the randomized comparison of Arm A versus Arm B and for the intra-patient comparison in Arms A and C.

4.5.1 Primary Efficacy Endpoint

The primary efficacy objective is to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis on the number of bleeds over time. The definition of a bleed is described in Section 2.3.2, with the primary endpoint comparing bleeds requiring treatment.

The comparison of the number of bleeds over time between the randomized treatment arms will be performed using a NB regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study (efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥ 9, according to eCRF) in the last 24 weeks prior to study entry as a stratification factor.

This analytic model estimates the rate ratio, λ_t / λ_c, which quantifies the risk of bleeding associated with prophylactic emicizumab (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level, and the estimated risk ratio is compared with 1, assuming the following statistical hypothesis:

H_0 *(null hypothesis): Rate Ratio* $= 1$ *versus* H_1 *(alternative hypothesis): Rate Ratio* $\neq 1$.

The treatment effect therein is based on a contrast statement in the model with use of the SAS GENMOD procedure. Statistical significance at the prespecified alpha level will be based on a Wald testing procedure. Bleed rates for prophylactic emicizumab and no prophylaxis and the rate ratio will be presented and include 95% confidence intervals.

The number of bleeds will also be annualized for each patient using the following formula:

$$ABR = (\text{Number of bleeds/number of days during the efficacy period}) \times 365.25.$$

In other words, there is two ways to derive the ABR: the NB model (model based, estimated ABR) and the above formula (calculated ABR). Both methods will be used to describe the study results.

If the NB model converges, the Wilcoxon Rank Sum to compare the ABR between the randomized arms will be provided as a sensitivity analysis. However, if the convergence of the NB model is not achieved or is questionable, the primary efficacy analysis will be based on the Wilcoxon Rank Sum of ABR according to the above formula.

[no notes on this page]

4.5.2 Secondary Efficacy Endpoint

Type I error for secondary endpoints is controlled through the hierarchical testing framework. The α-level is 0.05. The endpoints are included in the following order:

- A versus B randomized comparison: all bleeds
- A intra-patient: all bleeds
- A intra-patient: treated bleeds
- A versus B randomized comparison: joint bleeds
- C intra-patient: all bleeds
- C intra-patient: treated bleeds
- A versus B randomized comparison: spontaneous bleeds
- A versus B randomized comparison: target joint bleeds
- A versus B randomized comparison: Haem-A-QoL physical health subscale at 24 weeks
- A versus B randomized comparison: Haem-A-QoL total score at 24 weeks
- A versus B randomized comparison: EQ-5D-5L VAS at 24 weeks
- A versus B randomized comparison: EQ-5D-5L index utility score at 24 weeks
- A versus B randomized comparison: Haemo-QoL-SF physical health subscale at 24 weeks
- A versus B randomized comparison: Haemo-QoL-SF total score at 24 weeks

4.5.2.1 All Bleeds

The definition of all bleeds is described in Section 2.3.2.1. The analysis methodology is the NB regression model as for the primary endpoint.

4.5.2.2 Joint Bleeds

The definition of joint bleeds is described in Section 2.3.2.2. The analysis methodology is the NB regression model as for the primary endpoint.

4.5.2.3 Target Joint Bleeds

The definition of bleeds in target joints is described in Section 2.3.2.3. The analysis methodology is the NB regression model as for the primary endpoint.

4.5.2.4 Spontaneous Bleeds

The definition of spontaneous bleeds is described in Section 2.3.2.4. The analysis methodology is the NB regression model as for the primary endpoint.

4.5.2.5 Intra-Patient Comparison

The definition of treated bleeds and all bleeds is as for the primary and secondary endpoints. The analysis methodology is the NB regression model as for the primary endpoint with the exception that the SAS GENMOD procedure will include the REPEATED statement to account for the intra-patient comparison.

[no notes on this page]

4.5.2.6 EQ-5D-5L at 24 Weeks

ANOVA will be used for the analysis of the EQ-5D-5L index utility score using the UK value set and VAS. The model will include, in addition to treatment group, baseline score, time, and treatment by baseline interaction term as covariates.

4.5.2.7 Haem-A-QoL/Haemo-QoL-SF at 24 Weeks

The analysis methodology is the same as for EQ-5D-5L.

4.5.3 Exploratory Efficacy Endpoints

The number of days away from school/work and days hospitalized will be analyzed using descriptive statistics and 95% confidence intervals.

All bleeds will be characterized descriptively, including the type, location, and cause of bleed (surgery/procedure, traumatic, spontaneous). Bleed rates for spontaneous and traumatic bleeds will be calculated.

For EQ-5D-5L, Haem-A-QoL, and Haemo-QoL-SF, exploratory analyses include descriptive analyses of change from baseline and between group comparisons over time for each individual subscale and the overall score. In addition, a paired t-test will be conducted to compare the 24-week with the baseline score for each questionnaire and treatment arm separately.

For EQ-5D-5L number of patients who reported a clinically meaningful change from baseline to Week 24 will be reported. For EQ-VAS a meaningful change is 7 points and for the index scale it is 0.7 points (Walters et al. 2005; Pickard et al. 2007).

Separately, for each EQ-5D-5L completed in connection with a bleed, the level of pain associated with that episode, as well as the other four dimensions, utility score, and general health VAS score will be reported.

4.5.4 Sensitivity Analyses

The sensitivity analyses will include different methods to define bleeds or eligible bleed data and different statistical models.

Different ways to define bleeds or eligible bleed data include:

- Include all bleeds recorded by patients in the electronic patient-reported outcomes device (i.e., without the 72-hour rule)
- Include only patients who received at least 12 weeks of emicizumab treatment
- Count days when treatment for bleeds was administered instead of the bleeds themselves
- For secondary endpoint with intra-patient comparison, include only patients who have at least 12 weeks of follow-up in the NIS

[no notes on this page]

Different statistical models for the bleed rate include:

- ANOVA
- Wilcoxon Rank Sum (calculated ABR)

4.5.5 Subgroup Analyses

Comparative subgroup analyses describing the primary endpoint, treated bleed rate, will be conducted for the randomized portion of the study. In addition, estimated ABR including 95% confidence interval will be calculated for all treatment arms in each subgroup. Note, due to the small sample size, all subgroup analyses will be highly sensitive to variability caused by individual patients and need to be interpreted with caution. No p-values will be calculated.

The prespecified subgroups are:

- Age: <18, ≥ 18
- Age: <65, ≥ 65
- Race: Asian, Black or African American, White, Other
- Hemophilia severity: mild, moderate, severe
- Number of bleeds during 24 weeks prior to study entry: ≤ 9, >9
- Number of target joints: no target joint, any target joint
- Arm C only: by type of pre-study hemophilia treatment

Subgroup analyses are subject to having sufficient patients in a subgroup to provide meaningful results.

In addition, region- and/or country-specific analyses will be performed to support regulatory submission as needed.

4.6 PHARMACOKINETIC ANALYSES

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively at each timepoint by dose group, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will be used to analyze the dose-concentration-time data of emicizumab following SC administration. Population PK parameters, such as clearance and volume of distribution, will be estimated, and the influence of various covariates, such as age, gender, and body weight, on these parameters will be investigated. Secondary PK parameters, such as area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies. These analyses will be reported in a dedicated report.

[no notes on this page]

In addition, region- and/or country-specific analyses will be performed to support regulatory submission as needed (e.g., PK analysis in Japanese vs. non-Japanese patients or analyses based on race/ethnicity).

4.7 SAFETY ANALYSES

Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology, including complete blood count with differential), ECGs, vital signs, and antibodies to emicizumab.

4.7.1 Exposure of Study Medication

Information on study drug administration will be summarized by duration and cumulative dose. In addition, treatment exposure will be summarized, including delays and interruptions. The number of patients whose dose was up-titrated will be summarized.

Patient withdrawals from study treatment will be reported as listings and summary tables.

4.7.2 Adverse Events

Adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade (WHO Criteria) for each treatment arm. All adverse events will be coded using the current version of MedDRA at time of database closure. The total number and percentage of patients with at least one adverse event and total number of adverse events will be summarized. Separate adverse event summaries for serious adverse events, adverse events of special interest, severity, relatedness, and discontinuation/modification will be provided.

4.7.3 Laboratory Data

For clinical laboratory data which were collected from local laboratories, summary statistics in SI units will be presented by treatment arm. Laboratory data not collected in SI units will be converted to SI units as applicable. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

Data on the impact of immunogenicity (anti-emicizumab antibodies) on safety, efficacy, and/or clinical pharmacology and pharmacokinetics will be summarized using standard language/terminology (Shankar et al. 2014).

4.7.4 Vital Signs

Vital signs will be summarized by treatment arm using mean change from baseline tables over time. Measurements consist of heart and respiratory rate, temperature, and systolic and diastolic blood pressures.

[no notes on this page]

4.8 EXPLORATORY BIOMARKER ANALYSES

PD parameters (e.g., aPTT, parameters derived from thrombin generation, FVIII activity) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

4.9 ECG

ECG results and corresponding changes from baseline will be summarized by cohort and visit for QT, RR, HR, QTcB, QTcF, PR, and QRS and T- and U-wave morphology.

4.10 BIOMARKER

All biomarker endpoints are analyzed descriptively with summaries over time and individual patient plots.

4.11 MISSING DATA

On the electronic, handheld device, it is not possible to leave questions unanswered or to enter partial data. Therefore, the data for primary and secondary bleed-related endpoints coming from the electronic, handheld device are complete.

In the site data entry system it is possible to leave the time of a treatment or a bleed blank because the patient might not be able to remember these in a reliable way. In addition, the symptoms of joint and muscle bleed are not collected.

- In order to implement the 72-hour rule, it is assumed that the bleeds and treatments with missing time occurred at 12:00 a.m.
- All bleeds in with an anatomical location in a joint are considered joint bleeds

4.12 INTERIM ANALYSIS

No efficacy interim analysis is planned.

[no notes on this page]

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[no notes on this page]

Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC *EMICIZUMAB* VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
PROTOCOL NUMBER:	BH29884
VERSION NUMBER:	2
EUDRACT NUMBER:	2015-002866-21
IND NUMBER:	122,954
TEST PRODUCT:	*Emicizumab (*RO5534262*)*
PHASE:	Phase III
INDICATION:	Hemophilia A with inhibitors
SPONSORS:	F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.

Objectives and Endpoints

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of prophylactic *emicizumab* compared with no prophylaxis in patients with hemophilia A with inhibitors *(Arms A and B)* on the basis of the following endpoint:

- Number of bleeds over time (i.e., bleed rate)

The primary definition of a bleed is a bleed for which coagulation factors are administered (see protocol).

Secondary Efficacy Objectives

The secondary efficacy objectives and endpoints for this study are as follows:

- Prophylactic *emicizumab* compared with no prophylaxis *(Arms A and B):*
  - To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate
  - To evaluate the efficacy in reducing the number of joint bleeds over time
  - To evaluate the efficacy in reducing the number of target joint bleeds over time
  - *To evaluate the efficacy in reducing the number of all bleeds (i.e., those treated and not treated with coagulation factors) over time*
  - *To evaluate the efficacy in reducing the number of all bleeds over time compared with the patient's historical bleed rate*
  - To evaluate the health-related quality of life (HRQoL) of patients according to Haem-A-QoL (aged ≥ 18) or Haemo-QoL-Short Form (ages 12–17) scores at 24 weeks
  - To evaluate the health status of patients according to EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) scores at 24 weeks

[no notes on this page]

- *Non-randomized,* prophylactic *emicizumab (Arms C and D)*

  To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate

  To evaluate the efficacy in reducing the number of all bleeds over time compared with the patient's historical bleed rate

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of prophylactic *emicizumab* compared with no prophylaxis on the basis of the following endpoints:

- To assess differences in number of days away from school/work
- To assess differences in number of days hospitalized

Safety Objective

The safety objective for this study is as follows:

- To evaluate the overall safety of prophylactic *emicizumab* compared with no prophylaxis in patients with hemophilia A with inhibitors on the basis of the following endpoints:

  The incidence and severity of adverse events

  The incidence and severity of thromboembolic events

  Changes in physical examination findings and vital signs

  Incidence of laboratory abnormalities

  Incidence and severity of injection-site reactions

  Incidence of adverse events leading to drug discontinuation

  Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events

  Incidence and clinical significance of anti-*emicizumab* antibodies

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the exposure (C_{trough}) of *emicizumab* prior to drug administration on Day 1 at the following timepoints:

- Every week during Weeks 1–4 on *emicizumab*
- Every 2 weeks during Weeks 5–8 on *emicizumab*
- Every 4 weeks during Weeks 9–24 on *emicizumab*
- Every 8 weeks during Weeks 25–48 on *emicizumab*
- Every 12 weeks thereafter while on *emicizumab*, until the end of the study

Exploratory Biomarker Objectives

The exploratory biomarker objectives for this study are as follows:

- *To assess potential pharmacodynamic (PD) biomarkers of emicizumab, including but not limited to aPTT, thrombin generation, and factor VIII (FVIII) activity, at timepoints throughout the study*
- [redacted]

Study Design

Description of Study

This randomized, multicenter, open-label, Phase III clinical study will enroll patients aged 12 years or older with hemophilia A who have inhibitors against FVIII. Approximately 51 patients with inhibitors who received episodic treatment with bypassing agents prior to study

[no notes on this page]

entry will be enrolled globally and randomized in a 2:1 ratio (see protocol) to receive either prophylactic *emicizumab* at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously thereafter (Arm A), or to the control arm (Arm B), which will consist of no prophylaxis. Given the potential heterogeneity of bleed rates in the study patient population, randomized patients will be stratified according to the number of bleeds they experienced over the last 24 weeks prior to study entry (<9 or ≥ 9 bleeds) to ensure a balance of inhibitor patients with lower versus higher number of bleeds, respectively, at baseline across the two randomized arms of the proposed Phase III study. All patients will continue to receive standard of care/background treatment with their usual episodic bypassing agent therapy to treat breakthrough bleeds, as needed.

In addition, given that some patients with hemophilia A with inhibitors are also currently treated with bypassing agents on a prophylactic basis, approximately *30-50* patients with inhibitors on prophylactic bypassing agents will be enrolled in a separate therapeutic arm (Arm C) to receive prophylactic *emicizumab* at the same dose and schedule (see protocol). *Enrollment into Arm C will continue for 24 weeks after Arms A and B have been closed to enrollment or until 50 patients have been enrolled, whichever occurs earlier, in order to collect additional safety and efficacy from patients previously on prophylactic bypassing agents.*

Of note, all patients who participated in Study BH29768 (a non-interventional study; described at the end of this section) received priority to participate in a future emicizumab interventional study. A separate, therapeutic arm (Arm D) will open at a future timepoint if there remain patients on episodic bypassing agents who participated in Study BH29768 but were unable to enroll in Arms A or B before they closed to enrollment. Arm D will yield additional efficacy, safety, PK, and PD data and enable collection of plasma samples [redacted].

The primary efficacy analysis, defined as comparing the number of bleeds over time for patients randomized to receive prophylactic *emicizumab* versus no prophylaxis, will be conducted after *all randomized patients have completed 24 weeks in the study or* the last randomized patient *who has not completed* 24 weeks in the study discontinues study participation, whichever occurs first.

To obtain additional safety and efficacy data, prior episodic bypassing agent patients who had been randomized to not receive *emicizumab* (control arm, Arm B) will *be offered treatment with* prophylactic *emicizumab* at the same dose and schedule as patients who started Study BH29884 on *emicizumab* once they complete 24 weeks in the study. In addition, after *at least* 24 weeks on prophylactic *emicizumab*, all patients will be able to continue on their 1.5 mg/kg/week maintenance dose or may be provided the option to increase their dose to 3 mg/kg/week if they meet protocol-defined criteria of suboptimal response and receive approval from the Medical Monitor to do so (see protocol). Patients who continue to derive clinical benefit will be given the opportunity to continue receiving prophylactic *emicizumab* [redacted].

During the study, patients (or their legally authorized representative) will be asked to record their bleeds and medication use on an electronic, handheld device (see protocol). The bleed/medication questionnaire should be completed whenever a bleed or medication use occurs. In the event of no bleed or medication use, the patient should complete the questionnaire at least once a week to serve as confirmation that no bleed or medication use occurred. In addition, health status information will be collected whenever a bleed is reported. HRQoL, health status, patient safety, and days of school or work missed will be assessed every 4 weeks for approximately 24 weeks and every 4–12 weeks thereafter, as outlined in the schedule of assessments.

Physical examinations, vital sign assessments, ECG, and laboratory assessments will be collected as per the schedule of assessments and will be the same for all patients receiving *emicizumab*, regardless of whether they are enrolled in the randomized portion of the study or in the separate non-randomized arms. Adverse events will be captured on an ongoing basis, as they occur during the study.

All patients who receive *emicizumab* in the study will undergo PK assessment. As *emicizumab* is intended in this study for prophylactic use only (i.e., not to treat bleeds that have already occurred), neither activated prothrombin complex concentrate (aPCC) nor recombinant

[no notes on this page]

activated factor VIII (rFVIIa) interfere with *emicizumab* PK assessments, and some patients with hemophilia A with inhibitors require frequent dosing with bypassing agents due to having many bleeds or being on prophylaxis, a washout period is not required prior to *enrollment* so that new bleeds are minimized and treatment for any *prior* bleed is not interrupted.

Exploratory PD biomarkers (e.g., aPTT, FVIII activity, thrombin generation assay) will be collected as per the schedule of assessments. As values for these tests are normalized by even low plasma concentrations of *emicizumab* (see protocol), a variety of assay formats (one-stage, chromogenic) and modifications (pre-dilution of patient plasma) will be investigated for assessment of PD response at higher *emicizumab* plasma concentrations. [redacted] In addition, factor IX (FIX) and factor X (FX) antigen levels will be monitored.

Throughout the study, biomarkers related to thromboembolism (e.g., D-dimer, prothrombin 1.2 fragment) and *emicizumab* trough concentrations, will be collected as per the schedule of assessments. Immunologic biomarkers (i.e., anti-*emicizumab* antibodies) will also be measured as per the schedule of assessments (see protocol).

An independent Data Monitoring Committee (iDMC) composed of, at minimum, hemostasis/thrombosis experts and a statistician will be in place throughout the duration of the study and will monitor patient safety at pre-specified intervals and ad hoc as needed throughout the study.

Breakthrough bleeds will be treated with bypassing agents according to standard-of-care and captured as they occur on the *electronic, handheld* device. Of note, the clinical experience in the ongoing Phase I/II clinical studies includes the treatment of over [redacted] breakthrough bleeds in patients receiving *emicizumab* with either FVIII or bypassing agents, without any related safety concerns reported. Investigators will be asked to contact the Medical Monitor in the event of suspected lack or loss of efficacy of *emicizumab* in order to discuss potential laboratory evaluations (e.g., anti-*emicizumab* antibodies, coagulation tests) to be performed as well as to re-evaluate the patient's benefit-risk of continued treatment. When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, category of bleed, time of each individual bleed (day, start time), symptoms of bleed, and treatment for bleed. Health status information will also be collected on the day a bleed occurs.

The reason for the use of coagulation products (e.g., aPCC or rFVIIa) will be documented (e.g., bleeding, prophylaxis). A thorough documentation of the treatments for bleeds will be requested, including agent, start time, dose, and *reason for treatment*. *The* number of infusions needed to treat the bleed *will be derived from the medication log*.

A non-interventional study (BH29768) has been initiated to document the number and types of bleeds and current treatment with episodic or prophylactic bypassing agents, as well as collect information on HRQoL, health status, and safety in patients with hemophilia A with FVIII inhibitors. The assessments in the non-interventional study will mitigate the risk of underreporting of bleeds that oftentimes occurs in the real world, and the resulting data will serve as a source of comparator information for some analyses conducted in the Phase III clinical study (Study BH29884). The non-interventional study will also allow an investigation of the feasibility of using an electronic, *handheld* device that has been developed to record data related to bleeds, *hemophilia treatments,* HRQoL, and health status. In addition, the non-interventional study will enable earlier identification and confirmation of patients who may qualify for the Phase III clinical study. It is anticipated that a significant number of patients participating in Study BH29768 will enroll in Study BH29884, as long as they meet the inclusion and exclusion criteria of the study and are able to enroll at a participating site while the study is open for enrollment.

[no notes on this page]

Appendix 1
Protocol Synopsis (cont.)

Number of Patients

This global study will enroll approximately *81–101 patients in Arms A, B, and C, as well as additional patients in Arm D if it is opened.*

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of patient-reported outcomes questionnaires and bleed/*medication* questionnaire through the use of an electronic device
- Aged 12 years or older at the time of informed consent
- Body weight ≥ 40 kg at the time of screening
- Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (i.e., ≥ 5 Bethesda Units)
- Documentation of treatment with episodic or prophylactic bypassing agents for at least the last 24 weeks
- ≥ 6 *bleeds in the last 24 weeks prior to screening* (if on an episodic bypassing agent regimen) or ≥ 2 *bleeds in the last 24 weeks prior to screening* (if on a prophylactic bypassing agent regimen)
- Adequate hematologic function, defined as platelet count ≥ 100,000/μL and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin ≤ 1.5 × the upper limit of normal (ULN) (excluding Gilbert's syndrome) and AST and/or ALT ≤ 3 × ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine ≤ 2.5 × ULN and creatinine clearance by Cockcroft-Gault formula ≥ 30 mL/min
- For women who are not postmenopausal (≥ 48 weeks of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined highly effective contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of contraceptive methods with a failure rate of <1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a *non-lipid-based* spermicide.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Inherited or acquired bleeding disorder other than hemophilia A
- Ongoing (or plan to receive during the study) immune tolerance induction therapy or prophylaxis with FVIII *with the exception of patients who have received a treatment regimen of FVIII prophylaxis with concurrent bypassing agent prophylaxis*

[no notes on this page]

- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Previous *(in the past 12 months)* or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which antithrombotic treatment is not currently ongoing) or *current* signs of thromboembolic disease
- *Other conditions (e.g., certain* autoimmune *diseases) that may increase the risk of bleeding* or *thrombosis*
- History of *clinically significant* hypersensitivity associated with monoclonal antibody therapies or components of the *emicizumab* injection
- Known HIV infection with CD4 count < 200 cells/μL within 24 weeks prior to screening
- Use of systemic immunomodulators (e.g., interferon or rituximab) at enrollment or planned use during the study, with the exception of antiretroviral therapy
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study or that would, in the opinion of the investigator or Sponsor, preclude the patient's safe participation in and completion of the study or interpretation of the study results
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Receipt of

  Emicizumab in a prior investigational study

  An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration

  A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter

  An investigational drug concurrently
- Unwillingness to use highly effective contraception methods for the specified duration in the protocol (females only, unless required otherwise by the local health authority)
- Clinically significant abnormality on screening evaluations or laboratory tests that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient
- Pregnancy or lactation, or intent to become pregnant during the study

  Women who are not postmenopausal (≥ 48 weeks of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

End of Study and Length of Study

The approximate length of the entire study from the first patient enrolled to the Last Patient Last Visit (LPLV; *see below*) is approximately 108 weeks.

