Help your patients with type 2 diabetes

REALISE THE POTENTIAL

Ozempic®—a **once-weekly** treatment unifying superior efficacy[1-4,28,30] and CV benefits[1,5]

SUPERIOR GLYCAEMIC CONTROL[1,2,28,30*]

SUPERIOR AND SUSTAINED WEIGHT LOSS[1,2,5,28,30*]

PROVEN CV BENEFITS[1,5†]

For adults with type 2 diabetes and established ASCVD or indicators of high ASCVD risk

2019 update of ADA/EASD consensus report recommends GLP-1 RA therapy with proven CVD benefit[31]

ASCVD=atherosclerotic cardiovascular disease; CV=cardiovascular; CVD=cardiovascular disease; ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes; GLP-1 RA=glucagon-like peptide-1 receptor agonist.

*Results apply to Ozempic® across SUSTAIN trials, which included placebo, sitagliptin, dulaglutide, exenatide extended release, insulin glargine U100, canagliflozin and liraglutide.[1,2,28,30]

†In SUSTAIN 6, Ozempic® reduced CV risk (CV death, nonfatal myocardial infarction [MI] or nonfatal stroke) versus placebo in patients with type 2 diabetes at high CV risk treated with standard of care.[1]

Ozempic® outperformed dulaglutide in reducing HbA_{1c}[2]