The end of this study is defined as the date when the last *remaining patient has completed the last visit (i.e., LPLV), as defined below:*

- *Has completed at least 24 weeks of emicizumab treatment and either transferred to* [redacted] *receive further emicizumab as per Roche Global Policy on Continued Access to Investigational Medicinal Products or to commercial product*

  OR
- *Completes the end of study safety follow-up visit 24 weeks after discontinuing emicizumab*

  OR
- *Has withdrawn consent*

[no notes on this page]

OR

- *Is lost to follow-up*

Investigational Medicinal Products

Test Product (Investigational Drug)

Emicizumab 3 mg/kg/week subcutaneously for 4 weeks when initiating treatment, followed by 1.5 mg/kg/week subcutaneously for a minimum of 24 weeks total. There will be an option to increase the dose after *at least* 24 weeks of treatment to 3 mg/kg/week if a patient meets *the* criteri*on* for insufficient control of bleeds on the 1.5 mg/kg/week *emicizumab* dose and with approval from the Medical Monitor.

To support home administration of the drug, patients/caregivers will be required to complete in-person, instructional training on how to administer *emicizumab* as a subcutaneous (SC) injection. Patients/caregivers will be taught to perform the injections utilizing the Instructions for Use document. They will observe at least one SC injection performed by a healthcare provider (HCP) and will need to successfully administer at least one SC injection under an HCP's watch prior to starting home administration. The first five weekly treatments will be administered in a monitored setting, such as an infusion center, clinic, or hospital, in conjunction with *emicizumab* PK assessments. Patients will be observed for a minimum of 60 minutes after the first three doses. Patients/caregivers will be instructed on how to recognize signs/symptoms of hypersensitivity (including anaphylaxis) and obtain emergency care in the event of such reactions occurring. Each site will have the discretion to provide additional training or include additional observation (e.g. after the fourth and fifth doses), if deemed appropriate. If, despite additional training, the investigator determines that the patient/caregiver is unable to inject *emicizumab*, a trained and proficient caregiver or HCP should be identified to administer the SC injections. Patients/caregivers will be provided with contact information for the clinic in case they have questions related to self-administration between visits.

Compliance in the home setting is to be monitored by *reviewing reported* hemophilia medication *use and recording collected* used and unused *vials at each site*.

Statistical Methods

Efficacy Analyses

The primary and secondary efficacy analyses to evaluate the clinical effect of prophylactic *emicizumab* compared with no prophylaxis will include all randomized patients, with patients grouped according to the treatment assigned at randomization. For patients previously treated with prophylactic bypassing agents *in Arm C and episodic bypassing agents in Arm D (if opened)*, the efficacy analyses will include all enrolled patients.

Primary Efficacy Endpoint

The primary efficacy objective is to evaluate the clinical effect of prophylactic *emicizumab* compared with no prophylaxis on the number of bleeds over time. The definition of a bleed is described in the protocol, *with the primary endpoint comparing bleeds requiring treatment.*

The primary efficacy analysis will be conducted after all randomized patients have *completed* 24 weeks in the study or *the last randomized patient who has not completed 24 weeks in the study discontinues* study participation, whichever occurs first, and using an intent-to-treat principle. The comparison of the number of bleeds over time between the randomized treatment arms will be performed using a negative binomial (NB) regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study included as an offset in the model. The model also includes the number of bleeds (<9 or ≥ 9) in the last 24 weeks prior to study entry as a stratification factor in the randomization. This analytic model estimates the rate ratio, λ_t/λ_c., which quantifies the risk of bleeding associated with prophylactic *emicizumab* (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level, and the estimated risk ratio is compared with 1, assuming the following statistical hypothesis:

H_0 (null hypothesis): Rate Ratio $= 1$ versus H_1 (alternative hypothesis): Rate Ratio $\neq 1$

[no notes on this page]

The treatment effect therein is based on a contrast statement in the model with use of the SAS GENMOD procedure. Statistical significance at the pre-specified alpha level will be based on a Wald testing procedure. Bleed rates for prophylactic *emicizumab* and no prophylaxis and the rate ratio will be presented and include 95% confidence intervals.

The number of bleeds can also be annualized for each patient using the following formula: annualized bleed rate (ABR) = (Number of bleeds during the efficacy period/Total number of days during the efficacy period) × 365.25. If the *NB* model converges, an analysis of variance (ANOVA) to compare the mean ABR between the randomized arms will be provided only as a sensitivity analysis. However, if the convergence of the NB model is not achieved or is questionable, the primary efficacy analysis will be based on the *Wilcoxon Rank Sum* of ABR.

Although this is an open-label study, Sponsor personnel will not have access to efficacy summaries by treatment arms prior to the formal reporting of the study results.

A detailed description of the statistical methods that will be used for the primary and secondary efficacy analyses will be provided in the Statistical Analysis Plan (SAP).

Secondary Efficacy Endpoints

The number of all bleeds (i.e., those treated and not treated with coagulation factors) over time in patients who receive prophylactic emicizumab compared with no prophylaxis will be assessed as a secondary efficacy endpoint. Also, the number of *treated* bleeds *and all bleeds* over time will be compared with patients' bleed rate prior to study entry. *Finally,* the number of joint and target joint bleeds over time between the *emicizumab* prophylaxis and no prophylaxis arms will be evaluated.

HRQoL (using the Haem-A-QoL or the Haemo-QoL-SF) and health status (using the EQ-5D-5L) will be assessed on a regular basis, as per the schedule of assessments (scheduled). Health status will also be assessed in the event of a bleed (unscheduled).

Adherence with the HRQoL and health status measures will be summarized.

Because different HRQoL measures (Haem-A-QoL and the Haemo-QoL-SF) are being used for the adult and adolescent patients, all calculations and analyses will be conducted separately for adults and adolescents. Scale scores for the Haem-A-QoL and Haemo-QoL-SF will be calculated and summarized descriptively. The HRQoL scale scores for all patients will be evaluated at 24 weeks in the study, a timepoint that is consistent with other recent registrational studies in hemophilia and analyses of such data. For each treatment arm, paired t-tests will be used to compare the 24-week with the baseline scale scores for each HRQoL measure. Within-subject and between-group changes from baseline on the different HRQoL scale scores will also be calculated at 24 weeks.

For the assessments of the EQ-5D-5L performed every 4 weeks, the number and percentage of patients in each of the five categories for each question for each group will be assessed. Changes in the EQ-5D-5L index utility score from baseline will also be compared between groups. In addition, summary statistics including mean, standard deviation, median, minimum and maximum will be displayed for the patients' health state using the EQ-VAS both within and between groups. The proportion of patients who report changes in each group exceeding the clinically meaningful threshold on the EQ-5D-5L index and EQ-VAS scores in each group will be reported at 24 weeks.

Separately, for each EQ-5D-5L completed in connection with a bleed, the level of pain associated with that episode, as well as the utility score and general health score will be reported.

Secondary endpoints used for labeling and those that are solely for scientific interest will be specified in the SAP. The method used for controlling the type 1 error rate will also be described.

Exploratory Efficacy Analysis

Summary statistics of the number of work/school days missed and days hospitalized will be presented by treatment arm.

[no notes on this page]

Appendix 1
Protocol Synopsis (cont.)

Safety Analyses

The safety analyses population will be based on all enrolled patients grouped according to the actual treatment received. Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology, including complete blood count with differential), ECGs, vital signs, and antibodies to *emicizumab*.

To evaluate the overall safety of prophylactic *emicizumab* compared to no prophylaxis, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade for each treatment arm.

For clinical laboratory data, summary statistics will be presented by treatment arm. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

Data on the impact of immunogenicity (anti-*emicizumab* antibodies) on safety, efficacy, and/or clinical pharmacology and PK will be summarized *using* standard language/terminology.

Although this is an open-label study, Sponsor personnel will not have access to safety summaries by treatment arm prior to the formal reporting of the study results. HCPs at participating study sites, as well as the Sponsor's drug safety and medical monitoring staff, will have access to the treatment assignments of patients for safety monitoring purposes only.

The iDMC (see protocol) will evaluate safety at periodic safety reviews and recommend to the Sponsor whether the study should be stopped early. All summaries and analyses will be prepared by the independent Data Coordinating Center (iDCC) and presented by treatment arm for the iDMC's review. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

Pharmacokinetic Analysis

For all patients, pre-dose (trough) plasma concentrations of *emicizumab* will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will be used to analyze the dose-concentration-time data of *emicizumab* following SC administration. Population PK parameters, such as clearance and volume of distribution, will be estimated, and the influence of various covariates, such as age, gender, and body weight, on these parameters will be investigated graphically. Secondary PK parameters, such as area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies. These analyses will be reported in a dedicated report.

Exploratory *Biomarker* Analyses

PD parameters (e.g., aPTT, parameters derived from thrombin generation, FVIII activity) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Determination of Sample Size

The sample size for this study is based on clinical rather than statistical considerations, taking into account the limited number of patients with hemophilia A with inhibitors available for participation in clinical studies and in an effort to collect sufficient data to assess the safety and efficacy of *emicizumab*.

The sample size calculation is based on the evaluation of the primary efficacy endpoint, defined as the number of bleeds over time (i.e., bleed rate) with *emicizumab* (treatment group, λ_t) versus no prophylaxis (control group, λ_c), which are said to follow a NB distribution with γ_t and γ_c described as shape parameters for treatment and control groups, respectively. With consideration of enrollment feasibility, a sample size of 45 patients, assuming an allocation ratio of 2:1 (30 patients in treatment group and 15 patients in control group), will achieve a power of more than 95% for λ_t and λ_c ranging from 1 to 4 and 18 to 30, respectively (see protocol). Here, the patients from the two groups are followed up to 0.5 units of time (i.e., 24 weeks). *Of note, assuming λ_c =18 and λ_t =4 results in an expected ABR reduction of 78% in the treatment versus control*

[no notes on this page]

groups. Sample size calculations were performed with East®, Version 6 (Cytel, Cambridge, MA), which allows specific shape parameters for both the treatment and control groups.

However, the above approach to sample size calculation assumes similar follow-up for each patient. Because this is unlikely to be seen in the study, power was also estimated by simulation to account for different follow-up times among patients. Conducting simulations on the basis of a NB regression model including an offset variable to account for variable follow-up times, with all other assumptions remaining the same as previously described, the sample size is projected to have greater than 95% power at the 2-sided 0.05 level of significance.

The analysis will include all enrolled patients, regardless of *their length of follow-up. Therefore, to ensure the analysis is based on sufficient follow-up data and* with 2:1 treatment to control randomization, approximately 34 *patients in the randomized emicizumab* treatment *arm* and 17 patients *in the control arm* (approximately 51 patients in total) will be enrolled.

During the study, a re-assessment of the initially specified sample size based on aggregated (not by treatment arm) data to date (and potentially from the non-interventional study [BH29768] findings) may be performed. This may result in an increase in sample size, if necessary, to maintain adequate power without affecting the type 1 error rate. Study integrity will be upheld, as access to information via aggregated analyses and their results will be minimized to limit operational bias.

[no notes on this page]

Appendix 2
Schedule of Assessments

Schedule of Assessments–Arms A, C, *and D*																		
	Screen-ing	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Every 8 Weeks from Wk 33	Wk 49	Every 12 Weeks from Wk 61	*At Least Weekly* [a]	Study Completion/ ET	Safety F/U Visit [b]
Informed consent [c]	x																	
Inclusion/exclusion criteria	x																	
Medical history and demographics [d]	x																	
Physical examination [e]	*x*	x				x						x		x			x	x
Vital signs [f]	x	x [f]	x	x	x	x	*x*	x	x	x	x	x [f]	x	x [f]	x		x [f]	x [f]
Concomitant medications [g]		x				x		x	x	x	x	x	x	x	x		x	x
ECG [h]	x	x [h]				x						x	x [h]				x	
Safety laboratory assessments [i]	x [i]	x	x	x	x	x		x	x	x	x	x	x	x	x		x	x
Anti-FVIII antibodies [j]	x	*x*					*x*					*x*		*x*	*x* [j]			x
Anti-*emicizumab* ant bodies [k]		x [k]				x	*x*	x [k]	x	x [k]	x	x [k]	x [k]	x [k]	x [k]		x	x [k]
Bleed/*medication* questionnaire [l]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	x	*x*	
Bleed/*medication* data review [m]		x	*x*	*x*	*x*	x	*x*	x	x	x	x	x	x	x	x		x	x
Adverse events [n]		x	x	x	x	x	*x*	x	x	x	x	x	x	x	x		x	x
IMP management [o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
HRQoL [p]		x				x		x	x	x	x	x	x	x	x		x	
Health status (EQ-5D-5L) [q]		x				x		x	x	x	x	x	x	x	x		x	
PK assessment [r]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
PD biomarkers assessment [s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
RCR whole blood DNA sample [t]			*x*															

[no notes on this page]

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments–Arm B									
	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	*Every 4 Weeks from* Wk 9 *Until Switch to Emicizumab at Wk 25*	*At Least Weekly* [a]
Informed consent [c]	x								
Inclusion/exclusion criteria	x								
Medical history & demographics [d]	x								
Physical examination [e]	*x*	x							
Vital signs [f]	x	x [f]				x		x	
Concomitant medications [g]		x				x		x	
ECG [h]	x	x [h]							
Safety laboratory assessments [i]	x [i]	x							
Anti-FVIII antibodies [j]	x								
Bleed/*medication* questionnaire [l]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	x
Bleed/*medication* data review [m]		x				x		x	
Adverse events [n]		x				x		x	
HRQoL [p]		x				x		x	
Health status (EQ-5D-5L) [q]		x				x		x	
PD biomarkers assessment [s]	x	x							
RCR whole blood DNA sample [t]		x							

[no notes on this page]

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments–Arm B																	
	Wk 25	Wk 26	Wk 27	Wk 28	Wk 29	Wk 31	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	Every 8 Weeks from Wk 57	*Wk 73*	Every 12 Weeks from Wk 85	*At Least Weekly*[a]	Study Com-pletion/ ET	Safety F/U Visit [b]
Targeted physical exam [e]	x				x						x		*x*			x	x
Vital signs [f]	x [f]	x	x	x	x	*x*	x	x	x	x	x [f]	x	*x* [f]	x		x [f]	x [f]
Concomitant medications [g]	x				x		x	x	x	x	x	x	*x*	x		x	x
ECG [h]	x				x						x	x [h]				x	
Safety laboratory assessments [i]	x	x	x	x	x		x	x	x	x	x	x	*x*	x		x	x
Anti-FVIII antibodies [j]	x [j]					*x*					*x*		*x*	*x* [j]			x
Anti-*emicizumab* antibodies[k]	x [k]				x	*x*	x [k]	x	x [k]	x	x [k]	x [k]	*x* [k]	x [k]		x	x [k]
Bleed/*medication* questionnaire [l]															x		
Bleed/*medication* data review [m]	x				x		x	x	x	x	x	x	*x*	x		x	x
Adverse events [n]	x	x	x	x	x	*x*	x	x	x	x	x	x	*x*	x		x	x
IMP management [o]	x	x	x	x	x	x	x	x	x	x	x	x	*x*	x		x	
HRQoL [p]	x				x		x	x	x	x	x	x	*x*	x		x	
Health status (EQ-5D-5L) [q]	x				x		x	x	x	x	x	x	*x*	x		x	
PK assessment [r]	x	x	x	x	x	x	x	x	x	x	x	x	*x*	x		x	x
PD biomarkers assessment[s]	x	x	x	x	x	x	x	x	x	x	x	x	*x*	x		x	x

[no notes on this page]

Appendix 2
Schedule of Assessments (cont.)

eCRF = electronic Case Report Form; EQ-5D-5L = EuroQoL Five-Dimension-Five Levels Questionnaire; ET = early termination; F/U = follow-up; FVIII = factor VIII; HRQoL = health-related Quality of Life; IMP = investigational medicinal product, PD = pharmacodynamics; PK = pharmacokinetic; RCR = Roche Clinical Repository; Wk = Week.

Notes: *The maximum allowable time between Screening and enrollment is 4 weeks; if the elapsed time between Screening and enrollment is more than 4 weeks, Screening must be repeated.* All assessments should be performed within ± 2 days of the scheduled visit for the first 12 weeks, then ± 7 days thereafter; *for Arm B patients, emicizumab should be offered at Week 25, after which all assessments should be performed within ± 2 days of the scheduled visit for the first 12 weeks on emicizumab, then ± 7 days thereafter.* Except for the bleed/*medication* questionnaire, HRQoL, and health status, all other patient data will be collected during office visits. On treatment days, pre-injection blood collection should be made 0–*120* minutes before the injection.

[a] *Patients will complete the bleed/medication questionnaire when they have bleeds or hemophilia medication use, including emicizumab, or at minimum every week.*

[b] A safety follow-up visit will occur 24 weeks after discontinuing *emicizumab*.

[c] Obtain written informed consent (or patient assent and parent written informed consent if patient is an adolescent) before distribution of *an electronic, handheld* device and collection of any data. Randomization and enrollment form will be completed after informed consent and/or assent is obtained.

[d] Collected from patient medical records and documented in the eCRF, including information on target joint(s).

[e] *A complete physical examination will be performed at Screening and targeted physical examinations at visits indicated.* Targeted physical examination of joints (for bleeds, evidence of arthropathy) and skin (for bruises, hematomas, and injection-site reactions), in addition to other organ systems *should be performed* as clinically indicated. *If Screening and Week 1 occur on the same date, the physical examination entry may be entered once for the Week 1 visit.*

[f] Body temperature (oral*, rectal, axillary,* or tympanic), blood pressure, pulse, respiratory rate, and weight *will be measured and recorded in the eCRF at each clinic visit prior* to *any injections (if applicable). Height will be measured and recorded only at Screening and at Weeks 25 and 49 after starting emicizumab. At the investigator's discretion, vital signs may be taken to help monitor for hypersensitivity reactions during or after injections, but they should not be entered into the eCRF. If* Screening *and Week 1 occur on the same date, the vital signs entry may be entered once for the Week 1 visit.*

[g] Concomitant medications (e.g., extra pain medication with bleed) will be asked about at each clinic visit, excluding treatments for bleeds (i.e., bypassing agents and other medications to treat bleeds), which will be collected on the bleed questionnaire. Hemostatic medications to treat or prevent bleeds in the week prior to starting *emicizumab* will also be collected.

[h] If screening ECG *is* abnormal, repeat at Week 1 *(or Week 2, if Screening and Week 1 occur on the same date).* ECGs will also be performed 4–8 and 24 weeks after starting *emicizumab* or dose up-titration, as well as at study completion/early termination.

[i] Laboratory data (performed locally) include: complete blood count with differential *and* serum chemistries. Female patients with childbearing potential will be required to have a negative serum pregnancy test result at screening *(and again within 7 days prior to the first dose of emicizumab,*

[no notes on this page]

if applicable) and urine pregnancy tests performed at every clinic visit, with the exception of Weeks 2–4 and 7. If patients undergo up-titration of their dose after *≥ 24 weeks on emicizumab, an additional blood draw for safety laboratory assessments should be performed within the first 4 weeks after up-titration. If Screening and Week 1 occur on the same date, sufficient blood should be drawn to cover the required laboratory tests for both visits (and one entry recorded in the eCRF under Week 1). Safety laboratory assessments completed at Screening visit do not have to be repeated at Week 1 if the period between Screening and Week 1 is ≤ 5 days and there has been no change in the patient's health status as assessed by the investigator; however, PD biomarker samples should be collected at both visits if Screening and Week 1 occur on different dates.*

[j] Anti-FVIII antibodies will be *analyzed* at *Screening;* pre-dose *after starting emicizumab at Weeks 1, 7, 25, 49, and 73;* and at the safety follow-up visit (i.e., 24 weeks after discontinuing *emicizumab) at a central laboratory.*

[k] *Samples to detect anti-emicizumab* antibodies will be collected prior to *emicizumab* administration. Anti-*emicizumab* antibodies may also be drawn at the time of hypersensitivity events.

[l] Reported by the patient; includes start date and time, reason, type, location, and associated symptoms of *any* bleed, as well as start date and time, reason, type, and dose of *any hemophilia medication use*.

[m] At the Week 1 visit, patients will be trained on how to use and be provided their own *electronic, handheld* device *to record their bleeds and hemophilia medication use.* Investigator review of patient-reported bleed/*medication* questionnaire information *with the patient/caregiver for completeness and accuracy will occur at visits indicated.* Information regarding *all traumatic* events*, even if they do not result* in *a bleed, is required to* be collected in the eCRF.

[n] Injection-site reaction adverse events will be collected on a separate form from the adverse event form. *See Section 5.3.5.10 for how to record "increased clinical severity of hemophilia" as an adverse event.*

[o] Drug accountability will not be performed at the first visit of *emicizumab* receipt. Drug dispensation will not occur at the study completion/early termination visit.

[p] Haem-A-QoL questionnaire (age ≥ 18) and Haemo-QoL-Short Form (ages 12–17).

[q] On days that patients report having a new bleed and every 4 weeks, they will be prompted to also complete the EQ-5D-5L questionnaire on the *electronic, handheld* device.

[r] *Emicizumab* concentration. Plasma samples for this assessment should be taken prior to injection *of study drug.*

[s] See Appendix 2 for detailed explanation of PD biomarker assessments (Sets 1 and 2). Blood samples *may also* be *drawn to conduct* biomarker *assays at the central laboratory on an unscheduled basis (at the clinical judgment of the investigator) at any time. If Screening and Week 1 occur on the same date, sufficient blood should be drawn to cover the required laboratory tests for both visits (and one entry recorded in the eCRF under Week 1); however, baseline PD samples prior to administration of emicizumab (if applicable) must be drawn.*

[t] Sample for the RCR *is* optional and *requires* an additional signature. *This may be collected at Weeks 1 or 2 or at any other visit.*

[no notes on this page]

STATISTICAL ANALYSIS PLAN AMENDMENT

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC EMICIZUMAB VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
PROTOCOL NUMBER:	BH29884
STUDY DRUG:	Emicizumab (RO5534262)
VERSION NUMBER:	2
IND NUMBER:	122954
EUDRACT NUMBER:	2015-002866-21
SPONSOR:	F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.*
PLAN PREPARED BY:	[redacted]
DATE FINAL:	4 July 2016
DATE AMENDED:	See electronic date stamp below.