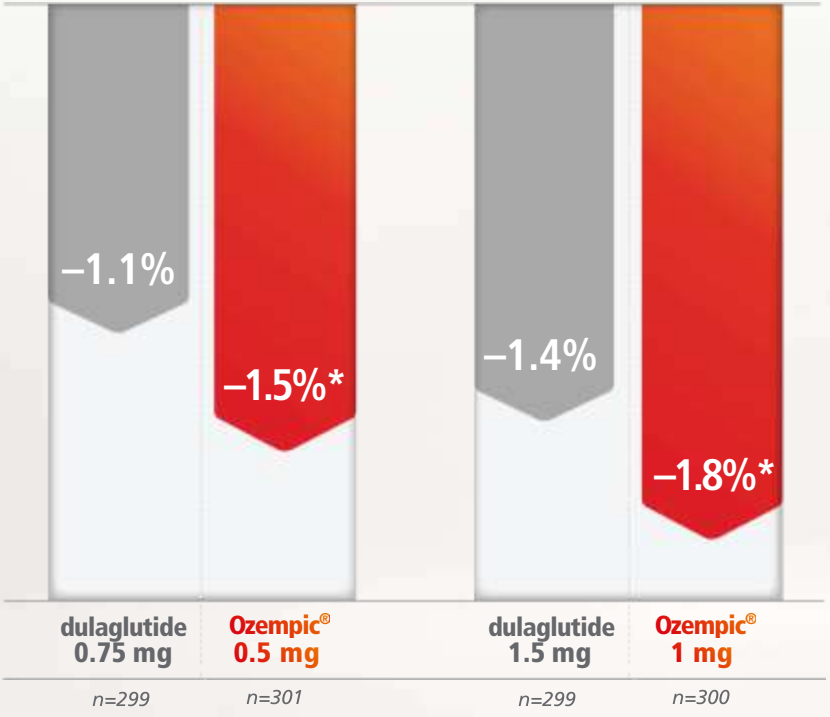
ABSOLUTE HbA_{1c}

HbA_{1c} <7%

CONSISTENT RESULTS

Change from baseline in HbA_{1c} at Week 40

*P<0.0001

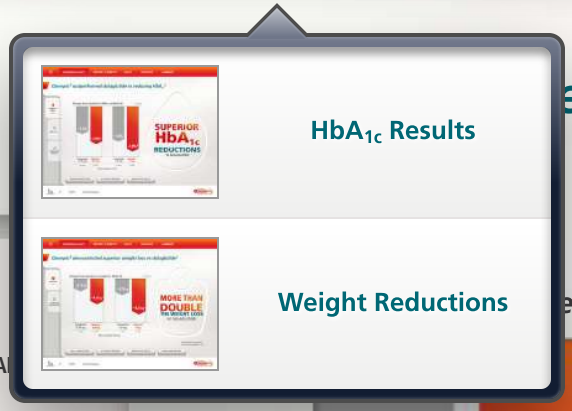


Mean baseline: 8.2%

SUPERIOR HbA_{1c} REDUCTIONS

VS DULAGLUTIDE

WEIGHT REDUCTION | VS BASAL INSULIN | ADD-ON TO SGLT2i



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HbA1c <7%

CONSISTENT RESULTS

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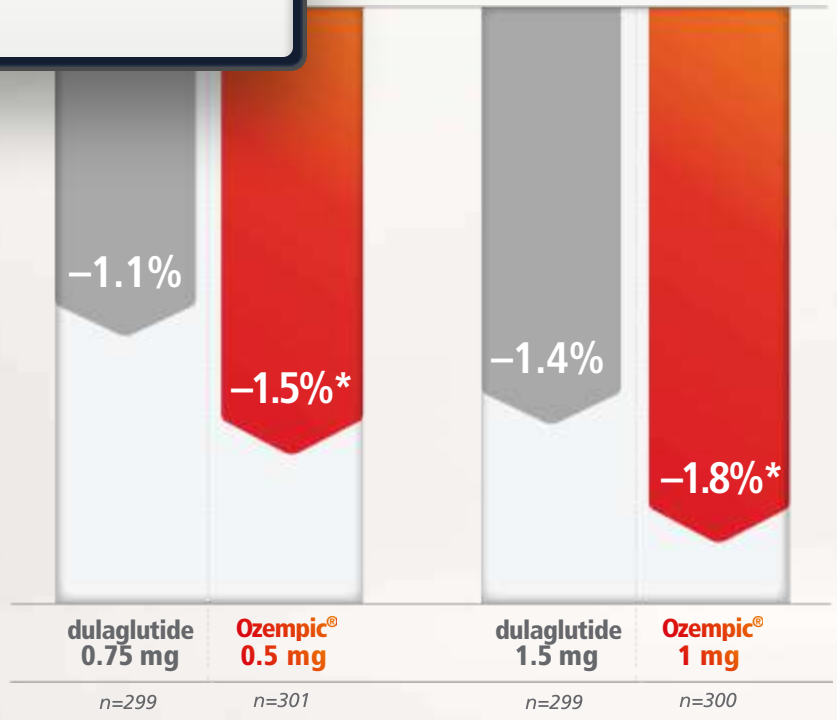


Mean baseline: 8.2%

SUPERIOR HbA_{1c} REDUCTIONS

VS DULAGLUTIDE

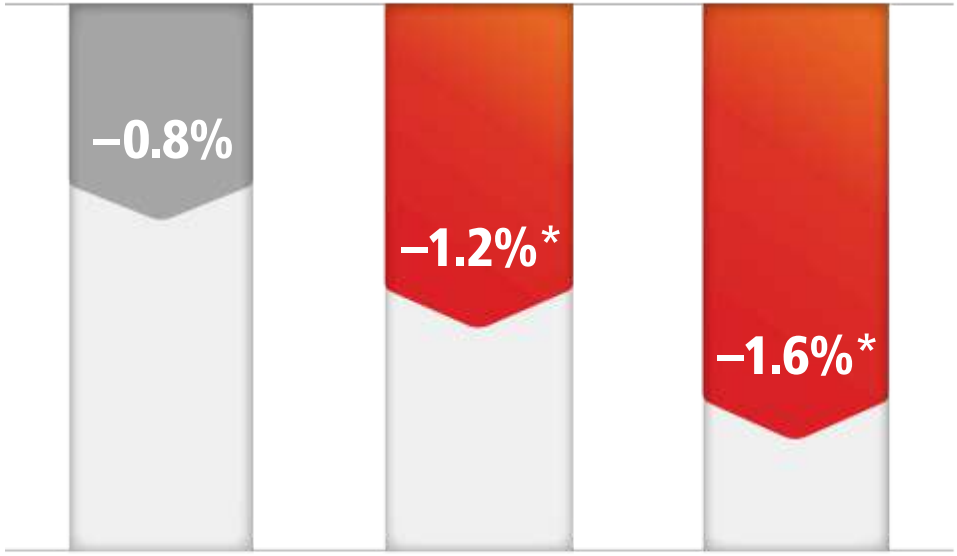
WEIGHT REDUCTION | VS BASAL INSULIN | ADD-ON TO SGLT2i

Ozempic® outperformed dulaglutide in reducing HbA_{1c}[2]

Once-weekly Ozempic® delivered superior HbA_{1c} reductions vs insulin glargine U100

Change from baseline in HbA_{1c} at Week 30[1]

*$P<0.0001$



Mean baseline: 8.2%

SUPERIOR HbA_{1c} REDUCTIONS VS INSULIN GLARGINE U100[1]

ABSOLUTE WEIGHT LOSS

WEIGHT REDUCTION | VS BASAL INSULIN | ADD-ON TO SGLT2i

Ozempic® outperformed dulaglutide in reducing HbA_{1c}[2]

Ozempic® delivered superior weight loss vs insulin glargine U100

Change from baseline in weight at Week 30[1]

**P<0.0001*

insulin glargine U100	Ozempic® 0.5 mg	Ozempic® 1 mg
n=360	n=362	n=360

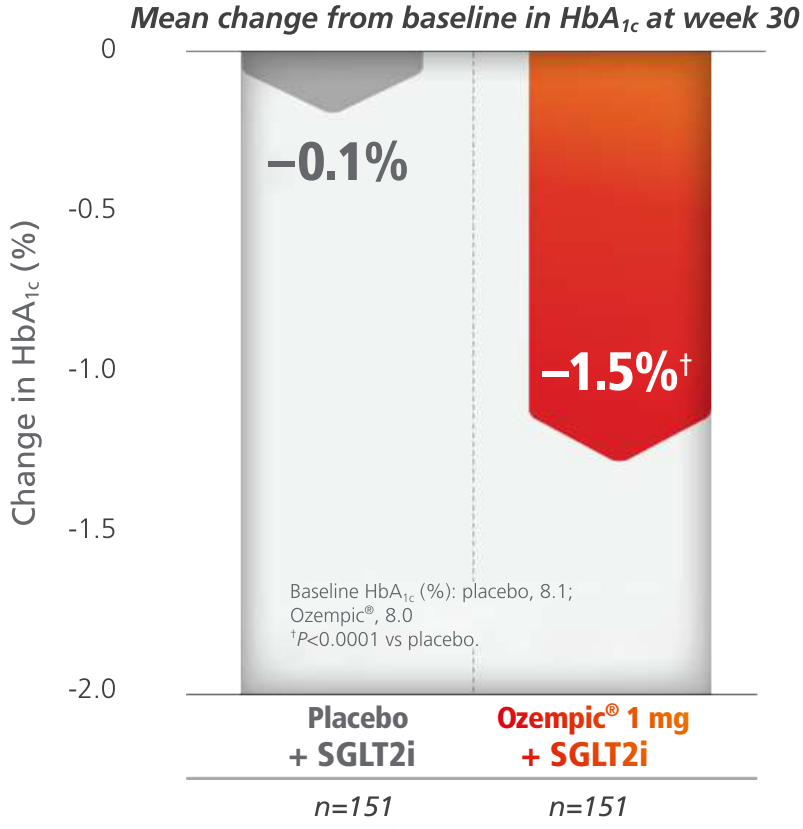
Mean baseline: 93.5 kg

ABSOLUTE HbA_{1c}

WEIGHT REDUCTION | VS BASAL INSULIN | ADD-ON TO SGLT2i

Ozempic® outperformed dulaglutide in reducing HbA_{1c}[2]

Ozempic® demonstrated superior HbA_{1c} reductions when used as add-on to an SGLT2i[29]



UP TO 15x

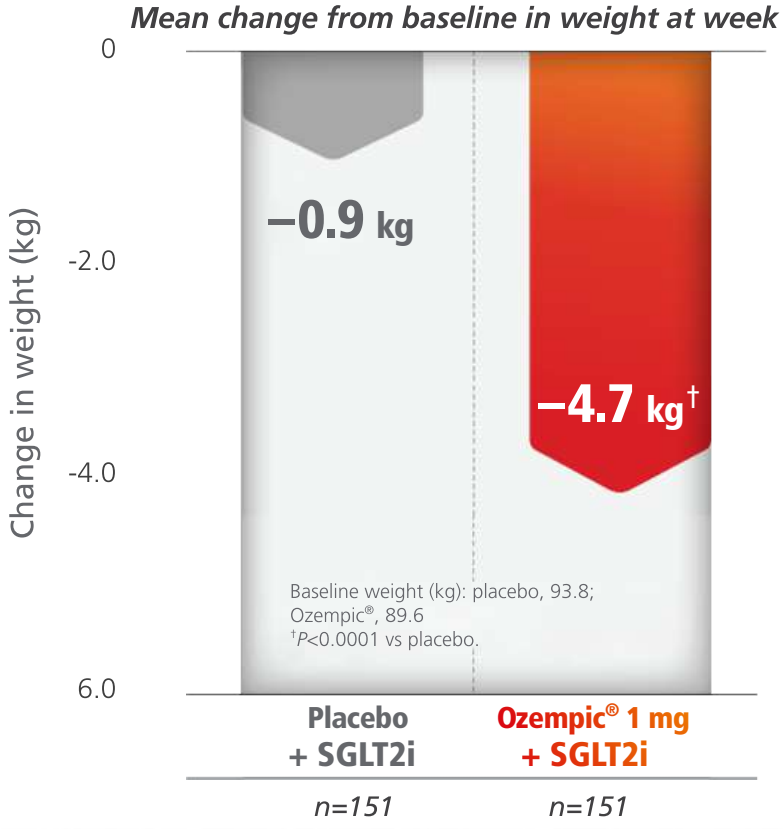
MORE HbA_{1c} REDUCTIONS SHOWN WITH OZEMPIC® VS PLACEBO, BOTH AS ADD-ONS TO AN SGLT2i (± MET/SU)[29]