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

Name	Reason for Signing	Date and Time (UTC)
[redacted]	Company Signatory	12-Dec-2016 15:55:32

*Chugai will act as the Sponsor only in South Korea, Taiwan, and Japan. The specific details of the legal/regulatory entity within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and the Clinical Trial Application with the Competent Authority.

[no notes on this page]

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The following changes have been made:

- Changed start of efficacy period from the “first entry from the handheld device” to the first entry from the bleed and medication questionnaire (BMQ), in order to better reflect the technical setup at the vendor
- Clarified the end of efficacy period for Arm B to include the cutoff date, because not all patients will have switched to emicizumab at the time of the clinical cutoff
- Changed the definition of treated joint bleeds to better correspond to the International Society on Thrombosis and Haemostasis (ISTH) definition
- Removed the secondary endpoints for Haemo-QoL-SF due to the small number of patients below 18 enrolled to Arms A and B, that is, no hypothesis testing is performed
- Removed the subgroup analysis on hemophilia severity due to the small number of patients in categories other than “severe”
- Added new sensitivity analysis based on health authority feedback.
- Changed the fall back method for primary analysis to be the Van Elteren test instead of the Wilcoxon Rank Sum, because the Van Elteren test corresponds to a stratified test which is more appropriate
- Corrected the limit for clinically meaningful change for EQ-5D-5L to 0.07
- Added example SAP code as an Appendix 3

Additional minor changes have been made to improve clarity and consistency.

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1. BACKGROUND

Hemophilia A is an X-linked recessive bleeding disorder that occurs in approximately 1 in 5000 live male births. Patients with hemophilia A have a deficiency or absence of blood coagulation factor VIII (FVIII), an essential component of the intrinsic pathway in the coagulation cascade (Mannucci and Tuddenham 2001; Franchini and Mannucci 2013).

The development of inhibitory alloantibodies (inhibitors) occurs in approximately 20 – 30% of patients with severe hemophilia A and in 3 – 13% of those with moderate or mild disease (Franchini and Mannucci 2013). Inhibitors neutralize the activity of endogenous FVIII as well as of FVIII administered as replacement therapy. For patients with a history of a high-titer (≥ 5 BU/mL) inhibitor following a re-challenge with FVIII administration (high-responding inhibitor), the only hemostatic options currently available are pro-thrombotic coagulation factors that augment other parts of the coagulation cascade (i.e., “bypassing agents”).

Current standard prophylactic regimens commonly use infusion therapy administered three times weekly; other regimens require daily or every other day administration, depending on the patient’s needs (Shapiro 2013). Major issues with current regimens are the need for adequate venous access and patient/family compliance with regular prophylaxis, especially in the very young pediatric population, in whom central venous access devices have been used to overcome technical difficulties. Thus, both the disease and its treatment have the potential to affect health-related quality of life, the latter through limitations on daily activities that treatment may impose.

The development of effective prophylactic treatment options with decreased immunogenicity and less frequent dosing requirements is a high, unmet medical need in the population of hemophilia A patients with FVIII inhibitors.

Emicizumab is a recombinant, humanized, bispecific, immunoglobulin G4 monoclonal antibody that binds with moderate affinity to activated factor IX and factor X, mimicking the co-factor function of FVIIIa. In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors, as emicizumab shares no sequence homology with FVIII. In addition, emicizumab offers the possibility of subcutaneous (SC) administration, removing the need for venous access. Finally, because of the pharmacokinetic properties of this antibody, markedly extending the dosing interval to once weekly or even less frequently, this novel compound has the potential to dramatically change the treatment of patients with hemophilia A with and without FVIII inhibitors who are in need of effective, safe, and convenient prophylactic therapy.

Currently available experience with emicizumab in humans includes data from one Phase I study (ACE001JP) and its ongoing extension, a Phase I/II study (ACE002JP).

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See Section 1.2 of the protocol for a detailed description of the study results. The results have also been published (Uchida et al. 2015; Shima et al. 2016). Based on these compelling Phase I/II data, a clinical development program in adult and pediatric patients with hemophilia A (both with and without FVIII inhibitors) has been initiated.

[redacted] meetings have been held with [redacted] to discuss the emicizumab development program and Study BH29884. In [redacted], the Sponsor initiated early dialogue with [redacted] and [redacted] through the [redacted] procedure for scientific advice. This procedure was initiated to agree on requirements to support the registration of emicizumab for the prevention of bleeding episodes in adults and adolescents (≥12 years of age) with hemophilia A and FVIII inhibitors. At these meetings, the study design and objectives were discussed. In particular, the methodology for the primary endpoint has been agreed upon [redacted]

2. STUDY DESIGN

This randomized, multicenter, open-label, Phase III clinical study is enrolling patients aged 12 years or older with hemophilia A who have inhibitors against FVIII. Approximately 51 inhibitor patients who received episodic treatment with bypassing agents prior to study entry will be randomized in a 2:1 ratio (see Figure 1). Patients will be randomized either to receive prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously (Arm A), or to the control arm (Arm B), which will consist of no prophylaxis. Given the potential heterogeneity of bleed rates in the study patient population, randomized patients will be stratified according to the number of bleeds they experienced over the last 24 weeks prior to study entry (<9 or ≥9 bleeds) to ensure a balance of inhibitor patients with lower versus higher number of bleeds, respectively, at baseline across the two randomized arms of the Phase III study.

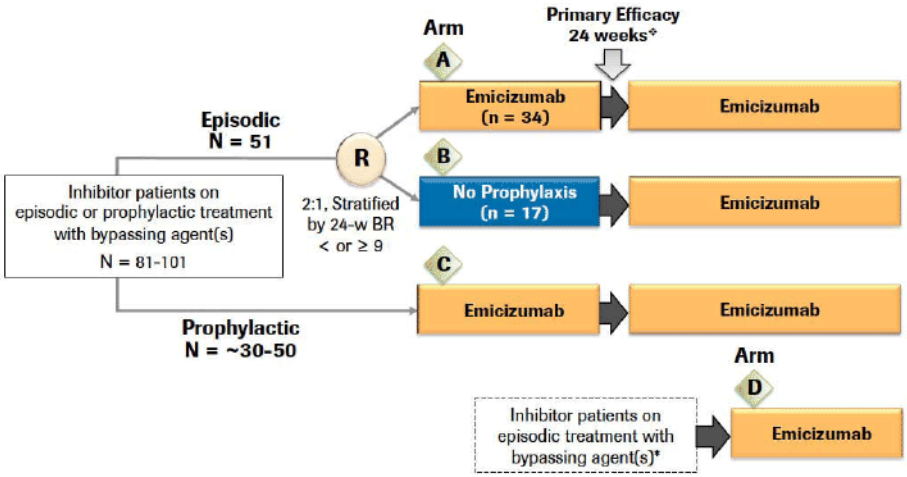
In addition, given that hemophilia A patients with inhibitors are currently treated with bypassing agents on both a prophylactic and episodic basis, approximately 30 – 50 patients with inhibitors previously treated with prophylactic bypassing agents will be enrolled in a separate therapeutic arm (Arm C) to receive prophylactic emicizumab at the same dose and schedule (see Figure 1). Enrollment into Arm C will continue for 24 weeks after Arms A and B have been closed to enrollment or until 50 patients have been enrolled, whichever occurs earlier, in order to collect additional safety and efficacy from patients previously on prophylactic bypassing agents.

Of note, all patients who participated in Study BH29768 (a non-interventional study [NIS]) received priority to participate in a future emicizumab interventional study. A separate, therapeutic arm (Arm D) will open at a future timepoint if there remain patients on episodic bypassing agents who participated in NIS BH29768 but were unable to

[no notes on this page]

enroll in Arms A or B before they closed to enrollment. Arm D will yield additional efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) data and enable collection of plasma samples [redacted] (see Figure 1).

Figure 1 Study Schema



R = randomized, 24-w BR = 24-week bleed rate (prior to study entry)
*Primary efficacy analysis: after all randomized patients have completed 24 weeks in the study or the last randomized patient who has not completed 24 weeks in the study discontinues study participation, whichever occurs first; Arms A and B will close when the last randomized patient has been enrolled; after this time point, Arm C will remain open for 24 additional weeks; potential to up-titrate dose in emicizumab arms if suboptimal response and opportunity to switch from no prophylaxis to emicizumab in control arm after participating in this study for at least 24 weeks
*If episodic patients from Study BH29768 are unable to enroll in Arms A or B before they close, Arm D will open only for such patients at a future timepoint after the last randomized patient has been enrolled

The primary efficacy analysis will be conducted at the earliest timepoint when all randomized patients have either completed 24 weeks of treatment or the last randomized patient who has not completed 24 weeks in the study discontinues from the study. To obtain additional safety and efficacy data on emicizumab, each patient who had been randomized to no prophylaxis (control arm, Arm B) will be provided the opportunity to switch to receive prophylactic emicizumab (at the same dose and schedule as patients who started Study BH29884 on emicizumab) once they complete 24 weeks in the study. In addition, those who had previously been enrolled to receive prophylactic emicizumab (Arms A, C, and D) and who are deriving clinical benefit will be given the opportunity to continue on their 1.5 mg/kg/week maintenance dose [redacted]. After receiving prophylactic emicizumab at a dose of 1.5 mg/kg/week for at least 24 weeks, all patients will be provided the option to increase their dose to 3 mg/kg/week, if they meet protocol-defined criteria of suboptimal response.

[no notes on this page]

Summary of treatments arms is provided below in a tabular format.

Table 1 Treatment Arms

	Treatment Regimen [a]	Randomized (Yes/No)	Previous Bypassing Agent Regimen
Arm A	Prophylactic emicizumab at 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week SC	Yes	Episodic
Arm B Control Arm	No prophylaxis	Yes	Episodic
Arm B After Switch to Emicizumab	Prophylactic emicizumab at 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week SC	Yes Patients in Arm B are allowed to switch to emicizumab after 24 weeks	Episodic
Arm C	Prophylactic emicizumab at 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week SC	No	Prophylaxis
Arm D	Prophylactic emicizumab at 3 mg/kg/week SC for 4 weeks, followed by 1.5 mg/kg/week SC	No	Episodic

SC = subcutaneous

[a] Opportunity for dose up-titration to 3 mg/kg after 24 weeks on emicizumab for all patients in all arms.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1.

2.2 COLLECTION OF BLEED AND MEDICATION DATA

Bleed and medication data are collected through a bleed and medication questionnaire (BMQ), which was developed by the Sponsor given that no standard questionnaire for collection of this data was available.

The BMQ was developed as a patient-reported measure of bleeding episodes (including cause, type, location, and symptoms of bleeds) and hemophilia-related medication use. The draft questions were developed following review of the hemophilia A literature and discussions with medical professionals regarding what information related bleeds was most important to capture. Prior to use in this study, qualitative interviews with patients with hemophilia A were conducted in order to evaluate the measure's content validity and to test the understanding and usability of the BMQ on an electronic, handheld device. Cognitive interviews were conducted in person with a total of 20 patients aged 12 years and older with hemophilia A; the results demonstrated that the BMQ was comprehensive and relevant to patients' experiences with bleeds and treatments.

[no notes on this page]

Recommendations for some minor wording changes based on patient feedback were incorporated in order to improve the content validity of the final BMQ used in this study.

The BMQ is completed by the patient or a caregiver using an electronic, handheld device. Patients are instructed to enter all bleeds and hemophilia-related medications, including emicizumab administrations, as they occur. In case a patient did not experience any bleeds or administer any treatments for a week, the patient is asked to log in to the device and fill in the questionnaire to confirm this. These weekly entries, in addition to the bleeds and medication entries can be also used to assess compliance. Of note, the patient is able to enter bleeds and medications for the past 8 days, including the day the entries are made. This retrospective data entry window was considered acceptable in terms of recall bias and was added in order to optimize the completeness of data collection.

The patient is able to edit and delete bleeds and medications immediately after they are entered. However, if the data have already been submitted to the vendor's database (i.e., after responses have been confirmed by the patient), the patient is no longer able to edit or delete the data. Furthermore, the investigator and patient are instructed to review the data together at every clinic visit. If the patient has been unable to enter data for any reason, the investigator is able to do so using a Web-based site data entry system (not subject to the previous 8-day data entry window). Note, the symptoms of joint and muscle bleeds are not collected in this case because the patient may not be able to reliably remember them. In addition, the investigator is able to request a change be made to the vendor's database by submitting a data clarification request (DCR).

Furthermore, the Sponsor's data manager and Medical Monitor review the patient-entered data for clear inconsistencies against data collected on the electronic Case Report Form (eCRF) or to identify obvious data points to be clarified (e.g., missing entry of the weekly emicizumab injection). These requests are sent to the investigator, who reviews them with the patient, and may enter the data via the site data entry system or request a change to be made in the vendor's database, via a DCR, if necessary.

The Haem-A-QoL, Haemo-QoL-SF, and EQ-5D-5L questionnaires and data regarding days away from school/work are filled in by the patients using the same electronic, handheld device. However, for this type of data, there is no possibility for retrospective data entry, entries through the site data entry system, data clarification requests, or corrections to data in the vendor's database.

Of note, an earlier version of the same BMQ and a comparable method of data collection were used in the NIS BH29768. For patients enrolled in both studies BH29678 and BH29884, this consistency allows data from the two studies to be compared for the secondary endpoint of intra-patient comparison.

[no notes on this page]

2.3 ENDPOINTS

2.3.1 Primary Efficacy Endpoint

Bleed rate is defined as the number of bleeds over the efficacy period. A bleed is included in the primary analysis if it was treated with coagulation factors and fulfills the adapted International Society on Thrombosis and Haemostasis (ISTH; Blanchette 2014) criteria ("treated bleed"), as described in the protocol. More specifically, the following rules are applied.

2.3.1.1 Efficacy Period

The start of the efficacy period for each individual patient is defined as the first day there is data available from the BMQ. For patients starting the study on emicizumab (Arms A, C, and D), this should coincide with the Week 1 visit and the day of the first emicizumab dose. For the patients who do not start the study on emicizumab (Arm B), this should coincide with the Week 1 visit. For these Arm B patients, if they switched to receive emicizumab, a second efficacy period starts on the day of their first emicizumab dose.

For patients on emicizumab, the end of the efficacy period is defined as the date of the clinical cutoff or the date of withdrawal from the initial study period (i.e., treatment phase according to eCRF), whichever is earlier. For patients randomized to no prophylaxis (Arm B) the end of the first efficacy period is defined as the day before the first emicizumab dose was administered for patients who switch to receive emicizumab after 24 weeks or the date of withdrawal from the initial study period (i.e., treatment phase according to eCRF) or the date of the clinical cutoff if neither of the aforementioned events has taken place. For patients whose dose is up-titrated, the efficacy period ends 1 day prior to the first day on the up-titrated dose.

For patients who withdraw from the study before reaching the Week 1 visit, the duration of efficacy period is set to 1 day, and it starts and ends on the day of randomization/enrollment.

For patients whose dose is up-titrated, the bleeds on the up-titrated dose are analyzed separately. The efficacy period on a given up-titrated dose starts with the first day on this dose and ends on the day of the clinical cutoff or the date of withdrawal.

2.3.1.2 Treated Bleed

A bleed is considered to be a "treated bleed" if it is directly followed (i.e., there is not an intervening bleed) by a hemophilia medication reported to be a "treatment for bleed," irrespective of the time between the treatment and the preceding bleed. A bleed and the first treatment thereafter are considered to be pairs (i.e., one treatment belongs to one bleed only), with the following exception: if multiple bleeds occur on the same calendar day, the subsequent treatment is considered to apply for each of these multiple bleeds (which are, however, counted as separate bleeds).

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Bleeds due to surgery/procedure are not included in the primary analysis. Only treatments that were recorded as “treatment for bleed” are included in the determination of a treated bleed.

72-Hour Rule:
Two bleeds of the same type (e.g., “joint,” “muscle,” or “other”) and at the same anatomical location are considered to be one bleed if the second occurs within 72 hours from the last treatment for the first bleed. The last treatment is defined as the last treatment before a new bleed occurs, either in the same or in a different location. This is in-line with the above definition that bleeds and treatments are considered to be pairs.

2.3.2 Secondary Efficacy Endpoints

The same definition of efficacy period for the primary endpoint is used for all bleeds related to the secondary endpoints (see Section 2.3.1.1).

2.3.2.1 All Bleeds

“All bleeds” comprise both treated and non-treated bleeds. In this definition, all bleeds are included, irrespective of treatment with coagulation factors, with the following exception: bleeds due to surgery/procedure are excluded as for the primary analysis.

The endpoint of all bleeds fulfills the adapted ISTH criteria, as described in the protocol for the primary endpoint and the 72-hour rule, in particular. For treated bleeds, it is implemented exactly as defined for the primary endpoint (see Section 2.3). For non-treated bleeds (not followed by any treatments with coagulation factors before the recording of a subsequent bleed), it is implemented by calculating a treatment-free period of 72 hours from the bleed itself.

2.3.2.2 Treated Joint Bleeds

In the analysis of joint bleeds, only treated bleeds that fulfill the 72-hour rule are included. Bleeds due to procedure/surgery are excluded.

Joint bleeds are defined as bleeds where the bleed type is “joint” and unusual sensation (e.g., tingling) has been observed in combination with at least one of the following symptoms: swelling or warmth, pain or decreased range of motion, or difficulty moving the joint compared with usual.

2.3.2.3 Treated Target Joint Bleeds

Target joints are major joints into which repeated bleeds occur (i.e., $\geq$3 bleeds into the same joint over the last 24 weeks prior to study entry). The target joints prior to study entry are identified through the eCRF. The bleeds in target joints during an efficacy period are defined by first selecting the bleeds that fulfill the definition of a treated joint bleed (see Section 2.3.2.2) and then counting how many of these occurred in a target joint prior to study entry. The locations to be taken into account are: shoulder, elbow,

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wrist, fingers/thumb, hip, knee, ankle, sole/heel, and toes. Left and right side of the same joint type are considered to be separate joints.

2.3.2.4 Treated Spontaneous Bleeds

In the analysis of spontaneous bleeds, only treated bleeds that fulfill the 72-hour rule are included.

Bleeds are classified as “spontaneous” if there is no other known contributing factor such as trauma or procedure/surgery.

2.3.2.5 Intra-Patient Comparison

In the intra-patient comparison, only patients who participated in the NIS BH29768 are included. This is because it is possible to apply the detailed definition only if the data are collected with the same granularity for both time periods. Of note, for some patients who participated in NIS BH29768, the total time in that study prior to enrollment in Study BH29884 may be less than 24 weeks.

The efficacy period in NIS BH29768 is defined as the time from the first entry on the electronic, handheld device or site data entry system to the day the patient completed the study. Usually, the date of the first entry is the date the Training Module on the electronic, handheld device is completed.

2.3.2.6 EQ-5D-5L at 24 Weeks

The EQ-5D-5L index utility score using the UK value set and visual analog scale will be evaluated at 24 weeks in the study.

2.3.2.7 Haem-A-QoL at 24 Weeks

Because different measures, Haem-A-QoL and Haemo-QoL-SF, are used for the adult and adolescent patients, respectively, all calculations and analyses will be conducted separately for these two measures. Total score and physical health sub-scale for the Haem-A-QoL will be evaluated at 24 weeks in the study. The secondary endpoints were defined in the protocol before the study started. However, only seven adolescent patients were finally randomized to arms A and B; therefore, the protocol specified secondary endpoints on Haemo-QoL-SF are classified as exploratory and analyses are descriptive only with no hypothesis testing.

2.3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

- Number of days away from school/work
- Number of days hospitalized
- EQ-5D-5L at the time of a bleed and at scheduled intervals not related to bleeding
- Haemo-QoL-SF

[no notes on this page]

2.3.4 Pharmacokinetic Endpoints

The PK endpoint for this study is the exposure (C_{trough}) of emicizumab prior to drug administration at the following time points:

- Every week during Weeks 1 – 4 on emicizumab
- Every 2 weeks during Weeks 5 – 8 on emicizumab
- Every 4 weeks during Weeks 9 – 24 on emicizumab
- Every 8 weeks during Weeks 25 – 48 on emicizumab
- Every 12 weeks, thereafter, while on emicizumab, until the end of the study

2.3.5 Safety Endpoints

Safety parameters to be measured include exposure, adverse events (including serious adverse events, adverse events of special interest, adverse events leading to drug discontinuation, and deaths), clinical laboratory results (hematology, chemistry, and anti-emicizumab antibodies), vital signs, electrocardiogram (ECG), and concomitant medication use.

2.3.6 Biomarker Endpoints

Biomarker endpoints include activated partial thromboplastin time, D-Dimer, peak height thrombin generation, factor IX antigen, factor XIII activity, factor VIII inhibitor, factor VIII activity, factor X antigen and vWF antigen, fibrinogen, prothrombin international normalized ratio and prothrombin fragment 1 + 2.

2.4 DETERMINATION OF SAMPLE SIZE

The sample size for this study is based on both clinical and statistical considerations, taking into account the limited number of patients with hemophilia A with inhibitors available for participation in clinical studies and the goal of collecting sufficient data to assess the safety and efficacy of emicizumab. Nonetheless, a sample size calculation was conducted to assess its adequacy.

The sample size calculation is based on the evaluation of the primary efficacy endpoint, defined as the number of bleeds over time (i.e., bleed rate) with emicizumab (treatment group, λ_t) versus no prophylaxis (control group, λ_c), which are said to follow a negative binomial (NB) distribution with γ_t and γ_c described as shape parameters for treatment and control groups, respectively. With consideration of enrollment feasibility, a sample size of 45 patients, assuming an allocation ratio of 2:1 (30 patients in treatment group and 15 patients in control group), will achieve a power of more than 95% for λ_t and λ_c ranging from 1 to 4 and 18 to 30, respectively (see Table 2). Here, the patients from the two groups are followed up for 0.5 units of time (i.e., 24 weeks). Of note, assuming $\lambda_c = 18$ and $\lambda_t = 4$ results in an expected annualized bleeding rate (ABR) reduction of 78% in the treatment versus control groups. Sample size calculations were performed with East®, Version 6 (Cytel, Cambridge, MA), which allows specific shape parameters for both the treatment and control groups.

[no notes on this page]

However, the above approach to sample size calculation assumes similar follow-up for each patient. Because this is unlikely to be seen in the study, power was also estimated by simulation to account for different follow-up times among patients. Conducting simulations on the basis of a NB regression model including an offset variable to account for unequal follow-up times, with all other assumptions remaining the same as previously described, the sample size is projected to have greater than 95% power at the 2-sided 0.05 level of significance.