ABSOLUTE WEIGHT LOSS

WEIGHT REDUCTION | VS BASAL INSULIN | ADD-ON TO SGLT2i

Ozempic® outperformed dulaglutide in reducing HbA_{1c}[2]

Ozempic® demonstrated superior weight reductions when used as add-on to an SGLT2i[29]



UP TO 5X

MORE WEIGHT REDUCTIONS SHOWN WITH OZEMPIC® VS PLACEBO, BOTH AS ADD-ONS TO AN SGLT2i (± MET/SU)[29]

ABSOLUTE HbA_{1c}

WEIGHT REDUCTION | VS BASAL INSULIN | ADD-ON TO SGLT2i

Ozempic® got more patients to target across all head-to-head trials[1,2,28,30]*

ABSOLUTE HbA_{1c}

HbA_{1c} <7%

CONSISTENT RESULTS

UP TO

80%

ACHIEVED ADA TARGET OF HbA_{1c}

<7%

VS OTHER DIABETES TREATMENTS[1,2,9,28,30]*

ADA=American Diabetes Association.
*Other diabetes treatments refer to sitagliptin, dulaglutide, exenatide ER, liraglutide and insulin glargine U100.

Ozempic® demonstrated superior HbA_{1c} reductions in all head-to-head trials[1,2,28]

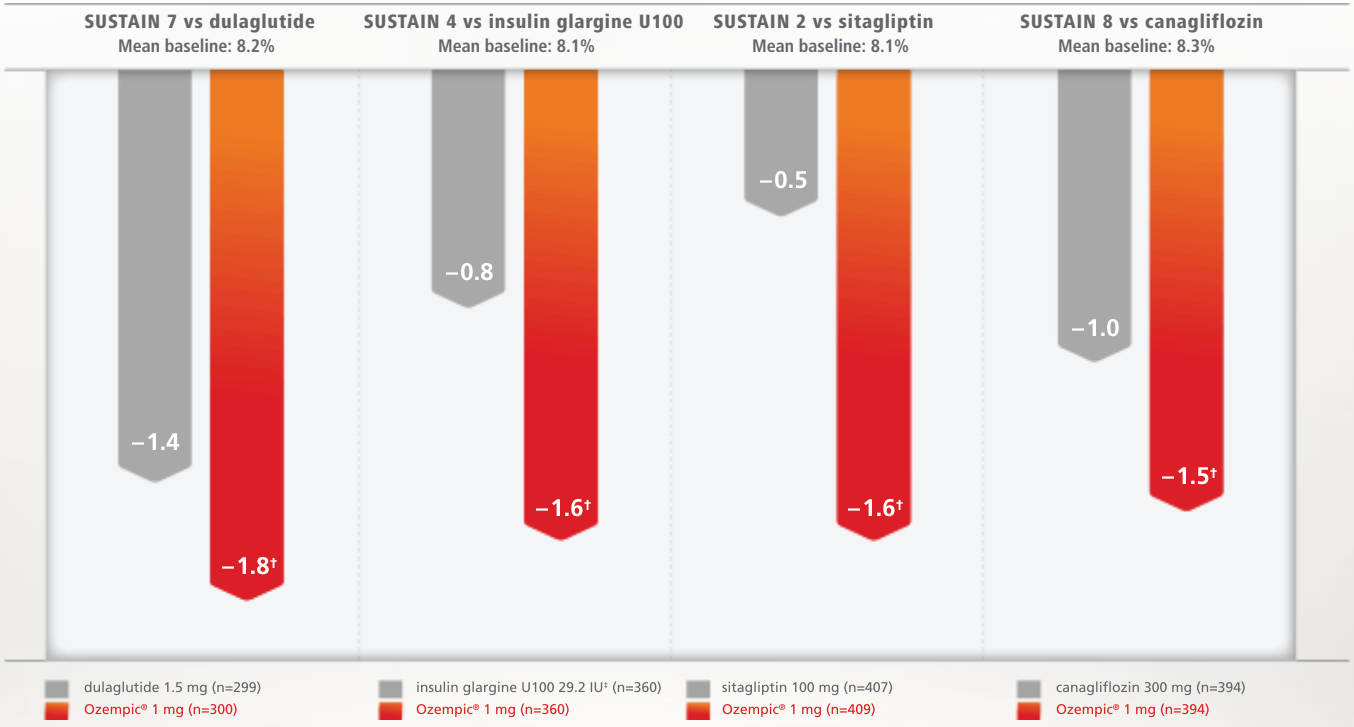
ABSOLUTE HbA_{1c}

HbA_{1c} <7%

CONSISTENT RESULTS

Change from baseline in HbA_{1c} (%)*[1,2,28]

†*P*<0.0001 for all trials



CONSISTENTLY SUPERIOR HbA_{1c} REDUCTIONS

vs other diabetes treatments[1,2,28§]

*At Week 56 for sitagliptin; at Week 30 for insulin glargine U100; at Week 40 for dulaglutide; at Week 52 for canagliflozin.[1,2,28]
‡Mean dose at end of treatment.[10]
§Other diabetes treatments refer to sitagliptin, dulaglutide, exenatide ER, and insulin glargine U100.

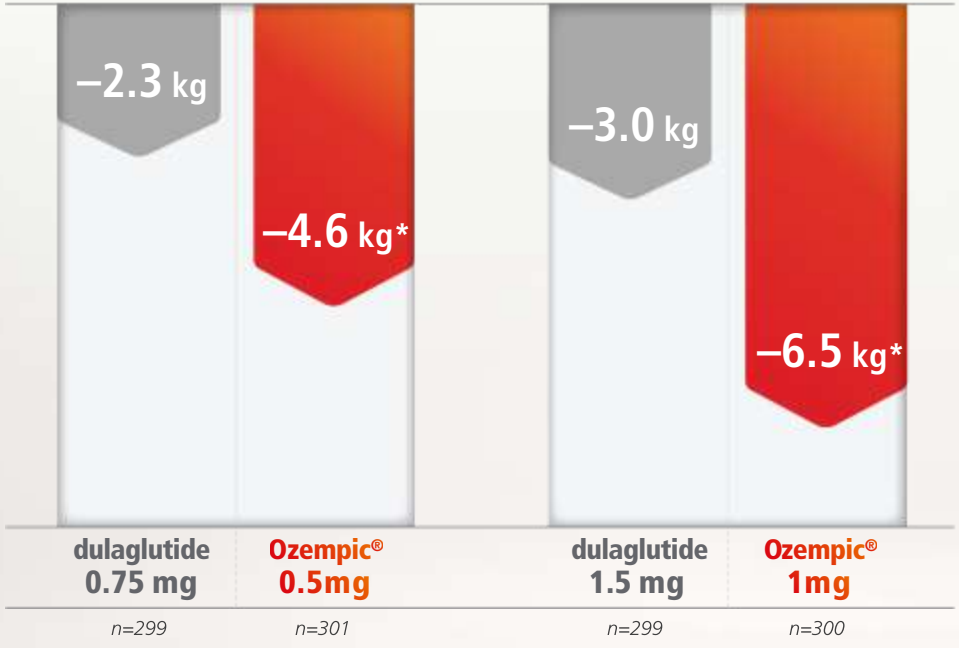
Ozempic® demonstrated superior weight loss vs dulaglutide²