The analysis will include all randomized patients, regardless of their length of follow-up. Therefore, to ensure the analysis is based on sufficient follow-up data and with 2:1 treatment to control randomization, approximately 34 patients in the randomized emicizumab treatment arm and 17 patients in the control arm (approximately 51 patients in total) will be randomized.

Table 2 Power Calculations for Arm A versus Arm B

Rate for Control Treatment Arm B (λ_c, n_c=15)	**Rate for Experimental Treatment Arm A** (λ_t, n_t=30)			
	1 (γ_t=0.11)	2 (γ_t=0.22)	3 (γ_t=0.33)	4 (γ_t=0.44)
18 (γ_c=2)	**1** (λ_t / λ_c=0.056)	**0.999** (λ_t / λ_c=0.111)	**0.99** (λ_t / λ_c=0.167)	**0.952** (λ_t / λ_c=0.222)
25 (γ_c=2.78)	**1** (λ_t / λ_c=0.04)	**1** (λ_t / λ_c=0.08)	**0.994** (λ_t / λ_c=0.12)	**0.973** (λ_t / λ_c=0.16)
30 (γ_c=.33)	**1** (λ_t / λ_c=0.033)	**0.999** (λ_t / λ_c=0.067)	**0.995** (λ_t / λ_c=0.1)	**0.978** (λ_t / λ_c=0.133)

2.5 ANALYSIS TIMING

The primary analysis takes place at the earliest time when all randomized patients reach 24 weeks in the study or have withdrawn. The primary comparison consists of Arms A and B. At this time, not all patients in Arms C and D will have been in the study for 24 weeks; however, all available data from these patients will be analyzed at this timepoint as well. Note, the results for Arms C and D need to be interpreted with caution due to the short follow-up for some patients.

The final analysis will occur at the end of the study as defined in the protocol. Additional updates may be performed between the primary and final analysis, as requested by Health Authorities or deemed necessary by the Sponsor.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Patients who received episodic treatment with bypassing agents prior to study entry will be randomized in a 2:1 ratio to receive either prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously, or to the control arm (no prophylaxis). A central randomization procedure will be used for all

[no notes on this page]

patients who fulfill the entry criteria at screening. A block-based randomization method will be used, stratified by the number of bleeds in the last 24 weeks (<9 or ≥ 9). The proposed randomization method is designed to balance treatment group assignment within the prognostic stratification factor.

Patients on prophylactic bypassing agents prior to study entry will be enrolled in a separate therapeutic arm (Arm C) to receive prophylactic emicizumab, at the same dose and schedule as described above. Patients on episodic bypassing agents prior to study entry who participated in the NIS BH29768 but were too late to be randomized due to enrollment of these arms being full, will have an opportunity to enroll in an additional, separate therapeutic arm (Arm D) to also receive prophylactic emicizumab.

3.2 DATA MONITORING

An independent Data Monitoring Committee (iDMC) has been assembled to review the safety data collected during the study. The iDMC consists of, at minimum, two independent hemostasis/thrombosis experts and a statistician, none of whom are otherwise involved in the conduct of study. All analyses for review by the iDMC will be prepared by an independent Data Coordinating Center (iDCC) that is independent of the Sponsor. Analyses of safety events will be conducted after the first 9 randomized patients have completed 8 weeks in the study and again after the first 18 randomized patients have completed 12 weeks in the study. Thereafter, the iDMC will meet at a frequency determined by the iDMC and the Sponsor according to the emerging safety profile.

An iDCC will perform unblinded analyses and provide tables and listings to support the iDMC reviews of safety data. The safety data under review will include demographic data, adverse events, serious adverse events, and laboratory abnormalities (coagulation, hematology, and chemistry). Further information will be given by the iDCC to the iDMC on request.

Following each meeting, the iDMC will recommend to the Sponsor whether the study should continue according to the protocol or may suggest changes to the protocol based on the outcome of the data review. In exceptional cases, the iDMC may recommend stopping the study or closing a treatment arm for safety reasons. The iDMC will monitor the incidence of the adverse events, as well as the overall safety of patients, during the study.

Further details are specified in a separate iDMC charter.

4. STATISTICAL METHODS

4.1 OUTPUT LAYOUTS

The key output layouts are designed to address the study objectives in a flexible manner and provide an overall view of the efficacy and safety of emicizumab. In particular,

[no notes on this page]

patients in Arm B are allowed to switch to receive emicizumab after the first 24 weeks in the study, yielding two “study periods” (i.e., when they receive no prophylaxis for the first 24 weeks [no prophylaxis period] and emicizumab prophylaxis thereafter [emicizumab period]). These two periods are analyzed separately, and either period can be displayed on outputs together with the other treatment arms.

The four key output layouts are:

- **Randomized patients**: comparison of emicizumab (Arm A) versus no prophylaxis (control arm [Arm B prior to switch to emicizumab]); these outputs form the core set of the efficacy comparisons and will be supported by a corresponding safety analysis
- **All patients**: these outputs will be used to describe the baseline characteristics and study conduct
- **All emicizumab patients**: these outputs will provide an overall view of all data collected under emicizumab prophylaxis (including control arm patients after switch) and will include analyses of safety and descriptive efficacy.
- **Intra-patient comparison**: each treatment arm is displayed separately with its own historical control; for evaluations of the secondary endpoint with intra-patient comparison, only patients who participated in the NIS BH29768 are included

Patients may be allowed to up-titrate their emicizumab dose after at least 24 weeks under prophylactic emicizumab if they meet the pre-specified criteria as described in the protocol. The data under the new, higher dose is analyzed and reported separately. Additional summaries will be produced for key safety and exposure on all data (i.e., data before and after up-titration). Note, with longer follow-up or in case up-titration occurs more frequently than expected, outputs on all data may form the core analysis and additional summaries will be produced by dose.

4.2 ANALYSIS POPULATIONS

4.2.1 Randomized Population (ITT)

The primary analysis population for efficacy is the ITT population, defined as all randomized patients (i.e., patients randomized to emicizumab will be counted in this arm even if they received no treatment). Note this population includes only patients in Arms A and B.

4.2.2 All Patients

All Patients includes all patients in their originally assigned treatment arms, according to the interactive voice or Web Response System (IxRS).

4.2.3 All Emicizumab Patients

All Emicizumab Patients is exactly the same for Arms A, C, and D, but for Arm B, it includes only the patients who switched to receive emicizumab.

[no notes on this page]

4.2.4 Pharmacokinetic-Evaluable Population

The PK population includes all patients who have received at least one dose of emicizumab and have at least one post-dose emicizumab concentration result.

4.2.5 Safety Populations

Safety Population 1 includes for Arms A, C, and D, all patients who received at least one dose of emicizumab, and for Arm B, all patients who started the study period (defined as having had the Week 1 visit). Safety Population 2 is exactly the same for Arms A, C, and D, but for Arm B it includes only the patients who received at least one dose of emicizumab.

4.2.6 Non-Interventional Study Population

This population includes patients who participated in NIS BH29768 prior enrollment to this study.

4.2.7 Up-Titrated Population

This population includes patients whose dose was up-titrated to 3 mg/kg.

4.3 ANALYSIS OF STUDY CONDUCT

The flow of patients through the study will be displayed in a “CONSORT” diagram. A clear account of all patients who entered the study, were enrolled and randomized, and entered and completed each period of the study will be displayed. In addition, reasons for premature discontinuation from study treatment and reasons for withdrawing from the study will be described.

Major protocol deviations will be summarized.

Observation time and duration of follow-up, as well as adherence to planned scheduled assessments (Appendix 2) and compliance with data entry into the electronic, handheld device, will also be evaluated.

4.4 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic characteristics (e.g., age, sex, race/ethnicity, weight, and height) and baseline disease characteristics (including number of bleeds in the past 24 weeks, hemophilia severity, previous hemophilia treatments, number of target joints) will be summarized by treatment group for all patients and for all randomized patients (i.e., the ITT population), in particular.

Note that unavoidable imbalances between the treatment groups may occur due to the small size of the study and inherent differences between patients on previous episodic and prophylactic bypassing agent treatment.

4.5 EFFICACY ANALYSIS

Formal hypothesis testing is conducted only for the randomized comparison of Arm A versus Arm B and for the intra-patient comparison in Arms A and C.

4.5.1 Primary Efficacy Endpoint

The primary efficacy objective is to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis on the number of bleeds over time. The definition of a bleed is described in Section 2.3.2, with the primary endpoint comparing bleeds requiring treatment.

The comparison of the number of bleeds over time between the randomized treatment arms will be performed using a NB regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study (efficacy period) included as an offset in the model. The model also includes the number of bleeds (<9 or ≥ 9, according to eCRF) in the last 24 weeks prior to study entry as a stratification factor.

This analytic model estimates the rate ratio, λ_t / λ_c, which quantifies the risk of bleeding associated with prophylactic emicizumab (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level and the estimated risk ratio is compared with 1, assuming the following statistical hypothesis:

H_0 (null hypothesis): Rate Ratio $= 1$ versus H_1 (alternative hypothesis): Rate Ratio $\neq 1$.

The treatment effect therein is based on a contrast statement in the model with use of the SAS GENMOD procedure. Statistical significance at the pre-specified alpha level will be based on a Wald testing procedure. Bleed rates for prophylactic emicizumab and no prophylaxis and the rate ratio will be presented and include 95% confidence intervals.

The number of bleeds will also be annualized for each patient using the following formula:

ABR = (Number of bleeds/number of days during the efficacy period) $\times$ 365.25

In other words, there is two ways to derive the ABR: the NB model (model based, estimated ABR) and the above formula (calculated ABR). Both methods will be used to describe the study results.

If the NB model converges, the Van Elteren test to compare the ABR between the randomized arms will be provided as a sensitivity analysis. However, if the convergence of the NB model is not achieved or is questionable or no bleeds at all were observed in one of the treatment arms, the primary efficacy analysis will be based on the Van Elteren test of ABR according to the above formula.

In addition, an unstratified negative binomial model and Wilcoxon Rank Sum test are performed.

[no notes on this page]

4.5.2 Secondary Efficacy Endpoint

Type I error for secondary endpoints is controlled through the hierarchical testing framework. The α-level is 0.05. The endpoints are included in the following order:

- A versus B randomized comparison: all bleeds
- A intra-patient: all bleeds
- A intra-patient: treated bleeds
- A versus B randomized comparison: treated joint bleeds
- C intra-patient: all bleeds
- C intra-patient: treated bleeds
- A versus B randomized comparison: treated spontaneous bleeds
- A versus B randomized comparison: treated target joint bleeds
- A versus B randomized comparison: Haem-A-QoL physical health subscale at 24 weeks
- A versus B randomized comparison: Haem-A-QoL total score at 24 weeks
- A versus B randomized comparison: EQ-5D-5L VAS at 24 weeks
- A versus B randomized comparison: EQ-5D-5L index utility score at 24 weeks

4.5.2.1 All Bleeds

The definition of all bleeds is described in Section 2.3.2.1. The analysis methodology is the NB regression model or the Van Elteren test as for the primary endpoint.

4.5.2.2 Treated Joint Bleeds

The definition of treated joint bleeds is described in Section 2.3.2.2. The analysis methodology is the NB regression model or the Van Elteren test as for the primary endpoint.

4.5.2.3 Treated Target Joint Bleeds

The definition of treated bleeds in target joints is described in Section 2.3.2.3. The analysis methodology is the NB regression model or the Van Elteren test as for the primary endpoint.

4.5.2.4 Treated Spontaneous Bleeds

The definition of treated spontaneous bleeds is described in Section 2.3.2.4. The analysis methodology is the NB regression model or the Van Elteren test as for the primary endpoint.

4.5.2.5 Intra-Patient Comparison

The definition of treated bleeds and all bleeds is as for the primary and secondary endpoints. The analysis methodology is the NB regression model as for the primary endpoint with the exception that the SAS GENMOD procedure will include a REPEATED statement, to account for the intra-patient comparison.

[no notes on this page]

4.5.2.6 EQ-5D-5L at 24 Weeks

Analysis of variance (ANOVA) will be used for the analysis of the EQ-5D-5L index utility score using the UK value set and visual analogue scale. The model will include, in addition to treatment group, baseline score, time, and treatment by baseline interaction term as covariates.

4.5.2.7 Haem-A-QoL at 24 Weeks

The analysis methodology is the same as for EQ-5D-5L.

4.5.3 Exploratory Efficacy Endpoints

The number of days away from school/work and days hospitalized will be analyzed using descriptive statistics and 95% confidence intervals.

All bleeds will be characterized descriptively, including the type, location, and cause of bleed (surgery/procedure, traumatic, spontaneous). Bleed rates for spontaneous and traumatic bleeds will be calculated.

For EQ-5D-5L, Haem-A-QoL, and Haemo-QoL-SF, exploratory analyses include descriptive analyses of change from baseline and between group comparisons over time for each individual subscale and the overall score. In addition, a paired t-test will be conducted to compare the 24-week with the baseline score for the EQ-5D-5L and Haem-A-QoL questionnaires and treatment arm separately. Due to the limited number of adolescent patients, paired t-tests will not be conducted on the Haemo-QoL-SF scales.

For EQ-5D-5L number of patients who reported a clinically meaningful change from baseline to Week 24 will be reported. For EQ-VAS a meaningful change is 7 points and for the index scale it is 0.07 points (Walters et al. 2005; Pickard et al. 2007).

Separately, for each EQ-5D-5L completed in connection with a bleed, the level of pain associated with that episode, as well as the other four dimensions, utility score, and general health VAS score will be reported.

4.5.4 Sensitivity Analyses

The sensitivity analyses will include different methods to define bleeds or eligible bleed data and different statistical models.

Different ways to define bleeds or eligible bleed data include:

- A versus B randomized comparison: Include all bleeds recorded by patients in the electronic patient-reported outcomes device (i.e., without the 72-hour rule)
- A versus B randomized comparison: Include only patients who received at least 12 weeks of emicizumab treatment
- A versus B randomized comparison: Count days when treatment for bleeds was administered instead of the bleeds themselves

[no notes on this page]

- A versus B randomized comparison: Include only the first 24 weeks of efficacy period in the analysis. Patients who withdraw from study treatment are included up to the point of study treatment withdrawal.
- A intra-patient and C intra-patient: For secondary endpoint with intra-patient comparison, include only patients who have at least 12 weeks of follow-up in the NIS

Different statistical models for the bleed rate include:

- ANOVA
- Van Elteren test (calculated ABR)

4.5.5 Subgroup Analyses

Comparative subgroup analyses describing the primary endpoint, treated bleed rate, will be conducted for the randomized portion of the study. In addition, estimated ABR including 95% confidence interval will be calculated for all treatment arms in each subgroup. Note, due to the small sample size, all subgroup analyses will be highly sensitive to variability caused by individual patients and need to be interpreted with caution. No p-values will be calculated.

The pre-specified subgroups are:

- Age: $<18, \geq 18$
- Age: $<65, \geq 65$
- Race: Asian, Black or African American, White, Other
- Number of bleeds during 24 weeks prior to study entry: $\leq 9, >9$
- Number of target joints: no target joint, any target joint
- Arm C only: by type of pre-study hemophilia treatment

Subgroup analyses are subject to having sufficient patients in a subgroup to provide meaningful results.

In addition, region- and/or country-specific analyses will be performed to support regulatory submission as needed.

4.6 PHARMACOKINETIC ANALYSES

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively at each timepoint by dose group, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will be used to analyze the dose-concentration-time data of emicizumab following SC administration. Population PK parameters, such as clearance and volume of distribution, will be estimated, and the influence of various covariates, such as age, gender, and body weight, on these parameters will be investigated. Secondary PK parameters, such as area under the curve, will be derived

[no notes on this page]

from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies. These analyses will be reported in a dedicated report.

In addition, region- and/or country-specific analyses will be performed to support regulatory submission as needed (e.g., PK analysis in Japanese vs. non-Japanese patients or analyses based on race/ethnicity).

4.7 SAFETY ANALYSES

Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology, including complete blood count with differential), ECGs, vital signs, and antibodies to emicizumab.

4.7.1 Exposure of Study Medication

Information on study drug administration will be summarized by duration and cumulative dose. In addition, treatment exposure will be summarized, including delays and interruptions. The number of patients whose dose was up-titrated will be summarized.

Patient withdrawals from study treatment will be reported as listings and summary tables.

4.7.2 Adverse Events

Adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade (WHO Criteria) for each treatment arm. All adverse events will be coded using the current version of MedDRA at time of database closure. The total number and percentage of patients with at least one adverse event and total number of adverse events will be summarized. Separate adverse event summaries for serious adverse events, adverse events of special interest, severity, relatedness, and discontinuation/modification will be provided.

4.7.3 Laboratory Data

For clinical laboratory data which were collected from local laboratories, summary statistics in SI units will be presented by treatment arm. Laboratory data not collected in SI units will be converted to SI units as applicable. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

Data on the impact of immunogenicity (anti-emicizumab antibodies) on safety, efficacy, and/or clinical pharmacology and pharmacokinetics will be summarized using standard language/terminology (Shankar et al. 2014).

4.7.4 Vital Signs

Vital signs will be summarized by treatment arm using mean change from baseline tables over time. Measurements consist of heart and respiratory rate, temperature, and systolic and diastolic blood pressures.

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4.8 EXPLORATORY BIOMARKER ANALYSES

PD parameters (e.g., aPTT, parameters derived from thrombin generation, FVIII activity) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

4.9 ELECTROCARDIOGRAM

ECG results and corresponding changes from baseline will be summarized by cohort and visit for QT, RR, HR, QTcB, QTcF, PR, and QRS and T- and U-wave morphology.

4.10 BIOMARKER

All biomarker endpoints are analyzed descriptively with summaries over time and individual patient plots.

4.11 MISSING DATA

On the electronic, handheld device, it is not possible to leave questions unanswered or to enter partial data. Therefore, the data for primary and secondary bleed-related endpoints coming from the electronic, handheld device are complete.

In the site data entry system it is possible to leave the time of a treatment or a bleed blank because the patient might not be able to remember these in a reliable way. In addition, the symptoms of joint and muscle bleed are not collected in the site data entry system and the question with regards to cause of bleed can be left unanswered.

- In order to implement the 72-hour rule, it is assumed that the bleeds and treatments with missing time occurred at 12:00 a.m.
- All bleeds with an anatomical location in a joint are considered joint bleeds
- All bleeds where a cause was not entered are included as spontaneous bleeds

4.12 INTERIM ANALYSIS

No efficacy interim analysis is planned.

[no notes on this page]

5. REFERENCES

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[no notes on this page]

Appendix 1 Protocol Synopsis

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC *EMICIZUMAB* VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS WITH INHIBITORS**
PROTOCOL NUMBER:	BH29884
VERSION NUMBER:	2
EUDRACT NUMBER:	2015-002866-21
IND NUMBER:	122,954
TEST PRODUCT:	Emicizumab (RO5534262)
PHASE:	Phase III
INDICATION:	Hemophilia A with inhibitors
SPONSORS:	F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.

Objectives and Endpoints

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis in patients with hemophilia A with inhibitors (Arms A and B) on the basis of the following endpoint:

- Number of bleeds over time (i.e., bleed rate)

The primary definition of a bleed is a bleed for which coagulation factors are administered (see protocol).

Secondary Efficacy Objectives

The secondary efficacy objectives and endpoints for this study are as follows:

- Prophylactic emicizumab compared with no prophylaxis (Arms A and B):
  - To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate
  - To evaluate the efficacy in reducing the number of joint bleeds over time
  - To evaluate the efficacy in reducing the number of target joint bleeds over time
  - To evaluate the efficacy in reducing the number of all bleeds (i.e., those treated and not treated with coagulation factors) over time
  - To evaluate the efficacy in reducing the number of all bleeds over time compared with the patient's historical bleed rate
  - To evaluate the health-related quality of life (HRQoL) of patients according to Haem-A-QoL (aged $\geq$ 18) or Haemo-QoL-Short Form (ages 12 – 17) scores at 24 weeks
  - To evaluate the health status of patients according to EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) scores at 24 weeks

[no notes on this page]

- Non-randomized, prophylactic emicizumab (Arms C and D)

  To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate

  To evaluate the efficacy in reducing the number of all bleeds over time compared with the patient's historical bleed rate

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis on the basis of the following endpoints:

- To assess differences in number of days away from school/work
- To assess differences in number of days hospitalized

Safety Objective

The safety objective for this study is as follows:

- To evaluate the overall safety of prophylactic emicizumab compared with no prophylaxis in patients with hemophilia A with inhibitors on the basis of the following endpoints:

  The incidence and severity of adverse events

  The incidence and severity of thromboembolic events

  Changes in physical examination findings and vital signs

  Incidence of laboratory abnormalities

  Incidence and severity of injection-site reactions

  Incidence of adverse events leading to drug discontinuation

  Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events

  Incidence and clinical significance of anti-emicizumab antibodies

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the exposure (Ctrough) of emicizumab prior to drug administration on Day 1 at the following timepoints:

- Every week during Weeks 1 – 4 on emicizumab
- Every 2 weeks during Weeks 5 – 8 on emicizumab
- Every 4 weeks during Weeks 9 – 24 on emicizumab
- Every 8 weeks during Weeks 25 – 48 on emicizumab
- Every 12 weeks thereafter while on emicizumab, until the end of the study

Exploratory Biomarker Objectives

The exploratory biomarker objectives for this study are as follows:

- To assess potential pharmacodynamic (PD) biomarkers of emicizumab, including but not limited to aPTT, thrombin generation, and factor VIII (FVIII) activity, at timepoints throughout the study
- [redacted]

Study Design

Description of Study

This randomized, multicenter, open-label, Phase III clinical study will enroll patients aged 12 years or older with hemophilia A who have inhibitors against FVIII. Approximately 51 patients with inhibitors who received episodic treatment with bypassing agents prior to study entry will be enrolled globally and randomized in a 2:1 ratio (see protocol) to receive either

[no notes on this page]

prophylactic emicizumab at 3 mg/kg/week subcutaneously for 4 weeks, followed by 1.5 mg/kg/week subcutaneously thereafter (Arm A), or to the control arm (Arm B), which will consist of no prophylaxis. Given the potential heterogeneity of bleed rates in the study patient population, randomized patients will be stratified according to the number of bleeds they experienced over the last 24 weeks prior to study entry (<9 or ≥ 9 bleeds) to ensure a balance of inhibitor patients with lower versus higher number of bleeds, respectively, at baseline across the two randomized arms of the proposed Phase III study. All patients will continue to receive standard of care/background treatment with their usual episodic bypassing agent therapy to treat breakthrough bleeds, as needed.