SUPERIOR

CLINICALLY MEANINGFUL

Change from baseline in weight at Week 40

*P<0.0001



Mean baseline: 95.2 kg

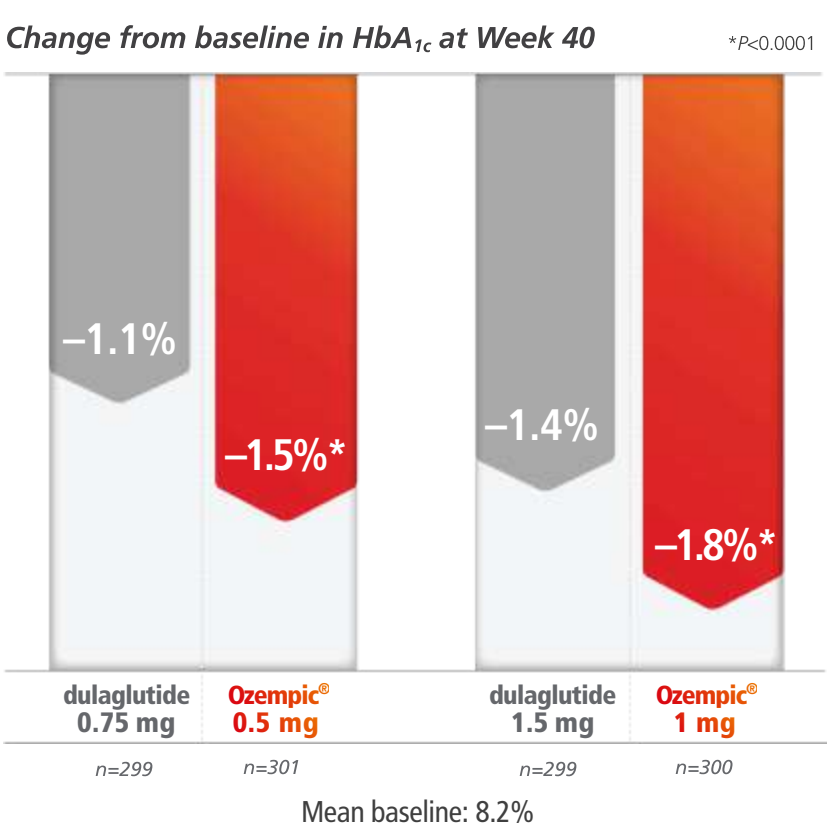
MORE THAN DOUBLE THE WEIGHT LOSS VS DULAGLUTIDE†

†Results apply to 1-mg dose of Ozempic® vs dulaglutide 1.5 mg.

HbA1c REDUCTION | VS BASAL INSULIN | ADD-ON TO SGLT2i | ADA/EASD REPORT

Ozempic® demonstrated superior weight loss vs dulaglutide[2]

Ozempic® outperformed dulaglutide in reducing HbA_{1c}[2]

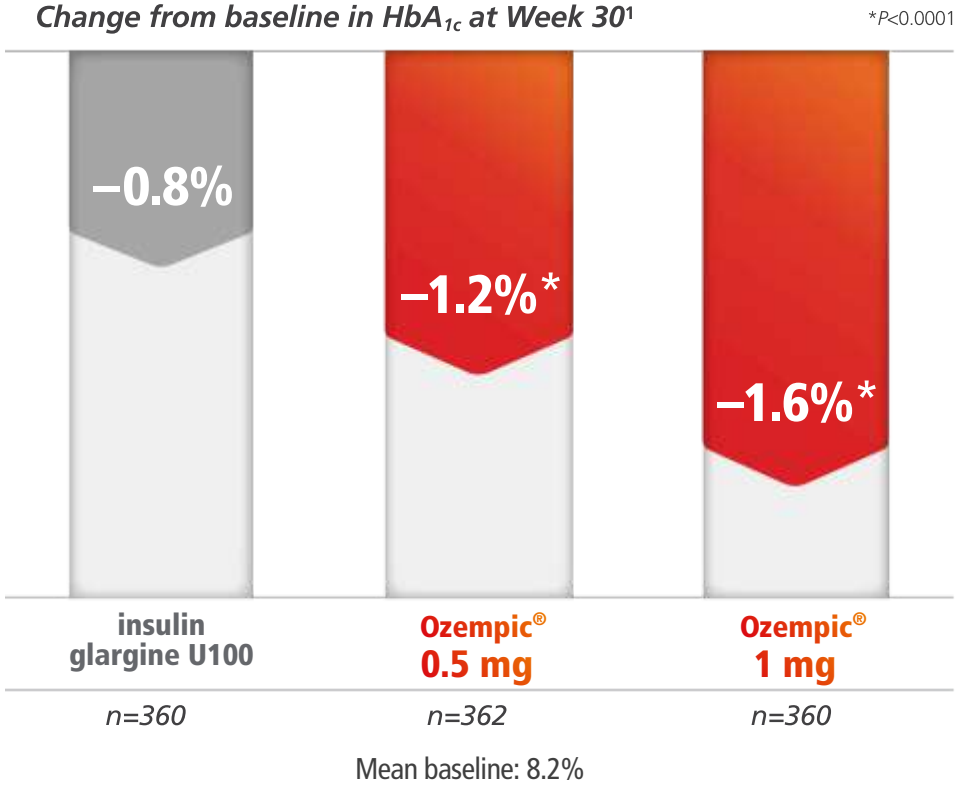


SUPERIOR HbA_{1c} REDUCTIONS
VS DULAGLUTIDE

HbA_{1c} REDUCTION | VS BASAL INSULIN | ADD-ON TO SGLT2i | ADA/EASD REPORT

Ozempic® demonstrated superior weight loss vs dulaglutide[2]