In addition, given that some patients with hemophilia A with inhibitors are also currently treated with bypassing agents on a prophylactic basis, approximately 30 – 50 patients with inhibitors on prophylactic bypassing agents will be enrolled in a separate therapeutic arm (Arm C) to receive prophylactic emicizumab at the same dose and schedule (see protocol). Enrollment into Arm C will continue for 24 weeks after Arms A and B have been closed to enrollment or until 50 patients have been enrolled, whichever occurs earlier, in order to collect additional safety and efficacy from patients previously on prophylactic bypassing agents.

Of note, all patients who participated in Study BH29768 (a non-interventional study; described at the end of this section) received priority to participate in a future emicizumab interventional study. A separate, therapeutic arm (Arm D) will open at a future timepoint if there remain patients on episodic bypassing agents who participated in Study BH29768 but were unable to enroll in Arms A or B before they closed to enrollment. Arm D will yield additional efficacy, safety, PK, and PD data and enable collection of plasma samples [redacted].

The primary efficacy analysis, defined as comparing the number of bleeds over time for patients randomized to receive prophylactic emicizumab versus no prophylaxis, will be conducted after all randomized patients have completed 24 weeks in the study or the last randomized patient who has not completed 24 weeks in the study discontinues study participation, whichever occurs first.

To obtain additional safety and efficacy data, prior episodic bypassing agent patients who had been randomized to not receive emicizumab (control arm, Arm B) will be offered treatment with prophylactic emicizumab at the same dose and schedule as patients who started Study BH29884 on emicizumab once they complete 24 weeks in the study. In addition, after at least 24 weeks on prophylactic emicizumab, all patients will be able to continue on their 1.5 mg/kg/week maintenance dose or may be provided the option to increase their dose to 3 mg/kg/week if they meet protocol-defined criteria of suboptimal response and receive approval from the Medical Monitor to do so (see protocol). Patients who continue to derive clinical benefit will be given the opportunity to continue receiving prophylactic emicizumab [redacted].

During the study, patients (or their legally authorized representative) will be asked to record their bleeds and medication use on an electronic, handheld device (see protocol). The bleed/medication questionnaire should be completed whenever a bleed or medication use occurs. In the event of no bleed or medication use, the patient should complete the questionnaire at least once a week to serve as confirmation that no bleed or medication use occurred. In addition, health status information will be collected whenever a bleed is reported. HRQoL, health status, patient safety, and days of school or work missed will be assessed every 4 weeks for approximately 24 weeks and every 4 – 12 weeks thereafter, as outlined in the schedule of assessments.

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Appendix 1 Protocol Synopsis (cont.)

Physical examinations, vital sign assessments, ECG, and laboratory assessments will be collected as per the schedule of assessments and will be the same for all patients receiving emicizumab, regardless of whether they are enrolled in the randomized portion of the study or in the separate non-randomized arms. Adverse events will be captured on an ongoing basis, as they occur during the study.

All patients who receive emicizumab in the study will undergo PK assessment. As emicizumab is intended in this study for prophylactic use only (i.e., not to treat bleeds that have already occurred), neither activated prothrombin complex concentrate (aPCC) nor recombinant activated factor VIII (rFVIIa) interfere with emicizumab PK assessments, and some patients with hemophilia A with inhibitors require frequent dosing with bypassing agents due to having many bleeds or being on prophylaxis, a washout period is not required prior to enrollment so that new bleeds are minimized and treatment for any prior bleed is not interrupted.

Exploratory PD biomarkers (e.g., aPTT, FVIII activity, thrombin generation assay) will be collected as per the schedule of assessments. As values for these tests are normalized by even low plasma concentrations of emicizumab (see protocol), a variety of assay formats (one-stage, chromogenic) and modifications (pre-dilution of patient plasma) will be investigated for assessment of PD response at higher emicizumab plasma concentrations. [redacted] In addition, factor IX and factor X antigen levels will be monitored.

Throughout the study, biomarkers related to thromboembolism (e.g., D-dimer, prothrombin 1.2 fragment) and emicizumab trough concentrations, will be collected as per the schedule of assessments. Immunologic biomarkers (i.e., anti-emicizumab antibodies) will also be measured as per the schedule of assessments (see protocol).

An independent Data Monitoring Committee (iDMC) composed of, at minimum, hemostasis/thrombosis experts and a statistician will be in place throughout the duration of the study and will monitor patient safety at pre-specified intervals and ad hoc as needed throughout the study.

Breakthrough bleeds will be treated with bypassing agents according to standard-of-care and captured as they occur on the electronic, handheld device. Of note, the clinical experience in the ongoing Phase I/II clinical studies includes the treatment of over [redacted] breakthrough bleeds in patients receiving emicizumab with either FVIII or bypassing agents, without any related safety concerns reported. Investigators will be asked to contact the Medical Monitor in the event of suspected lack or loss of efficacy of emicizumab in order to discuss potential laboratory evaluations (e.g., anti-emicizumab antibodies, coagulation tests) to be performed as well as to re-evaluate the patient's benefit-risk of continued treatment. When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, category of bleed, time of each individual bleed (day, start time), symptoms of bleed, and treatment for bleed. Health status information will also be collected on the day a bleed occurs.

The reason for the use of coagulation products (e.g., aPCC or rFVIIa) will be documented (e.g., bleeding, prophylaxis). A thorough documentation of the treatments for bleeds will be requested, including agent, start time, dose, and reason for treatment. The number of infusions needed to treat the bleed will be derived from the medication log.

A non-interventional study (BH29768) has been initiated to document the number and types of bleeds and current treatment with episodic or prophylactic bypassing agents, as well as collect information on HRQoL, health status, and safety in patients with hemophilia A with FVIII

[no notes on this page]

inhibitors. The assessments in the non-interventional study will mitigate the risk of underreporting of bleeds that oftentimes occurs in the real world, and the resulting data will serve as a source of comparator information for some analyses conducted in the Phase III clinical study (Study BH29884). The non-interventional study will also allow an investigation of the feasibility of using an electronic, handheld device that has been developed to record data related to bleeds, hemophilia treatments, HRQoL, and health status. In addition, the non-interventional study will enable earlier identification and confirmation of patients who may qualify for the Phase III clinical study. It is anticipated that a significant number of patients participating in Study BH29768 will enroll in Study BH29884, as long as they meet the inclusion and exclusion criteria of the study and are able to enroll at a participating site while the study is open for enrollment.

Number of Patients

This global study will enroll approximately 81 – 101 patients in Arms A, B, and C, as well as additional patients in Arm D if it is opened.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of patient-reported outcomes questionnaires and bleed/medication questionnaire through the use of an electronic device
- Aged 12 years or older at the time of informed consent
- Body weight ≥ 40 kg at the time of screening
- Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (i.e., ≥ 5 Bethesda Units)
- Documentation of treatment with episodic or prophylactic bypassing agents for at least the last 24 weeks
- ≥ 6 bleeds in the last 24 weeks prior to screening (if on an episodic bypassing agent regimen) or ≥ 2 bleeds in the last 24 weeks prior to screening (if on a prophylactic bypassing agent regimen)
- Adequate hematologic function, defined as platelet count ≥ 100,000/μL and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin ≤ 1.5 × the upper limit of normal (ULN) (excluding Gilbert's syndrome) and AST and/or ALT ≤ 3 × ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine ≤ 2.5 × ULN and creatinine clearance by Cockcroft-Gault formula ≥ 30 mL/min
- For women who are not postmenopausal (≥ 48 weeks of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined highly effective contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of contraceptive methods with a failure rate of <1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral

[no notes on this page]

or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a non-lipid-based spermicide.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Inherited or acquired bleeding disorder other than hemophilia A
- Ongoing (or plan to receive during the study) immune tolerance induction therapy or prophylaxis with FVIII with the exception of patients who have received a treatment regimen of FVIII prophylaxis with concurrent bypassing agent prophylaxis
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which antithrombotic treatment is not currently ongoing) or current signs of thromboembolic disease
- Other conditions (e.g., certain autoimmune diseases) that may increase the risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Known HIV infection with CD4 count < 200 cells/μL within 24 weeks prior to screening
- Use of systemic immunomodulators (e.g., interferon or rituximab) at enrollment or planned use during the study, with the exception of antiretroviral therapy
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study or that would, in the opinion of the investigator or Sponsor, preclude the patient's safe participation in and completion of the study or interpretation of the study results
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Receipt of

  Emicizumab in a prior investigational study

  An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration

  A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter

  An investigational drug concurrently
- Unwillingness to use highly effective contraception methods for the specified duration in the protocol (females only, unless required otherwise by the local health authority)
- Clinically significant abnormality on screening evaluations or laboratory tests that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient
- Pregnancy or lactation, or intent to become pregnant during the study

  Women who are not postmenopausal (≥ 48 weeks of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

[no notes on this page]

End of Study and Length of Study

The approximate length of the entire study from the first patient enrolled to the Last Patient Last Visit (LPLV; see below) is approximately 108 weeks.

The end of this study is defined as the date when the last remaining patient has completed the last visit (i.e., LPLV), as defined below:

- Has completed at at least 24 weeks of emicizumab treatment and either transferred to [redacted] receive further emicizumab as per Roche Global Policy on Continued Access to Investigational Medicinal Products or to commercial product

  OR
- Completes the end of study safety follow-up visit 24 weeks after discontinuing emicizumab

  OR
- Has withdrawn consent

  OR
- Is lost to follow-up

Investigational Medicinal Products

Test Product (Investigational Drug)

Emicizumab 3 mg/kg/week subcutaneously for 4 weeks was administered when initiating treatment, followed by 1.5 mg/kg/week subcutaneously for a minimum of 24 weeks total. There will be an option to increase the dose after at least 24 weeks of treatment to 3 mg/kg/week if a patient meets the criterion for insufficient control of bleeds on the 1.5 mg/kg/week emicizumab dose and with approval from the Medical Monitor.

To support home administration of the drug, patients/caregivers will be required to complete in-person, instructional training on how to administer emicizumab as a subcutaneous (SC) injection. Patients/caregivers will be taught to perform the injections utilizing the Instructions for Use document. They will observe at least one SC injection performed by a healthcare provider (HCP) and will need to successfully administer at least one SC injection under an HCP's watch prior to starting home administration. The first five weekly treatments will be administered in a monitored setting, such as an infusion center, clinic, or hospital, in conjunction with emicizumab PK assessments. Patients will be observed for a minimum of 60 minutes after the first three doses. Patients/caregivers will be instructed on how to recognize signs/symptoms of hypersensitivity (including anaphylaxis) and obtain emergency care in the event of such reactions occurring. Each site will have the discretion to provide additional training or include additional observation (e.g. after the fourth and fifth doses), if deemed appropriate. If, despite additional training, the investigator determines that the patient/caregiver is unable to inject emicizumab, a trained and proficient caregiver or HCP should be identified to administer the SC injections. Patients/caregivers will be provided with contact information for the clinic in case they have questions related to self-administration between visits.

Compliance in the home setting is to be monitored by reviewing reported hemophilia medication use and recording collected used and unused vials at each site.

Statistical Methods

Efficacy Analyses

The primary and secondary efficacy analyses to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis will include all randomized patients, with patients grouped according to the treatment assigned at randomization. For patients previously treated with prophylactic bypassing agents in Arm C and episodic bypassing agents in Arm D (if opened), the efficacy analyses will include all enrolled patients.

[no notes on this page]

Primary Efficacy Endpoint

The primary efficacy objective is to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis on the number of bleeds over time. The definition of a bleed is described in the protocol, with the primary endpoint comparing bleeds requiring treatment.

The primary efficacy analysis will be conducted after all randomized patients have completed 24 weeks in the study or the last randomized patient who has not completed 24 weeks in the study discontinues study participation, whichever occurs first, and using an intent-to-treat principle. The comparison of the number of bleeds over time between the randomized treatment arms will be performed using a negative binomial (NB) regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study included as an offset in the model. The model also includes the number of bleeds (<9 or ≥ 9) in the last 24 weeks prior to study entry as a stratification factor in the randomization. This analytic model estimates the rate ratio, λ_t/λ_c., which quantifies the risk of bleeding associated with prophylactic *emicizumab* (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level, and the estimated risk ratio is compared with 1, assuming the following statistical hypothesis:

H_0 (null hypothesis): Rate Ratio $= 1$ versus H_1 (alternative hypothesis): Rate Ratio $\neq 1$

The treatment effect therein is based on a contrast statement in the model with use of the SAS GENMOD procedure. Statistical significance at the pre-specified alpha level will be based on a Wald testing procedure. Bleed rates for prophylactic *emicizumab* and no prophylaxis and the rate ratio will be presented and include 95% confidence intervals.

The number of bleeds can also be annualized for each patient using the following formula:

Annualized bleed rate (ABR) = (Number of bleeds during the efficacy period/Total number of days during the efficacy period) $\times$ 365.25.

If the NB model converges, an analysis of variance (ANOVA) to compare the mean ABR between the randomized arms will be provided only as a sensitivity analysis. However, if the convergence of the NB model is not achieved or is questionable, the primary efficacy analysis will be based on the Wilcoxon Rank Sum of ABR.

Although this is an open-label study, Sponsor personnel will not have access to efficacy summaries by treatment arms prior to the formal reporting of the study results.

A detailed description of the statistical methods that will be used for the primary and secondary efficacy analyses will be provided in the Statistical Analysis Plan (SAP).

Secondary Efficacy Endpoints

The number of all bleeds (i.e., those treated and not treated with coagulation factors) over time in patients who receive prophylactic emicizumab compared with no prophylaxis will be assessed as a secondary efficacy endpoint. Also, the number of treated bleeds and all bleeds over time will be compared with patients' bleed rate prior to study entry. Finally, the number of joint and target joint bleeds over time between the emicizumab prophylaxis and no prophylaxis arms will be evaluated.

HRQoL (using the Haem-A-QoL or the Haemo-QoL-SF) and health status (using the EQ-5D-5L) will be assessed on a regular basis, as per the schedule of assessments (scheduled). Health status will also be assessed in the event of a bleed (unscheduled).

Adherence with the HRQoL and health status measures will be summarized.

[no notes on this page]

Because different HRQoL measures (Haem-A-QoL and the Haemo-QoL-SF) are being used for the adult and adolescent patients, all calculations and analyses will be conducted separately for adults and adolescents. Scale scores for the Haem-A-QoL and Haemo-QoL-SF will be calculated and summarized descriptively. The HRQoL scale scores for all patients will be evaluated at 24 weeks in the study, a timepoint that is consistent with other recent registration studies in hemophilia and analyses of such data. For each treatment arm, paired t-tests will be used to compare the 24-week with the baseline scale scores for each HRQoL measure. Within-subject and between-group changes from baseline on the different HRQoL scale scores will also be calculated at 24 weeks.

For the assessments of the EQ-5D-5L performed every 4 weeks, the number and percentage of patients in each of the five categories for each question for each group will be assessed. Changes in the EQ-5D-5L index utility score from baseline will also be compared between groups. In addition, summary statistics including mean, standard deviation, median, minimum and maximum will be displayed for the patients' health state using the EQ-VAS both within and between groups. The proportion of patients who report changes in each group exceeding the clinically meaningful threshold on the EQ-5D-5L index and EQ-VAS scores in each group will be reported at 24 weeks.

Separately, for each EQ-5D-5L completed in connection with a bleed, the level of pain associated with that episode, as well as the utility score and general health score will be reported.

Secondary endpoints used for labeling and those that are solely for scientific interest will be specified in the SAP. The method used for controlling the type 1 error rate will also be described.

Exploratory Efficacy Analysis

Summary statistics of the number of work/school days missed and days hospitalized will be presented by treatment arm.

Safety Analyses

The safety analyses population will be based on all enrolled patients grouped according to the actual treatment received. Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology, including complete blood count with differential), ECGs, vital signs, and antibodies to emicizumab.

To evaluate the overall safety of prophylactic emicizumab compared to no prophylaxis, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade for each treatment arm.

For clinical laboratory data, summary statistics will be presented by treatment arm. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

Data on the impact of immunogenicity (anti-emicizumab antibodies) on safety, efficacy, and/or clinical pharmacology and PK will be summarized using standard language/terminology.

Although this is an open-label study, Sponsor personnel will not have access to safety summaries by treatment arm prior to the formal reporting of the study results. HCPs at participating study sites, as well as the Sponsor's drug safety and medical monitoring staff, will have access to the treatment assignments of patients for safety monitoring purposes only.

[no notes on this page]

The iDMC (see protocol) will evaluate safety at periodic safety reviews and recommend to the Sponsor whether the study should be stopped early. All summaries and analyses will be prepared by the independent Data Coordinating Center (iDCC) and presented by treatment arm for the iDMC's review. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.

Pharmacokinetic Analysis

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will be used to analyze the dose-concentration-time data of emicizumab following SC administration. Population PK parameters, such as clearance and volume of distribution, will be estimated, and the influence of various covariates, such as age, gender, and body weight, on these parameters will be investigated graphically. Secondary PK parameters, such as area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies. These analyses will be reported in a dedicated report.

Exploratory Biomarker Analyses

PD parameters (e.g., aPTT, parameters derived from thrombin generation, FVIII activity) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Determination of Sample Size

The sample size for this study is based on clinical rather than statistical considerations, taking into account the limited number of patients with hemophilia A with inhibitors available for participation in clinical studies and in an effort to collect sufficient data to assess the safety and efficacy of emicizumab.

The sample size calculation is based on the evaluation of the primary efficacy endpoint, defined as the number of bleeds over time (i.e., bleed rate) with emicizumab (treatment group, λ_t) versus no prophylaxis (control group, λ_c), which are said to follow a NB distribution with γ_t and γ_c described as shape parameters for treatment and control groups, respectively. With consideration of enrollment feasibility, a sample size of 45 patients, assuming an allocation ratio of 2:1 (30 patients in treatment group and 15 patients in control group), will achieve a power of more than 95% for λ_t and λ_c ranging from 1 to 4 and 18 to 30, respectively (see protocol). Here, the patients from the two groups are followed up to 0.5 units of time (i.e., 24 weeks). Of note, assuming $\lambda_c = 18$ and $\lambda_t = 4$ results in an expected ABR reduction of 78% in the treatment versus control groups. Sample size calculations were performed with East®, Version 6 (Cytel, Cambridge, MA), which allows specific shape parameters for both the treatment and control groups.

However, the above approach to sample size calculation assumes similar follow-up for each patient. Because this is unlikely to be seen in the study, power was also estimated by simulation to account for different follow-up times among patients. Conducting simulations on the basis of a NB regression model including an offset variable to account for variable follow-up times, with all other assumptions remaining the same as previously described, the sample size is projected to have greater than 95% power at the 2-sided 0.05 level of significance.

The analysis will include all enrolled patients, regardless of their length of follow-up. Therefore, to ensure the analysis is based on sufficient follow-up data and with 2:1 treatment to control randomization, approximately 34 patients in the randomized emicizumab treatment arm and 17 patients in the control arm (approximately 51 patients in total) will be enrolled.

[no notes on this page]

During the study, a re-assessment of the initially specified sample size based on aggregated (not by treatment arm) data to date (and potentially from the non-interventional study [BH29768] findings) may be performed. This may result in an increase in sample size, if necessary, to maintain adequate power without affecting the type 1 error rate. Study integrity will be upheld, as access to information via aggregated analyses and their results will be minimized to limit operational bias.

[no notes on this page]

Appendix 2
Schedule of Assessments

Schedule of Assessments — Arms A, C, *and D*																		
	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Every 8 Weeks from Wk 33	Wk 49	Every 12 Weeks from Wk 61	At Least Weekly[a]	Study Completion/ET	Safety F/U Visit [b]
Informed consent [c]	x																	
Inclusion/exclusion criteria	x																	
Medical history and demographics [d]	x																	
Physical examination [e]	x	x				x						x		x			x	x
Vital signs [f]	x	x [f]	x	x	x	x	x	x	x	x	x	x [f]	x	x [f]	x		x [f]	x [f]
Concomitant medications [g]		x				x		x	x	x	x	x	x	x	x		x	x
ECG [h]	x	x [h]				x						x	x [h]				x	
Safety laboratory assessments [i]	x [i]	x	x	x	x	x		x	x	x	x	x	x	x	x		x	x
Anti-FVIII antibodies [j]	x	x					x					x		x	x [j]			x
Anti-emicizumab ant bodies [k]		x [k]				x	x	x [k]	x	x [k]	x	x [k]	x [k]	x [k]	x [k]		x	x [k]
Bleed/medication questionnaire [l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Bleed/medication data review [m]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Adverse events [n]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
IMP management [o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
HRQoL [p]		x				x		x	x	x	x	x	x	x	x		x	
Health status (EQ-5D-5L) [q]		x				x		x	x	x	x	x	x	x	x		x	
PK assessment [r]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
PD biomarkers assessment [s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
RCR whole blood DNA sample [t]			x															

[no notes on this page]

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments – Arm B									
	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	*Every 4 Weeks from* Wk 9 *Until Switch to Emicizumab at Wk 25*	*At Least Weekly* [a]
Informed consent [c]	x								
Inclusion/exclusion criteria	x								
Medical history & demographics [d]	x								
Physical examination [e]	x	x							
Vital signs [f]	x	x [f]				x		x	
Concomitant medications [g]		x				x		x	
ECG [h]	x	x [h]							
Safety laboratory assessments [i]	x [i]	x							
Anti-FVIII antibodies [j]	x								
Bleed/medication questionnaire [l]	x	x	x	x	x	x	x	x	x
Bleed/medication data review [m]		x				x		x	
Adverse events [n]		x				x		x	
HRQoL [p]		x				x		x	
Health status (EQ-5D-5L) [q]		x				x		x	
PD biomarkers assessment [s]	x	x							
RCR whole blood DNA sample [t]		x							

[no notes on this page]

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments – Arm B																	
	Wk 25	Wk 26	Wk 27	Wk 28	Wk 29	Wk 31	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	Every 8 Weeks from Wk 57	Wk 73	Every 12 Weeks from Wk 85	At Least Weekly[a]	Study Com-pletion/ ET	Safety F/U Visit [b]
Targeted physical exam [e]	x				x						x		x			x	x
Vital signs [f]	x [f]	x	x	x	x	x	x	x	x	x	x [f]	x	x [f]	x		x [f]	x [f]
Concomitant medications [g]	x				x		x	x	x	x	x	x	x	x		x	x
ECG [h]	x				x						x	x [h]				x	
Safety laboratory assessments [i]	x	x	x	x	x		x	x	x	x	x	x	x	x		x	x
Anti-FVIII antibodies [j]	x [j]					x					x		x	x [j]			x
Anti-emicizumab antibodies[k]	x [k]				x	x	x [k]	x	x [k]	x	x [k]	x [k]	x [k]	x [k]		x	x [k]
Bleed/medication questionnaire [l]															x		
Bleed/medication data review [m]	x				x		x	x	x	x	x	x	x	x		x	x
Adverse events [n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
IMP management [o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
HRQoL [p]	x				x		x	x	x	x	x	x	x	x		x	
Health status (EQ-5D-5L) [q]	x				x		x	x	x	x	x	x	x	x		x	
PK assessment [r]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
PD biomarkers assessment[s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x

[no notes on this page]

Appendix 2
Schedule of Assessments (cont.)

eCRF = electronic Case Report Form; EQ-5D-5L = EuroQoL Five-Dimension-Five Levels Questionnaire; ET = early termination; F/U = follow-up; FVIII = factor VIII; HRQoL = health-related Quality of Life; IMP = investigational medicinal product, PD = pharmacodynamics; PK = pharmacokinetic; RCR = Roche Clinical Repository; Wk = Week.

Notes: The maximum allowable time between Screening and enrollment is 4 weeks; if the elapsed time between Screening and enrollment is more than 4 weeks, Screening must be repeated. All assessments should be performed within ±2 days of the scheduled visit for the first 12 weeks, then ±7 days thereafter; for Arm B patients, emicizumab should be offered at Week 25, after which all assessments should be performed within ±2 days of the scheduled visit for the first 12 weeks on emicizumab, then ±7 days thereafter. Except for the bleed/medication questionnaire, HRQoL, and health status, all other patient data will be collected during office visits. On treatment days, pre-injection blood collection should be made 0−120 minutes before the injection.

[a] Patients will complete the bleed/medication questionnaire when they have bleeds or hemophilia medication use, including emicizumab, or at minimum every week.

[b] A safety follow-up visit will occur 24 weeks after discontinuing emicizumab.

[c] Obtain written informed consent (or patient assent and parent written informed consent if patient is an adolescent) before distribution of an electronic, handheld device and collection of any data. Randomization and enrollment form will be completed after informed consent and/or assent is obtained.

[d] Collected from patient medical records and documented in the eCRF, including information on target joint(s).

[e] A complete physical examination will be performed at Screening and targeted physical examinations at visits indicated. Targeted physical examination of joints (for bleeds, evidence of arthropathy) and skin (for bruises, hematomas, and injection-site reactions), in addition to other organ systems should be performed as clinically indicated. If Screening and Week 1 occur on the same date, the physical examination entry may be entered once for the Week 1 visit.

[f] Body temperature (oral, rectal, axillary, or tympanic), blood pressure, pulse, respiratory rate, and weight will be measured and recorded in the eCRF at each clinic visit prior to any injections (if applicable). Height will be measured and recorded only at Screening and at Weeks 25 and 49 after starting emicizumab. At the investigator's discretion, vital signs may be taken to help monitor for hypersensitivity reactions during or after injections, but they should not be entered into the eCRF. If Screening and Week 1 occur on the same date, the vital signs entry may be entered once for the Week 1 visit.

[g] Concomitant medications (e.g., extra pain medication with bleed) will be asked about at each clinic visit, excluding treatments for bleeds (i.e., bypassing agents and other medications to treat bleeds), which will be collected on the bleed questionnaire. Hemostatic medications to treat or prevent bleeds in the week prior to starting emicizumab will also be collected.

[h] If screening ECG is abnormal, repeat at Week 1 (or Week 2, if Screening and Week 1 occur on the same date). ECGs will also be performed 4−8 and 24 weeks after starting emicizumab or dose up-titration, as well as at study completion/early termination.

[no notes on this page]

Appendix 2
Schedule of Assessments (cont.)

[i] Laboratory data (performed locally) include: complete blood count with differential and serum chemistries. Female patients with childbearing potential will be required to have a negative serum pregnancy test result at screening (and again within 7 days prior to the first dose of emicizumab, if applicable) and urine pregnancy tests performed at every clinic visit, with the exception of Weeks 2−4 and 7. If patients undergo up-titration of their dose after ≥24 weeks on emicizumab, an additional blood draw for safety laboratory assessments should be performed within the first 4 weeks after up-titration. If Screening and Week 1 occur on the same date, sufficient blood should be drawn to cover the required laboratory tests for both visits (and one entry recorded in the eCRF under Week 1). Safety laboratory assessments completed at Screening visit do not have to be repeated at Week 1 if the period between Screening and Week 1 is ≤5 days and there has been no change in the patient's health status as assessed by the investigator; however, PD biomarker samples should be collected at both visits if Screening and Week 1 occur on different dates.

[j] Anti-FVIII antibodies will be analyzed at Screening; pre-dose after starting emicizumab at Weeks 1, 7, 25, 49, and 73; and at the safety follow-up visit (i.e., 24 weeks after discontinuing emicizumab) at a central laboratory.

[k] Samples to detect anti-emicizumab antibodies will be collected prior to emicizumab administration. Anti-emicizumab antibodies may also be drawn at the time of hypersensitivity events.

[l] Reported by the patient; includes start date and time, reason, type, location, and associated symptoms of any bleed, as well as start date and time, reason, type, and dose of any hemophilia medication use.

[m] At the Week 1 visit, patients will be trained on how to use and be provided their own electronic, handheld device to record their bleeds and hemophilia medication use. Investigator review of patient-reported bleed/medication questionnaire information with the patient/caregiver for completeness and accuracy will occur at visits indicated. Information regarding all traumatic events, even if they do not result in a bleed, is required to be collected in the eCRF.

[n] Injection-site reaction adverse events will be collected on a separate form from the adverse event form. See Section 5.3.5.10 of the protocol for how to record "increased clinical severity of hemophilia" as an adverse event.

[o] Drug accountability will not be performed at the first visit of emicizumab receipt. Drug dispensation will not occur at the study completion/early termination visit.

[p] Haem-A-QoL questionnaire (age≥18) and Haemo-QoL-Short Form (ages 12−17).

[q] On days that patients report having a new bleed and every 4 weeks, they will be prompted to also complete the EQ-5D-5L questionnaire on the electronic, handheld device.

[r] Emicizumab concentration. Plasma samples for this assessment should be taken prior to injection of study drug.

[s] See Appendix 2 of the protocol for detailed explanation of PD biomarker assessments (Sets 1 and 2). Blood samples may also be drawn to conduct biomarker assays at the central laboratory on an unscheduled basis (at the clinical judgment of the investigator) at any time. If Screening and Week 1 occur on the same date, sufficient blood should be drawn to cover the required laboratory tests for both visits (and one entry recorded in the eCRF under Week 1); however, baseline PD samples prior to administration of emicizumab (if applicable) must be drawn.

[t] Sample for the RCR is optional and requires an additional signature. This may be collected at Weeks 1 or 2 or at any other visit.

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Appendix 3 Example SAS code

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Appendix 3 Example SAS code (cont.)

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Appendix 3 Example SAS code (cont.)

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Appendix 3 Example SAS code (cont.)

[no notes on this page]

Appendix 3 Example SAS code (cont.)

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HAVEN 1 (BH29884)_Summary of changes to SAP

A summary of the changes to the statistical analysis plan (SAP) is provided below.

Within the SAP documents, information was redacted based on Roche's policy to redact all protected personal data and commercially confidential information; additional information was redacted if it involved:

1. Unpublished data that may be published in the future

2. Discussion of future studies/activities that may be conducted in the future

3. Copyrighted material held by external, non-Roche parties

SUMMARY OF CHANGES TO SAP (BH29884)_Amendment version 2
Changed start of efficacy period from the “first entry from the handheld device” to the first entry from the bleed and medication questionnaire (BMQ).
Clarified the end of efficacy period for Arm B to include the cutoff date.
Changed the definition of treated joint bleeds to better correspond to the International Society on Thrombosis and Haemostasis (ISTH) definition.
Removed the secondary endpoints for Haemo-QoL-SF.
Removed the subgroup analysis on hemophilia severity.
Added new sensitivity analysis based on health authority feedback.
Changed the fall back method for primary analysis to be the Van Elteren test instead of the Wilcoxon Rank Sum.
Corrected the limit for clinically meaningful change for EQ-5D-5L to 0.07
Additional minor changes have been made to improve clarity and consistency.

[no notes on this page]

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med 2017;377:809-18. DOI: 10.1056/NEJMoa1703068

(PDF last updated August 16, 2017.)

[no notes on this page]

Supplementary Appendix

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Contents

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[no notes on this page]

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Trial Registration

The HAVEN 1 study was registered on clinicaltrials.gov on December 2, 2015. The date of enrollment of the first participant was November 18, 2015. There was only one participant enrolled prior to study registration. While Roche/Genentech always strives to meet the ICJME requirements of posting protocols before the first participant in (FPI) for all clinical trials, in this instance, a delay occurred due to an unexpected issue in the internal tracking systems, which prevented an accurate assessment of the estimated timing of FPI. Importantly, all study investigators were aware of the study and informed of the details before it was posted on clinicaltrials.gov. Additionally, the NIH/FDA's regulatory compliance deadline of posting the study within 21 days of FPI was met.

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METHODS

ADDITIONAL ELIGIBILITY CRITERIA

Inclusion criteria: willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of participant-reported outcomes questionnaires and bleed questionnaire through the use of an electronic device; body weight ≥40 kg at the time of screening; documentation of treatment with episodic or prophylactic bypassing agents (BPAs) for ≥24 weeks prior to study entry; ≥6 (if on episodic BPAs) or ≥2 (if on prophylactic BPAs) bleeding events in the last 24 weeks; adequate hematologic function, defined as a platelet count ≥100,000/µL and hemoglobin ≥8 g/dL (4.97 mmol/L); adequate hepatic function, defined as total bilirubin ≤1.5 times the upper limit of normal (ULN) (excluding Gilbert's syndrome), both AST and ALT ≤3 times ULN at the time of screening, and no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis; and, adequate renal function, defined as serum creatinine ≤2.5 times ULN and creatinine clearance by Cockcroft-Gault formula ≥30 mL/min.

Exclusion criteria: inherited or acquired bleeding disorder other than hemophilia A; ongoing (or plan to receive during the study) immune tolerance induction therapy or prophylaxis with factor VIII (FVIII); participants with treatment within the last 12 months for, or current signs of, thromboembolic (TE) disease.

SECONDARY ENDPOINTS

Arm A versus Arm B randomized comparison for: all bleeds; treated joint bleeds; treated spontaneous bleeds; treated target joint bleeds; Haem-A-QoL physical health subscale at 24 weeks; Haem-A-QoL total score at 24 weeks; EQ-5D-5L visual analog scale at 24 weeks; EQ-5D-5L Index utility score at 24 weeks.

Arm A intra-individual comparison for all bleeds and treated bleeds. Arm C intra-individual comparison for all bleeds and treated bleeds.

UP-TITRATION OF EMICIZUMAB DOSE

After at least 24 weeks on emicizumab prophylaxis once weekly, participants had the opportunity to increase their maintenance dose from 1.5 mg/kg to 3 mg/kg weekly, providing they met the following

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criteria: ≥2 spontaneous and clinically significant bleeds in the last 24 weeks on emicizumab that occurred after the end of the loading dose period; at least one of the bleeds verified by a physician (e.g., with diagnostic imaging, photograph); and, approval to up-titrate maintenance dose from the Medical Monitor.

If the investigator believed that a specific participant warranted dose up-titration based on a different reason (e.g., traumatic bleed out of proportion to degree of injury), the case was discussed with the Medical Monitor for consideration and potential approval.

COLLECTION OF BLEED AND HEMOPHILIA MEDICATION INFORMATION

Information on bleeds (day, start time, cause, type, location, symptoms of joint/muscle bleeds), hemophilia medication use (day, start time, type, dose, purpose), HRQoL, and health status were recorded by participants/caregivers on an electronic, handheld device following its activation at the week 1 visit.

DEFINITIONS OF A TREATED BLEED

A bleed was considered to be a "treated bleed" if it was directly followed by a hemophilia medication reported to be a "treatment for bleed," without an intervening bleed and irrespective of the time between the treatment and the preceding bleed. A bleed and the first treatment thereafter were considered to be pairs (i.e., one treatment belonged to one bleed only), with the following exception: if multiple bleeds occurred on the same calendar day, the subsequent treatment was considered to apply for each of these multiple bleeds (which were, however, counted as separate bleeds). Bleeds due to surgery/procedure were not included in the primary analysis. Only treatments that were recorded as "treatment for bleed" were included in the determination of a treated bleed.

72-Hour Rule:

Two bleeds of the same type (e.g., "joint," "muscle," or "other") and at the same anatomical location were considered to be one bleed if the second occurred within 72 hours from the last treatment for the first bleed. The last treatment was defined as the last treatment before a new bleed occurred, either in the same or in a different location. This is in-line with the above definition that bleeds and treatments were considered to be pairs.

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BYPASSING AGENTS FOR TREATMENT OF BREAKTHROUGH BLEEDS

Doses of bypassing agents for treatment of breakthrough bleeds were not defined in the first version of the protocol. The investigators were subsequently requested to use the lowest dose to achieve hemostasis and to avoid the use of aPCC. The protocol was later amended to include the same dosing guidance.

ANTI-DRUG ANTIBODY ASSAY

A validated bridging enzyme-linked immunosorbent assay (ELISA) was used to analyze anti-emicizumab antibodies in plasma. Samples were collected at trough emicizumab concentrations to minimize drug interference with the detection of anti-emicizumab antibodies. The analysis was performed by QPS Netherlands B.V. (Groningen, Netherlands). The ELISA had a sensitivity of 6.04 ng/mL and provided a drug tolerance factor of approximately 59.2-fold. Inter- and intra-assay precision was 2.2% to 2.9% and 1.2% to 1.3%, respectively.

STATISTICAL ANALYSIS

The comparison of the number of bleeding events over time among study arms was performed using a negative binomial regression model.[1] The model accounted for different follow-up times, with the number of bleeding events (for each participant) as a function of randomization and the time that each participant stayed in the study included as an offset in the model. The model also included the number of bleeds (<9 or ≥9) in the last 24 weeks prior to study entry. The model was used to estimate the rate ratio, λ_t / λ_c, to quantify the risk of bleeding associated with emicizumab prophylaxis (λ_t) compared with no prophylaxis (λ_c).[1]

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RESULTS

MEDIAN (RANGE) DURATION OF EMICIZUMAB TREATMENT EXPOSURE

Arm A, 29.5 (3.3 to 47.9) weeks; Arm B, 8.0 (4.0 to 16.0) weeks (after switching to emicizumab prophylaxis following ≥24 weeks on episodic bypassing agents); Arm C, 19.0 (5.9 to 45.0) weeks; Arm D, 5.8 (3.0 to 14.0) weeks.

CASE DETAILS OF THROMBOEMBOLIC AND THROMBOTIC MICROANGIOPATHY (TMA) EVENTS

TMA Case (#1)

The participant received his regular scheduled weekly dose of emicizumab 1.5 mg/kg on Study Day 43. On Study Days 48 and 49 the participant experienced two joint bleeds (one spontaneous, one traumatic), each of which was treated with one dose of aPCC 94 U/kg.

On Study Day 50, the participant experienced back pain and administered two doses of rFVIIa 85 µg/kg spaced 2.5 hours apart for a right lower back bleed. Three hours later, he administered an emicizumab dose, as scheduled. Later on the same day, the participant administered two additional doses of aPCC 94 U/kg each.

On Study Day 51, he was hospitalized and reported jaundice and weakness. His laboratory values were notable for thrombocytopenia (17 x 10^9/L), decreased hemoglobin (12.7 g/dL, hemolysis noted in the sample), hyperbilirubinemia (7.5 mg/dL), increased creatinine (4.08 mg/dL), and elevated lactate dehydrogenase (LDH; 4130 U/L). A Coombs test was negative and ADAMTS13 activity collected prior to the start of therapeutic plasma exchange was 75%. A peripheral blood smear showed single schistocytes. Coagulation tests, including prothrombin time, activated partial thromboplastin time (aPTT), and fibrinogen were within normal limits. The participant was diagnosed with TMA, and emicizumab and aPCC were discontinued.

On Study Day 52, the participant was started on therapeutic plasma exchange. Peri-procedurally, the participant received 3 doses of intravenous rFVIIa (85 µg/kg) for central venous catheter placement. The participant continued therapeutic plasma exchange once daily for 5 days and over the course of the next week, the participant's platelet count (150 X 10^9/L) and LDH (383 U/L) had returned to normal, and TMA was deemed to be resolved on Study Day 65. Emicizumab was not resumed.

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On Study Day 174, the participant experienced a left elbow joint bleed, treated with aPCC 87 U/kg that day and aPCC 87 U/kg on Study Day 177.

There were no subsequent adverse events for this participant at the time of the data cutoff.

TMA Case (#2)

On Study Day 217, the participant experienced a traumatic joint bleed, which was treated with aPCC 74 U/kg on Study Day 218. The participant also received his regular scheduled weekly dose of emicizumab 1.5 mg/kg on Study Day 218. The participant then received two doses of aPCC 74 U/kg, 15 and 27 hours, respectively, after the first aPCC dose.

On Study Day 220, an additional 2 doses of aPCC 74 U/kg each were administered, 39 and 49 hours after the first aPCC dose.

On Study Day 222, the participant presented to the emergency room complaining of emesis, mild abdominal pain, without fever or diarrhea. Laboratory values were notable for thrombocytopenia (35×10^9/L), decreased hemoglobin (12.1 g/dL), increased creatinine (6.31 mg/dL), and elevated LDH (830 U/L) with undetectable haptoglobin levels. Prothrombin time and fibrinogen were within normal limits, while aPTT was shortened (22.0 sec; normal range: 23.1-33.1 sec). ADAMTS13 activity was 98%, von Willebrand factor multimer analysis was normal, and C3, C4 and CH50 levels were all within normal limits. A peripheral blood smear demonstrated low platelet numbers with large platelets and 3-4 schistocytes per high-power field. A renal ultrasound was performed and showed that there was no evidence of renal vein thrombosis. A blood culture was positive for *Staphylococcus epidermidis*. The participant was diagnosed with TMA. Emicizumab was interrupted, and aPCC was discontinued.

The participant was treated with supportive care without therapeutic plasma exchange or hemodialysis, and platelet count (270×10^9/L) and LDH (191 U/L) had returned to normal on Day 239, at which time the TMA was deemed to be resolved. The participant resumed emicizumab that same day and had not experienced subsequent adverse events or used BPA at the time of the data cutoff.

TMA Case (#3)

The participant suffered a rectal hemorrhage on Study Day 237, and presented to the hospital on Study Day 238 with rectal bleeding, postural dizziness, and exertional dyspnea. He had taken his regular weekly dose of emicizumab 1.5 mg/kg 1 day early on this day. Laboratory results were notable for a

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decreased hemoglobin (11.8 g/dL), mild creatinine elevation (1.6 mg/dL), and normal LDH level (175 U/L); platelet count on this day was undeterminable due to clumping, but was 141 x 10^9/L on Study Day 239. The participant was treated with 11 doses of rFVIIa 87 μg/kg over 3 consecutive days, with 5 of these doses occurring on Study Day 240, and underwent multiple interventions in attempt to identify the source of and control the bleeding, which were unsuccessful. Of note, the participant declined receipt of blood and blood products throughout his entire hospital course. Additional arterial embolization and surgery were deemed not to be feasible.

On Study Day 240, the participant received an aPCC dose of 98 U/kg followed by 2 doses of 65 U/kg. On Study Days 241-243 he received 3 doses of 65 U/kg aPCC each day.

On Study Day 243 the participant developed abdominal pain and confusion, was found to have schistocytes on peripheral blood smear, elevated LDH (2746 U/L), decreased platelet count (33 x 10^9/L) and elevated creatinine (5.54 mg/dL), and was diagnosed with TMA. aPTT and fibrinogen were within normal limits; prothrombin time was not measured. ADAMTS13 activity was 101%; C3 (0.62 g/L) was slightly low (normal range: 0.75-1.61 g/L) and C4 (0.14 g/L) was normal (normal range: 0.13-0.40 g/L). Emicizumab and aPCC were discontinued.

The participant underwent therapeutic plasma exchange twice with albumin as the replacement fluid on Study Days 244 and 245.

At the time of the participant's last laboratory assessment 3 days after discontinuing aPCC, platelet count (114 x 10^9/L) and LDH (775 U/L) were improving, and the investigator assessed the participant's TMA to be recovering/resolving; his hemoglobin level was markedly decreased (4.6 g/dL). The participant continued to decline receipt of blood and blood products and was placed on comfort care before passing away that same day. The death was deemed to be due to rectal hemorrhage.

<u>Thrombosis Case (#4; cavernous sinus thrombosis)</u>

The participant received his usual scheduled weekly dose of emicizumab 1.5 mg/kg on Study Day 130.

On Study Day 131, the participant experienced a traumatic joint bleed, which he treated with aPCC 83 U/kg on this day, as well as 3 doses of aPCC 86 U/kg on Day 132, totaling 257 U/kg within 24 hours.

On Study Day 133, he administered 2 doses of aPCC 86 U/kg and a third dose of 104 U/kg, totaling 276 units/kg within 24 hours.

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On Study Day 134, he administered 1 dose of aPCC 87 U/kg. Later the same day, he presented to the emergency department complaining of left eye swelling with blurred vision, headache, nausea, and vomiting. MRI/MRV of the brain revealed a partially occlusive cavernous sinus thrombosis. Emicizumab was interrupted and aPCC was discontinued. Laboratory values were notable for revealed decreased platelet count ($85 \times 10^3/\mu L$) and low fibrinogen (<35 mg/dL). Thrombophilia testing results were negative.

Additional intervention was not recommended and the participant did not receive anticoagulation. The participant's fibrinogen level (214 mg/L) and platelet count (171 K/UL) had returned to normal levels on Study Days 136 and 139, respectively.

On Study Day 151, a repeat MRI/MRV brain was normal with no evidence of thrombus, and on Study Day 162 emicizumab was resumed.

On Study Day 190, the participant experienced traumatic joint bleed, which he treated with 2 doses of rFVIIa 242 µg/kg. On Study Day 228, the participant received a preventative dose of rFVIIa 242 µg/kg, prior to a dental procedure.

There was no recurrence of thrombotic event and no additional adverse events at the time of the data cutoff.

Thrombosis Case (#5; Superficial Thrombophlebitis)

On Study Day 145, the participant experienced a spontaneous joint bleed, which he treated with 1 dose of aPCC 101 U/kg.

On Study Day 146, the participant experienced a spontaneous shin bleed, which was treated with 1 dose of aPCC 101 U/kg, 24 hours after the first dose.

On Study Day 147, he administered his regular weekly dose of emicizumab 1.5 mg/kg (6 days after the prior dose). The participant applied ice on his right shin for several hours and subsequently noticed changes in the appearance of the skin overlying his right shin, where the ice pack had been placed. The participant was diagnosed with extensive skin necrosis over the right shin and locally limited skin necrosis of the left calf. Emicizumab and aPCC were discontinued.