Once-weekly Ozempic® delivered superior HbA_{1c} reductions vs insulin glargine U100



SUPERIOR HbA_{1c} REDUCTIONS VS INSULIN GLARGINE U100[1]

ABSOLUTE WEIGHT LOSS

Ozempic® demonstrated superior weight loss vs dulaglutide[2]

Ozempic® delivered superior weight loss vs insulin glargine U100

Change from baseline in weight at Week 30[1]

*P<0.0001

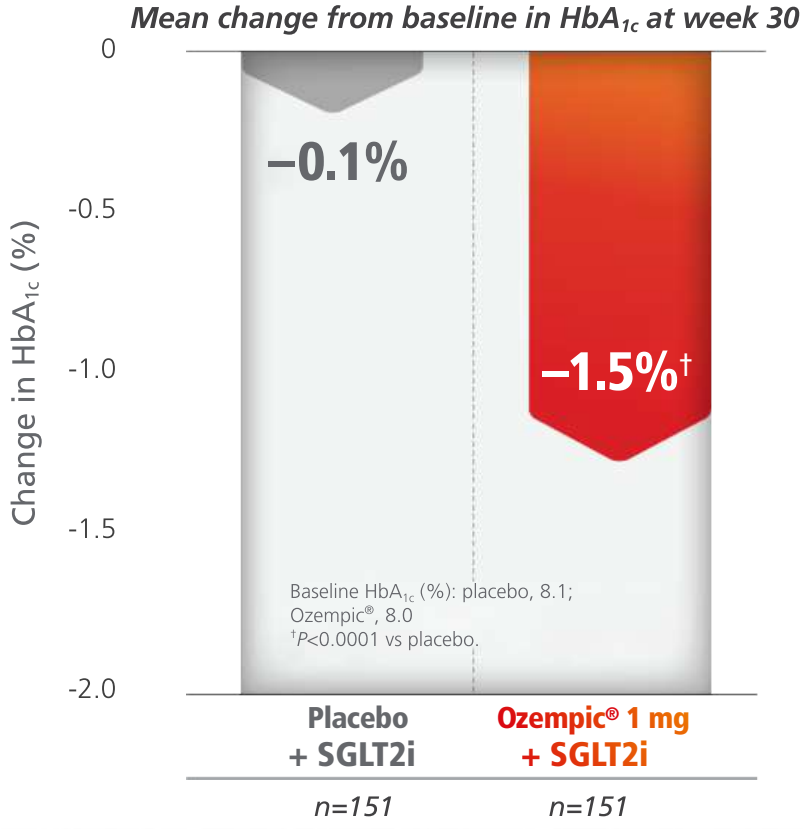
Mean baseline: 93.5 kg

>5 KG WEIGHT LOSS
WITH OZEMPIC® 1 MG
VS INSULIN GLARGINE U100[1]

ABSOLUTE HbA_{1c}

Ozempic® demonstrated superior weight loss vs dulaglutide[2]

Ozempic® demonstrated superior HbA_{1c} reductions when used as add-on to an SGLT2i[29]