An ultrasound of both lower extremities did not show deep vein or arterial thrombosis but did reveal a superficial thrombosis of the right saphenous vein. Laboratory values were notable for a normal PT

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(12.5 sec) and fibrinogen (1.99 g/L), and shortened aPTT (20.5 sec). Thrombophilia testing results revealed that he is heterozygous for Factor V Leiden. He was treated with supportive care without anticoagulation, as well as surgical debridement of the wound.

The events of skin necrosis and superficial thrombophlebitis were resolving, and no subsequent adverse events or BPA use were reported at the time of the data cutoff.

CHARACTERIZATION OF THROMBOEMBOLIC AND TMA EVENTS

Characterization of treatment events for these participants in relation to other aPCC treatment episodes that were not associated with the development of TMA or thrombosis are included in **Table S5**; all TMA and thrombotic events were preceded by participants receiving an average daily dose of aPCC of >100 U/kg for >1 day. Treatment events per average daily exposure of rFVIIa are shown in **Table S6.**

The median (range) dose of aPCC administered per treatment event was 79.71 (45.6–246.7) U/kg. The median (range) dose of rFVIIa administered per treatment event was 229.17 (79.7–694.1) μg/kg.

The maximum cumulative dose per 24-hour interval per treatment event for the 18 participants who received aPCC and for the 28 participants who received rFVIIa during the study are shown in **Figures S5 and S6**, respectively.

PHARMACOKINETIC PROFILES OF 2 PARTICIPANTS WITH DECLINING EMICIZUMAB EXPOSURE

Participant 1002 had emicizumab plasma concentrations that consistently declined, starting at Week 13, from 80.2 μg/mL to 26.3 μg/mL at Week 33 (**Figure S7**). This participant had not experienced any bleeding events at the time of data cutoff.

Participant 1121 presented with emicizumab plasma concentrations that consistently declined starting at Week 5, from 45.3 μg/mL to 21.1 μg/mL at Week 25 (**Figure S7**). This participant qualified for up-titration to 3 mg/kg/week based on the pre-specified criteria in the protocol. His emicizumab plasma concentration after up-titration, however, was lower than anticipated (29.6 μg/mL at Week 33). The

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participant experienced one bleed (spontaneous left ankle hemarthrosis) 14 days after up-titration but no additional bleeds thereafter.

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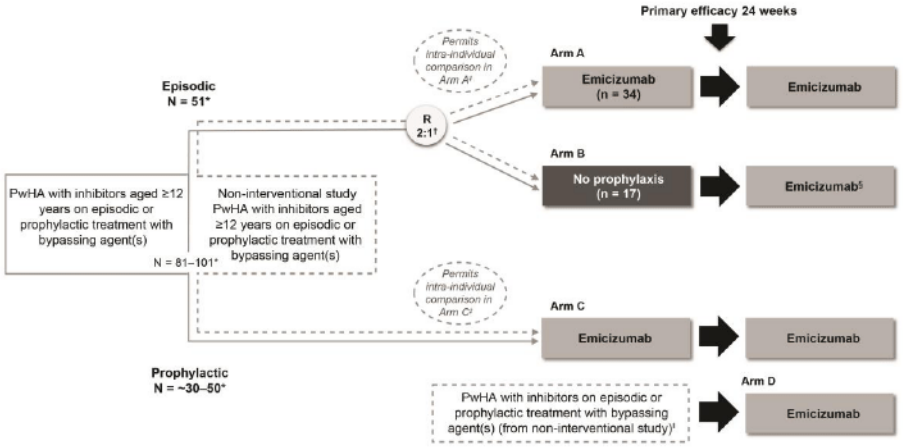
FIGURES

Figure S1. HAVEN 1 Study Schema.



*Planned participant numbers.
†Participants receiving prior episodic treatment with bypassing agents were randomized in 2:1 ratio to Arm A or Arm B using permutated blocks method, and were stratified by bleeds in the prior 24 weeks (conducted centrally by a vendor via interactive voice/web response system); participants in Arm C (prior prophylactic bypassing agent treatment) and Arm D (prior episodic or prophylactic bypassing agent treatment) were enrolled without randomization.
‡Participants entering Arms A or C from the non-interventional study (BH29768, NCT02476942) permitted an intra-individual comparison of outcomes on emicizumab prophylaxis versus their prior bypassing agent treatment (episodic for Arm A, prophylactic for Arm C).
§Participants in Arm B could receive emicizumab prophylaxis once completing ≥24-weeks on study on episodic bypassing agents (and remained in Arm B).
‖Arm D comprised participants who were unable to enroll into Arms A, B or C before they closed to enrollment.

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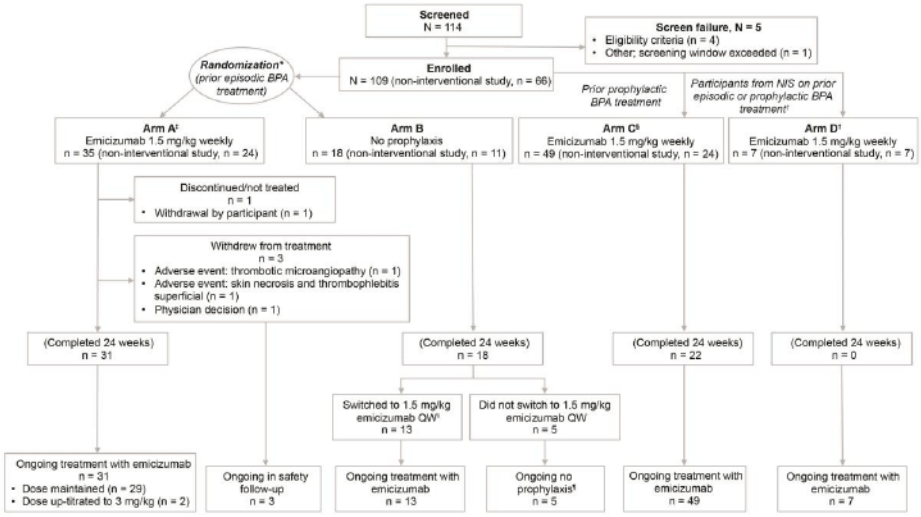
Figure S2. Participant Disposition.



*Participants receiving prior episodic treatment with bypassing agents were randomized in 2:1 ratio to Arm A or Arm B using permutated blocks method, and were stratified by bleeds in the prior 24 weeks (conducted centrally by a vendor via interactive voice/web response system); participants in Arm C (prior prophylactic bypassing agent treatment) and Arm D (prior episodic and prophylactic bypassing agent treatment) were enrolled without randomization.

†Arm D comprised participants who were unable to enroll into Arms A, B or C before they closed to enrollment.

‡An intra-individual comparison in Arm A enabled bleed rates with emicizumab prophylaxis to be compared to those with an individual's prior episodic bypassing agent treatment.

§An intra-individual comparison in Arm C enabled bleed rates with emicizumab prophylaxis to be compared to those with an individual's prior prophylactic bypassing agent treatment.

‖Participants remained in Arm B upon receiving emicizumab prophylaxis once they had completed ≥24 weeks on study on episodic bypassing agents.

¶At time of clinical cut-off, five participants in Arm B were waiting to start emicizumab prophylaxis.

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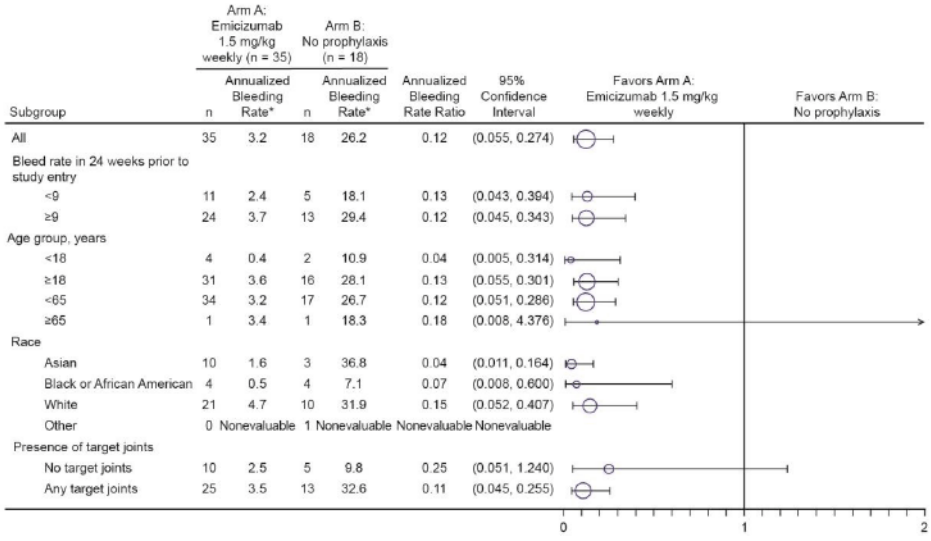
Figure S3. Risk Ratio for Treated Bleeds by Subgroup for Emicizumab Prophylaxis Versus No Prophylaxis.



*Calculated with negative binomial regression model.

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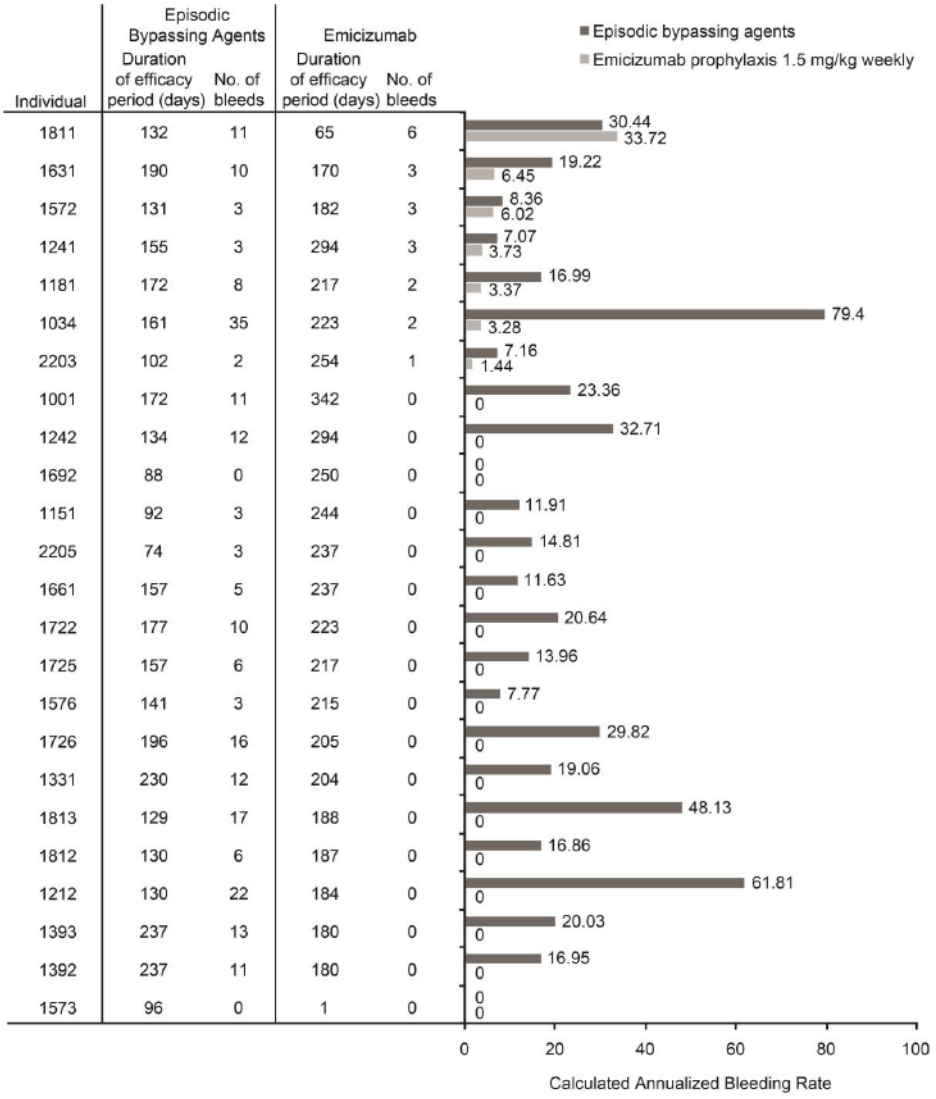
Figure S4. Intra-Individual Comparison for Treated Bleeds in Participants Receiving Emicizumab Prophylaxis (Arm A) Versus No Previous Prophylaxis (Only Episodic Bypassing Agent Treatment).



Intra-individual comparison for emicizumab prophylaxis versus no prior prophylaxis (only episodic bypassing treatment) showed a statistically significant reduction in the risk of treated bleeds (92%: risk ratio 0.08; P≤0.0001).

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Figure S5. Maximum Cumulative Dose of aPCC per 24-Hour Interval per Treatment Event in 18 Participants at Time of Data Cutoff.

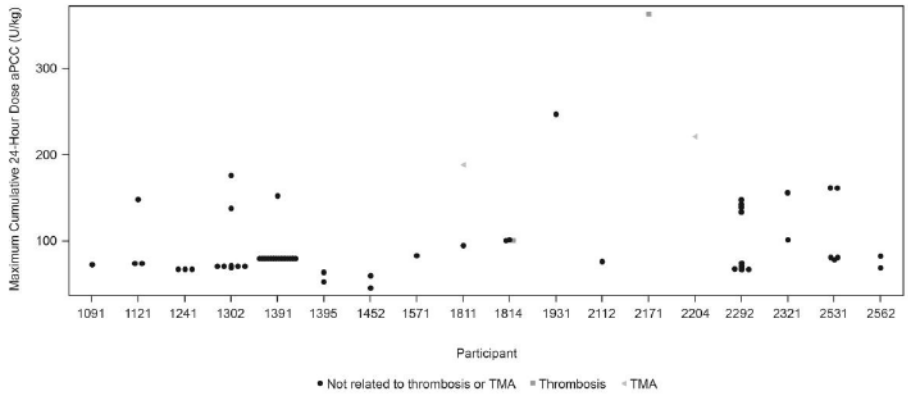

Figure S6. Maximum Cumulative Dose of rFVIIa per 24-Hour Interval per Treatment Event in 28 Participants at Time of Data Cutoff.

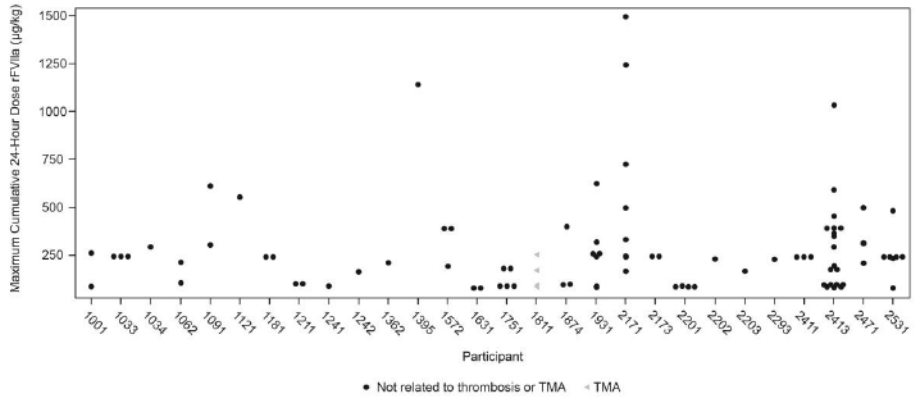

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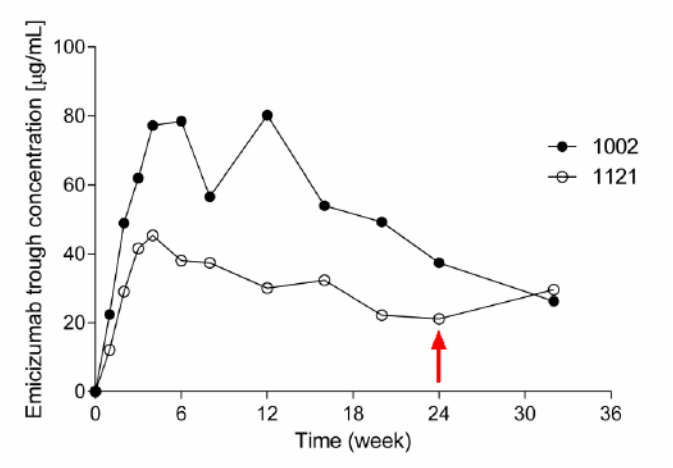
Figure S7. PK Profiles of 2 Participants with Declining Emicizumab Exposure at Primary Analysis Data Cutoff.



Arrow indicates time of up-titration of emicizumab to 3 mg/kg in Participant 1121; emicizumab was not up-titrated in Participant 1002.

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TABLES

Table S1. Participant Demographics and Baseline Characteristics.

	Study Arm*				
	A: Emicizumab Prophylaxis (n = 35)	**B: No Prophylaxis (n = 18)**	**C: Emicizumab Prophylaxis (n = 49)**	**D: Emicizumab Prophylaxis (n = 7)**	**Total (N = 109)**
Age, years, median (min–max)	38.0 (12–68)	35.5 (13–65)	17.0 (12–75)	26.0 (19–49)	28.0 (12–75)
Age, <18 years, n (%)	4 (11.4)	2 (11.1)	26 (53.1)	0	32 (29.4)
Hemophilia severity at baseline, n (%)					
Mild	2 (5.7)	0	1 (2.0)	0	3 (2.8)
Moderate	2 (5.7)	0	1 (2.0)	1 (14.3)	4 (3.7)
Severe	31 (88.6)	18 (100)	47 (95.9)	6 (85.7)	102 (93.6)
Bleeding events in 24 weeks prior to study entry, n (%)					
≥9	24 (68.6)	13 (72.2)	26 (53.1)	3 (42.9)	66 (60.6)
Target joints,† n (%)					
Yes	25 (71.4)	13 (72.2)	34 (69.4)	4 (57.1)	76 (69.7)
>1	18 (72.0)	10 (76.9)	24 (70.6)	1 (25.0)	53 (69.7)
Highest historical inhibitor titer (Bethesda units)					
Median, min–Max	84.5 (5–1570; n=32)	102.0 (18–4500; n=16)	309.0 (11–5000; n=47)	240.0 (28–2125; n=6)	180.0 (5–5000; n=101)
≥5 Bethesda units, n/N (%)	32/35 (91.4)	16/18 (88.9)	47/49 (95.9)	6/7 (85.7)	101/109 (92.7)
Unknown, n/N (%)	3/35 (8.6)	2/18 (11.1)	2/49 (4.1)	1/7 (14.3)	8/109 (7.3)
Previously treated with immune tolerance induction, n (%)	14 (40.0)	7 (38.9)	33 (67.3)	3 (42.9)	57 (52.3)
Episodic coagulation product use in 24 weeks prior to study entry, n (%)‡§	35 (100)	18 (100)	23 (47)	7 (100)	83 (76)
Activated prothrombin complex concentrate	27 (77.1)	13 (72.2)	15 (65.2)	5 (71.4)	60 (72.3)
Recombinant activated factor VII	22 (62.9)	17 (94.4)	15 (65.2)	5 (71.4)	59 (71.1)
Factor VIII	1 (2.9)	0	1 (4.3)	2 (28.6)	4 (4.8)
Other	1 (2.9)	0	0	1 (14.3)	2 (2.4)

[no notes on this page]

Prophylactic coagulation product use in 24 weeks prior to study entry, n (%)	0	0	49 (100)	0	49 (45)
Activated prothrombin complex concentrate	0	0	36 (73.5)	0	36 (73.5)
Recombinant activated factor VII	0	0	15 (30.6)	0	15 (30.6)
Factor VIII	0	0	1 (2.0)	0	1 (2.0)
Other	0	0	1 (2.0)	0	1 (2.0)

*Participants who received episodic bypassing agent treatment prior to study entry were randomized in a 2:1 ratio to receive subcutaneous emicizumab prophylaxis (Arm A) or to the control arm (no emicizumab prophylaxis, only episodic bypassing agent treatment; Arm B). Participants previously on prophylactic BPAs were assigned to Arm C, and Arm D comprised participants who were unable to enroll into Arms A, B or C before they closed to enrollment. Participants randomized to Arm B had the opportunity to receive emicizumab prophylaxis once they completed ≥24 weeks on study (and remained in Arm B; **Figures S1 and S2 in Supplementary Appendix**).

†% based on number of participants with target joints; all numbers are based on electronic case report form and not non-interventional study data.

‡Use of multiple products was possible.

§Participants on prophylactic bypassing agents may have also used episodic bypassing agent treatment for breakthrough bleeds.

[no notes on this page]

Table S2. Bleeds Across Study Arms.

	Study Arm*		
	A: Emicizumab Prophylaxis (n = 35)	**B: No Prophylaxis (n = 18)**	**C: Emicizumab Prophylaxis (n = 49)**
Duration of efficacy period (weeks), median (min–max)	29.29 (0.1–48.9)	24.14 (23.0–26.0)	19.14 (6.9–45.3)
Treated bleeds (with BPAs)			
Annualized bleeding rate, model based† (95% confidence interval)	2.9 (1.69, 5.02)	23.3 (12.33, 43.89)	5.1 (2.28, 11.22)
% reduction (risk ratio), P value	87% (0.13), P<0.0001		--
Median annualized bleeding rate, calculated (interquartile range)	0.0 (0.0–3.7)	18.8 (13.0–35.1)	0.0 (0.0–1.7)
All bleeds (treated/not treated with BPAs)			
Annualized bleeding rate, model based† (95% confidence interval)	5.5 (3.58, 8.60)	28.3 (16.79, 47.76)	6.5 (3.43, 12.43)
% reduction (risk ratio), P value	80% (0.20), P<0.0001		--
Median annualized bleeding rate, calculated (interquartile range)	2.0 (0.0–9.9)	30.2 (18.3–39.4)	0.0 (0.0–6.0)
Treated spontaneous bleeds			
Annualized bleeding rate, model based† (95% confidence interval)	1.3 (0.73, 2.19)	16.8 (9.94, 28.30)	3.1 (1.20, 8.02)
% reduction (risk ratio), P value	92% (0.08), P<0.0001		--
Median annualized bleeding rate, calculated (interquartile range)	0.0 (0.0–3.3)	15.2 (6.6–30.4)	0.0 (0.0–0.0)
Treated joint bleeds			
Annualized bleeding rate, model based† (95% confidence interval)	0.8 (0.26, 2.20)	6.7 (1.99, 22.42)	0.6 (0.21, 1.48)
% reduction (risk ratio), P value	89% (0.11), P=0.0050		--
Median annualized bleeding rate, calculated (interquartile range)	0.0 (0.0–0.0)	1.0 (0.0–14.4)	0.0 (0.0–0.0)
Treated target joint bleeds			
Annualized bleeding rate, model based† (95% confidence interval)	0.1 (0.03, 0.58)	3.0 (0.96, 9.13)	0.3 (0.10, 0.95)
% reduction (risk ratio), P value	95% (0.05), P=0.0002		--
Median annualized bleeding rate, calculated (interquartile range)	0.0 (0.0–0.0)	1.0 (0.0–6.5)	0.0 (0.0–0.0)
Participants with zero bleeds, % (95% confidence interval)	62.9 (44.9, 78.5)	5.6 (0.1, 27.3)	69.4 (54.6, 81.7)

*Participants who received episodic BPA treatment prior to study entry were randomized in a 2:1 ratio to receive subcutaneous emicizumab prophylaxis (Arm A) or to the control arm (no emicizumab prophylaxis, only episodic bypassing agent treatment; Arm B). Participants previously on prophylactic bypassing agents were assigned to Arm C. Participants randomized to Arm B had the opportunity to receive emicizumab prophylaxis once they completed ≥24 weeks on study (**Figures S1 and S2 in Supplementary Appendix**). Arm D was not included due to the short follow-up at the time of data cutoff.

†Negative binomial regression model.

[no notes on this page]

Table S3. Adverse Events in Participants Receiving Emicizumab Prophylaxis by Study Arm.

Adverse Event	Study Arm* (all participants on emicizumab prophylaxis, including Arm B after switch)				Total (N = 103)
	A: Emicizumab prophylaxis (n = 34)	B: Emicizumab prophylaxis† (n = 13)	C: Emicizumab prophylaxis (n = 49)	D: Emicizumab prophylaxis (n = 7)	
Median (range) emicizumab exposure, weeks	29.5 (3.3–47.9)	8.0 (4.0–16.0)	19.0 (5.9–45.0)	5.8 (3.0–14.0)	24.0 (3.0–47.9)
Number of adverse events	85	16	93	4	198
Participants with ≥1 adverse event, n (%)	29 (85.3)	7 (53.8)	35 (71.4)	2 (28.6)	73 (70.9)
Participants with ≥1 serious adverse event, n (%)	4 (11.8)	1 (7.7)	4 (8.2)	0	9 (8.7)
Grade ≥3 adverse event, n (%)	3 (8.8)	1 (7.7)	4 (8.2)	0	8 (7.8)
Treatment-related adverse event, n (%)	13 (38.2)	1 (7.7)	9 (18.4)	0	23 (22.3)
Common adverse events (occurring in ≥5% of participants, overall), n (%)					
Injection-site reaction	8 (23.5)	1 (7.7)	5 (10.2)	1 (14.3)	15 (14.6)
Headache	3 (8.8)	1 (7.7)	6 (12.2)	2 (28.6)	12(12.6)
Fatigue	3 (8.8)	1 (7.7)	2 (4.1)	0	6 (5.8)
Upper respiratory tract infection	7 (20.6)	0 (0)	2 (4.1)	0	9 (8.7)
Arthralgia	2 (5.9)	1 (7.7)	3 (6.1)	0	6 (5.8)
Serious adverse events, n (%)					
Thrombotic microangiopathy‡‖	1 (2.9)	0	1 (2.0)	0	2 (1.9)
Skin necrosis‡	1 (2.9)§	0	0	0	1 (1.0)
Thrombophlebitis superficial ‡	1 (2.9)§	0	0	0	1 (1.0)
Cavernous sinus thrombosis ‡	0	0	1 (2.0)	0	1 (1.0)
Iron deficiency anemia	1 (2.9)	0	0	0	1 (1.0)
Sepsis	0	0	1 (2.0)	0	1 (1.0)
Hemarthrosis	0	1 (7.7)	0	0	1 (1.0)
Muscle hemorrhage	1 (2.9)	0	0	0	1 (1.0)
Gastric ulcer hemorrhage	0	0	1 (2.0)	0	1 (1.0)
Headache	0	0	1 (2.0)	0	1 (1.0)
Hematuria	0	0	1 (2.0)	0	1 (1.0)

*Participants who received episodic BPA treatment prior to study entry were randomized in a 2:1 ratio to receive subcutaneous emicizumab prophylaxis (Arm A) or to the control arm (no emicizumab prophylaxis, only episodic BPA treatment; Arm B). Participants previously on prophylactic BPAs were assigned to Arm C, and Arm D comprised participants who were unable to enroll into Arms A, B or C before they closed to enrollment. Participants randomized to Arm B had the opportunity to receive emicizumab prophylaxis once they completed ≥24 weeks on study on episodic bypassing agents (and remained in Arm B; **Figures S1 and S2 in Supplementary Appendix**).

[no notes on this page]

[†]Includes emicizumab prophylaxis time period only.
[‡]Selected adverse event (**see thromboembolic and thrombotic microangiopathy events section in Supplementary Appendix**).
[§]Occurred in one participant contemporaneously.
[‖]One additional participant (Arm C) developed thrombotic microangiopathy after the data cutoff for the primary analysis.

[no notes on this page]

Table S4. Bypassing Agent Use in Participants Receiving Emicizumab Prophylaxis (1.5 mg/kg).

	Study Arm* (all participants on emicizumab prophylaxis, including Arm B after switch)				
	A: Emicizumab Prophylaxis (n = 35)	**B: Emicizumab Prophylaxis† (n = 13)**	**C: Emicizumab Prophylaxis (n = 49)**	**D: Emicizumab Prophylaxis (n = 7)**	**Total (N = 104)**
Participants exposed to activated prothrombin complex concentrate, n (%)	**11 (31.4)**	**1 (7.7)**	**15 (30.6)**	**1 (14.3)**	**28 (26.9)**
No. of doses, median (min–max)	4 (1–27)	6 (6–6)	3 (1–19)	1 (1–1)	3 (1–27)
Total cumulative dose (U/kg), median (min–max)	295.7 (51–1907)	318.8 (319–319)	232.2 (42–1507)	90.9 (91–91)	239.5 (42–1907)
Highest single dose‡ used (U/kg), n (%)					
<50	0	0	1 (6.7)	0	1 (3.6)
50–75	5 (45.5)	1 (100)	4 (26.7)	0	10 (35.7)
76–100	5 (45.5)	0	7 (46.7)	1 (100)	13 (46.4)
>100	1	0	3 (20.0)	0	4 (14.3)
Participants exposed to recombinant activated factor VII, n (%)	**12 (34.3)**	**4 (30.8)**	**16 (32.7)**	**2 (28.6)**	**34 (32.7)**
No. of doses‡, median (min–max)	3.0 (1–10)	2.5 (1–5)	9.5 (1–142)	8.0 (8–8)	5 (1–142)
Total cumulative dose (µg/kg), median (min–max)	502.2 (89–2251)	349.2 (231–444)	1000.9 (208–15654)	943.5 (796–1091)	700.8 (89–15654)
Highest single dose‡ used (µg/kg), n (%)					
<90	4 (33.3)	0	2 (12.5)	0	6 (17.6)
90–180	3 (25.0)	2 (50.0)	7 (43.8)	1 (50.0)	13 (38.2)
181–270	3 (25.0)	1 (25.0)	6 (37.5)	1 (50.0)	11 (32.4)
>270	2 (16.7)	1 (25.0)	1 (6.3)	0	4 (11.8)
Participants exposed to activated prothrombin complex concentrate and recombinant activated factor VII§, n (%)	**6 (17.1)**	**1 (7.7)**	**5 (10.2)**	**1 (14.3)**	**13 (12.5)**
Used aPCC and rFVIIa but only separately, n (%)	2 (5.7)	0	3 (6.1)	1 (14.3)	6 (5.8)

*Participants who received episodic bypassing agent treatment prior to study entry were randomized in a 2:1 ratio to receive subcutaneous emicizumab prophylaxis (Arm A) or to the control arm (no emicizumab prophylaxis, only episodic bypassing agent treatment; Arm B). Participants previously on prophylactic bypassing agents were assigned to Arm

[no notes on this page]

C, and Arm D comprised participants who were unable to enroll into Arms A, B or C before they closed to enrollment. Participants randomized to Arm B had the opportunity to receive emicizumab prophylaxis once they completed ≥24 weeks on study on episodic bypassing agents (and remained in Arm B; **Figures S1 and S2 in Supplementary Appendix**).

[†]Includes emicizumab prophylaxis phase only.

[‡]A dose is an infusion of aPCC or rFVIIa at a given time. Treatment for a bleed/surgery procedure may consist of several doses.

[§]At any time during the study, not necessarily concomitantly.

[no notes on this page]

Table S5. Treatment Events per Average Daily Exposure of aPCC in 18 Participants at Time of Data Cutoff.

Duration (24-hour intervals) of aPCC Treatment	Average Daily Dose of aPCC (U/kg/day)				Total No. of Treatment Events per 24 Hours
	<50	50–100	101–150	>150	
1	1	44	7	5	**57**
2	0	1	1[†2]	0	**2**
3	0	0	3[*1; *2]	1[†1]	**4**
4	0	0	2	0[‡]	**2**
>4	0	0	0	0	**0**
Total no. of treatment events per average daily dose category	1	45	13	6	65

[*1]TMA #1.
[†1]Cavernous sinus thrombosis.
[*2]TMA #2.
[†2]Skin necrosis/thrombophlebitis.
[‡]TMA #3 (after data cutoff for primary analysis).

Table S6. Treatment Events per Average Daily Exposure of rFVIIa in 28 Participants at Time of Data Cutoff.

Duration (24-hour intervals) of rFVIIa Treatment	Average Daily Dose of rFVIIa (µg/kg/day)				Total No. of Treatment Events per 24 Hours
	<90	90–180	181–270	>270	
1	12	21	27	14	**74**
2	1	2	6	5	**14**
3	0	1	1	4	**2**
4	0	0	2	0	**0**
>4	0	0	1	4	**5**
Total no. of treatment events per average daily dose category	13	24	35	23	95

REFERENCE

1. Cameron AC, Trivedi PK. Econometric models based on count data: comparisons and applications of some estimators and tests. J Appl Econ 1986;1:29-53.

[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

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Entity: government agency, foundation, commercial sponsor, academic institution, etc.
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1. Given Name (First Name): Elina
2. Surname (Last Name): Asikanius
3. Date: 10-March-2017

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

6. Manuscript Identifying Number (if you know it): 17-03068

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Roche	☐	☑	☐	☑	Employment and stock

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Dr. Asikanius reports personal fees and other support from Roche outside the submitted work.

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Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

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3. Relevant financial activities outside the submitted work.

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Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
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2. Surname (Last Name): Callaghan
3. Date: 03-March-2017

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

6. Manuscript Identifying Number (if you know it): 17-03068

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

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Baxalta	☑	☑	☐	☐	Speaker Bureau, Advisory Panel
Biogen	☐	☑	☐	☐	Advisory panel
Grifols	☐	☑	☐	☐	Advisory panel
CSL Behring	☐	☑	☐	☐	Advisory Panel
Bayer	☐	☑	☐	☐	Advisory panel
Shire	☐	☑	☐	☐	Speaker Bureau, Advisory panel

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Global Blood Therapeutics	☐	☑	☐	☐	Site PI

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Callaghan reports grant support and personal fees from Roche/Genentech, Baxalta, and Pfizer, personal fees from Biogen, Grifols, CSL Behring, Bayer, Shire, Novo Nordisk, Octapharma, Sancillio, and Global Blood Therapeutics outside the submitted work.

[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Evaluation and Feedback

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

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3. Relevant financial activities outside the submitted work.

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Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
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Royalties: Funds are coming in to you or your institution due to your patent

[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Craig
2. Surname (Last Name): Kessler
3. Date: 20-April-2017

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

6. Manuscript Identifying Number (if you know it): 17-03068

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Genentech	☑	☐	☐	☐	Research grant awarded to University; no personal salary offset

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Genentech	☐	☑	☐	☐	Participation in Advisory Board

[no notes on this page]

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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Section 4. Intellectual Property -- Patents & Copyrights

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Dr. Kessler reports grant support from Genentech during the conduct of the study; personal fees from Genentech outside the submitted work.

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[no notes on this page]

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Benjamin
2. Surname (Last Name): Kim
3. Date: 30-June-2017

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Adolescent/Adult Patients with Hemophilia A with Inhibitors - HAVEN 1 Study

6. Manuscript Identifying Number (if you know it): 17-03068.R2

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Kim has nothing to disclose.

Evaluation and Feedback

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[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Rebecca
2. Surname (Last Name): Kruse-Jarres
3. Date: 03-March-2017

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

6. Manuscript Identifying Number (if you know it): 17-03068

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Pfizer	☑	☑	☐	☐	fees for consulting
Roche	☑	☑	☐	☐	fees for consulting
Baxalta	☐	☑	☐	☐	fees for consulting
Bayer	☐	☑	☐	☐	fees for consulting
CSL Behring	☐	☑	☐	☐	fees for consulting
Grifols	☐	☑	☐	☐	fees for consulting

[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Royalties: Funds are coming in to you or your institution due to your patent

[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Gallia G.
2. Surname (Last Name): Levy
3. Date: 10-March-2017

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

6. Manuscript Identifying Number (if you know it): 17-03068

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Genentech/Roche	☐	☑	☐	☐	Employee
Roche	☐	☐	☐	☑	Stock/shareholder

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

[no notes on this page]

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Section 5. Relationships not covered above

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Dr. Levy reports personal fees from Genentech/Roche, other support from Roche outside the submitted work.

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[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Johnny
2. Surname (Last Name): Mahlangu
3. Date: 03-March-2017

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

6. Manuscript Identifying Number (if you know it): 17-03068

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Bayer	☑	☑	☐	☐	Speaker bureau
Biogen Idec	☑	☑	☐	☐	Speaker bureau
CLS berhing	☑	☑	☐	☐	Speaker bureau
Novo Nordisk	☑	☑	☐	☐	Speaker bureau
Roche	☑	☑	☐	☐	Speaker bureau
Baxalta	☐	☑	☐	☐	Protocol review
Amgen	☐	☑	☐	☐	Advisory board
Biotest	☐	☑	☐	☐	Speaker bureau

[no notes on this page]

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Mahlangu reports grant support and personal fees from Bayer, Biogen Idec, CLS Behring, Novo Nordisk, and Roche, personal fees from Baxalta, Amgen, and Biotest outside the submitted work.

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

[no notes on this page]

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Instructions

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Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
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Royalties: Funds are coming in to you or your institution due to your patent

[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Claude
2. Surname (Last Name): Negrier
3. Date: 06-June-2017

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

6. Manuscript Identifying Number (if you know it): 17-03068

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
CSL Behring	☑	☑	☐	☐	honoraria for consulting and lectures, research grants
LFB Biotechnologies	☑	☑	☐	☐	honoraria for consulting and lectures
Octapharma	☑	☑	☐	☐	honoraria for consulting and lectures, research grants
Pfizer	☑	☑	☐	☐	honoraria for consulting and lectures, research grants
Sobi	☑	☑	☐	☐	honoraria for consulting and lectures, research grants
Novo Nordisk	☑	☑	☐	☐	honoraria for consulting and lectures, research grants

[no notes on this page]

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Alnylam	☑	☑	☐	☐	honoraria for consulting and lectures, research grants
Bayer	☐	☑	☐	☐	honoraria for consulting and lectures
Roche	☐	☑	☐	☐	honoraria for consulting and lectures
Baxalta/Shire	☑	☑	☐	☐	honoraria for consulting and lectures, research grants

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Negrier reports grant support and personal fees from CSL Behring, LFB Biotechnologies, Octapharma, Pfizer, Sobi, Novo Nordisk, Alnylam, and Baxalta/Shire; personal fees from Bayer and Roche outside the submitted work.

[no notes on this page]

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Royalties: Funds are coming in to you or your institution due to your patent

[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Johannes
2. Surname (Last Name): Oldenburg
3. Date: 24-April-2017

4. Are you the corresponding author? ☑ Yes ☐ No

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

6. Manuscript Identifying Number (if you know it): 17-03068

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Baxalta	☑	☑	☐	☐	Baxalta is now Shire Fees for Advisory Boards, consulting lectures, speakers' bureaus.
Bayer	☑	☑	☐	☐	Fees for Advisory Boards, consulting lectures, speakers' bureaus,
Biotest	☑	☑	☐	☐	Fees for Advisory Boards, consulting lectures, speakers' bureaus,
CSL Behring	☑	☑	☐	☐	Fees for Advisory Boards, consulting lectures, speakers' bureaus,
Grifols	☑	☑	☐	☐	Fees for Advisory Boards, consulting lectures, speakers' bureaus,

[no notes on this page]

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Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Novo Nordisk	☑	☑	☐	☐	Fees for Advisory Boards, consulting lectures, speakers' bureaus,
Octapharma	☑	☑	☐	☐	Fees for Advisory Boards, consulting lectures, speakers' bureaus,
Pfizer	☑	☑	☐	☐	Fees for Advisory Boards, consulting lectures, speakers' bureaus,
Biogen Idec	☐	☑	☐	☐	Fees for Advisory Boards, consulting lectures, speakers' bureaus,
Chugai	☐	☑	☐	☐	Fees for Advisory Boards, consulting lectures, speakers' bureaus,
Roche	☐	☑	☐	☐	Fees for Advisory Boards, consulting lectures, speakers' bureaus,
Swedish Orphan Biovitrium	☐	☑	☐	☐	Fees for Advisory Boards, consulting lectures, speakers' bureaus,
Baxter	☑	☑	☐	☐	Fees for Advisory Boards, consulting lectures, speakers' bureaus,

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Oldenburg reports grant support and personal fees from Baxalta, Bayer, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer and Baxter, personal fees from Biogen Idec, Chugai, Roche, and Swedish Orphan Biovitrium outside the submitted work.

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4. Intellectual Property.

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Royalties: Funds are coming in to you or your institution due to your patent

[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Elena
2. Surname (Last Name): Santagostino
3. Date: 03-March-2017

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

6. Manuscript Identifying Number (if you know it): 17-03068

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Pfizer	☑	☑	☐	☐	Advisory Boards and speaker fees
Bayer	☐	☑	☐	☐	Advisory Boards and speaker fees
CSL Behring	☐	☑	☐	☐	Advisory Boards and speaker fees
Novo Nordisk	☐	☑	☐	☐	Advisory Boards and speaker fees
Grifols	☐	☑	☐	☐	Advisory Boards and speaker fees
Baxalta	☐	☑	☐	☐	Advisory Boards and speaker fees
Shire	☐	☑	☐	☐	Advisory Boards and speaker fees
Biogen Idec	☐	☑	☐	☐	Advisory Boards and speaker fees

[no notes on this page]

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Sobi	☐	☑	☐	☐	Advisory Boards and speaker fees
Octapharma	☐	☑	☐	☐	Advisory Boards and speaker fees
Kedrion	☐	☑	☐	☐	Advisory Boards and speaker fees
Roche	☐	☑	☐	☐	Advisory Boards and speaker fees

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

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Dr. Santagostino reports grant support and personal fees from Pfizer, personal fees from Bayer, CSL Behring, Novo Nordisk, Grifols, Baxalta, Shire, Biogen Idec, Sobi, Octapharma, Kedrion, and Roche outside the submitted work.

[no notes on this page]

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Christophe
2. Surname (Last Name): Schmitt
3. Date: 03-March-2017

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

6. Manuscript Identifying Number (if you know it): 17-03068

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Roche	☐	☑	☐	☐	Employment

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

[no notes on this page]

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Dr. Schmitt reports personal fees from Roche outside the submitted work.

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The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
Grant: A grant from an entity, generally [but not always] paid to your organization
Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
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Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Midori
2. Surname (Last Name): Shima
3. Date: 10-March-2017

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

6. Manuscript Identifying Number (if you know it): 17-03068

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Roche	☐	☑	☐	☐	honorarium

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Bayer	☑	☑	☐	☐	honorarium
Biogen	☑	☑	☐	☐	honorarium
Chugai	☑	☑	☐	☐	honorarium

[no notes on this page]

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
CSL Behring	☑	☑	☐	☐	honoraria
Novo Nordisk	☑	☑	☐	☐	honoraria
Baxalta	☑	☑	☐	☐	honoraria
Pfizer	☑	☑	☐	☐	honoraria

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Shima reports personal fees from Roche during the conduct of the study; grant support and personal fees from Bayer, Biogen, Chugai, CSL Behring, Novo Nordisk, Baxalta, and Pfizer outside the submitted work.

[no notes on this page]

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Evaluation and Feedback

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[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Nancy
2. Surname (Last Name): Valente
3. Date: 10-March-2017

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

6. Manuscript Identifying Number (if you know it): 17-03068

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Genentech	☐	☑	☐	☐	employee
Roche	☐	☐	☐	☑	Stockholder

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

[no notes on this page]

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Dr. Valente reports personal fees from Genentech, other support from Roche outside the submitted work.

Evaluation and Feedback

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[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Jerzy
2. Surname (Last Name): Windyga
3. Date: 10-March-2017

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

6. Manuscript Identifying Number (if you know it): 17-03068

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Roche	☑	☑	☐	☐	grants/research support

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Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Baxalta	☑	☑	☐	☐	grants/research support, honoraria for lectures
Biogen Idec	☑	☑	☐	☐	grants/research support, honoraria for lectures

[no notes on this page]

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Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Bayer	☑	☑	☐	☐	grants/research support, honoraria for lectures
CSL Behring	☑	☑	☐	☐	grants/research support, honoraria for lectures
Novo Nordisk	☑	☑	☐	☐	grants/research support, honoraria for lectures
Octapharma	☑	☑	☐	☐	grants/research support, honoraria for lectures
Sanofi	☑	☑	☐	☐	honoraria for lectures
Alexion	☑	☑	☐	☐	grants/research support, honoraria for lectures
Baxter Healthcare	☑	☑	☐	☐	grants/research support, honoraria for lectures

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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[no notes on this page]

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Guy
2. Surname (Last Name): Young
3. Date: 03-March-2017

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Johannes Oldenburg

5. Manuscript Title: Emicizumab Prophylaxis in Hemophilia A With Inhibitors

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Alnhylam	☐	☑	☐	☐	Honoraria
Bayer	☐	☑	☐	☐	Consulting Fees
Biogen	☐	☑	☐	☐	Honoraria
Kedrion	☐	☑	☐	☐	Consulting Fees
Novo Nordisk	☐	☑	☐	☐	Honoraria and consulting fees
Roche	☐	☑	☐	☐	Honoraria
Shire	☐	☑	☐	☐	Honoraria

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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