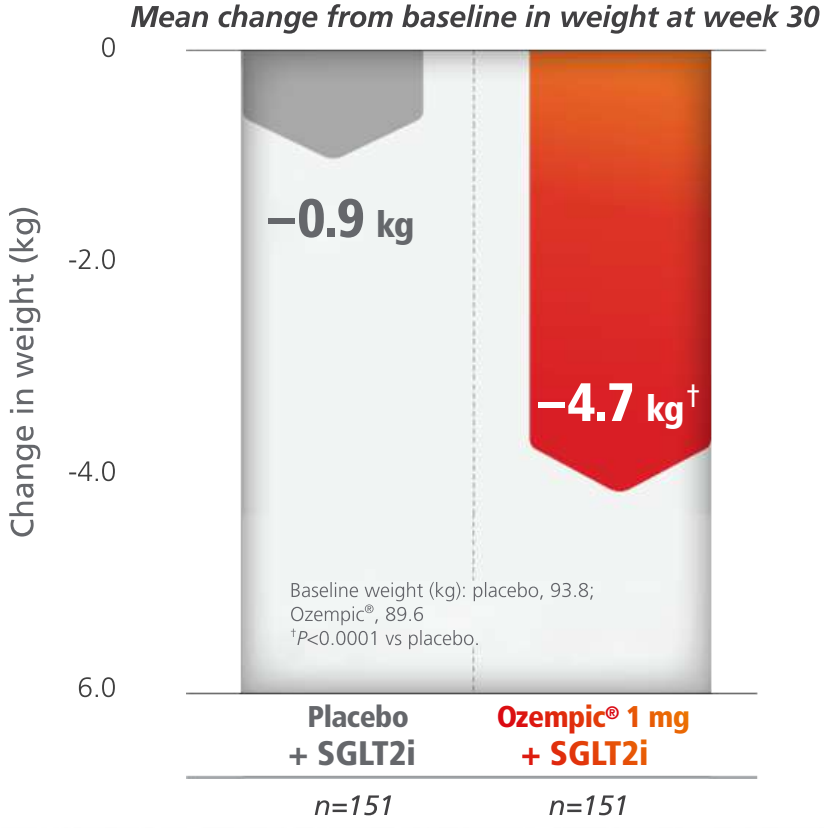
UP TO 15x

MORE HbA_{1c} REDUCTIONS SHOWN WITH OZEMPIC® VS PLACEBO, BOTH AS ADD-ONS TO AN SGLT2i (± MET/SU)[29]

ABSOLUTE WEIGHT LOSS

Ozempic® demonstrated superior weight loss vs dulaglutide[2]

Ozempic® demonstrated superior weight reductions when used as add-on to an SGLT2i[29]



UP TO 5X

MORE WEIGHT REDUCTIONS SHOWN WITH OZEMPIC® VS PLACEBO, BOTH AS ADD-ONS TO AN SGLT2i (± MET/SU)[29]

ABSOLUTE HbA_{1c}

Ozempic® demonstrated superior weight loss vs dulaglutide[2]

2019 update of ADA/EASD consensus report: Consider a GLP-1 RA for weight loss[31]

For adults with type 2 diabetes and a need to prioritise weight loss

2019 UPDATE OF ADA/EASD CONSENSUS REPORT

RECOMMENDS A GLP-1 RA WITH GOOD EFFICACY FOR WEIGHT LOSS[31]*

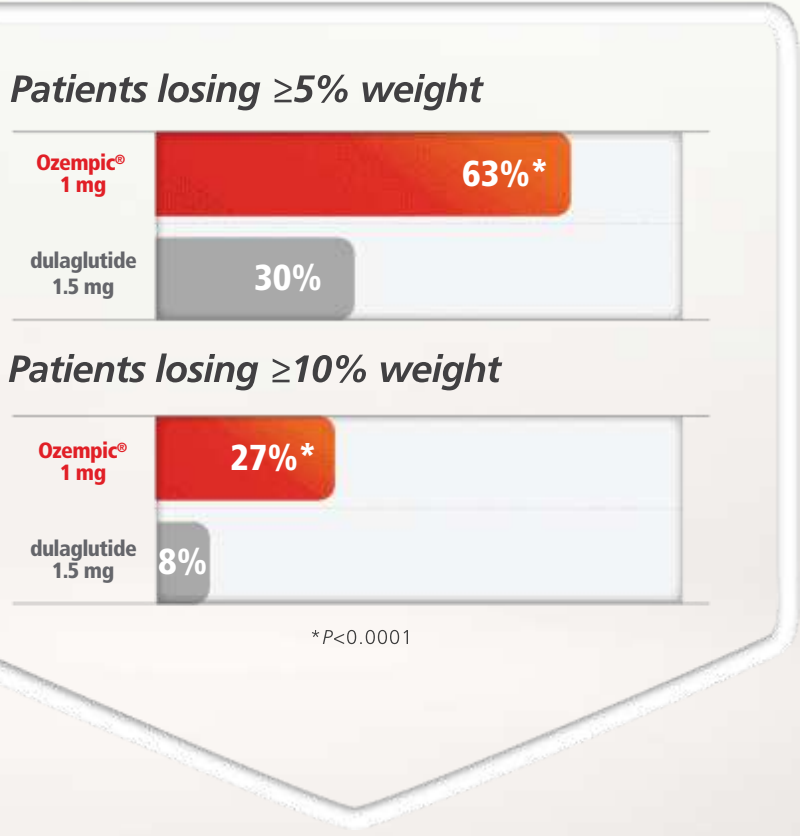
***Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide**

ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes; GLP-1 RA=glucagon-like peptide-1 receptor agonist.

Ozempic®—substantially more patients experienced clinically meaningful weight loss vs dulaglutide[2]

SUPERIOR

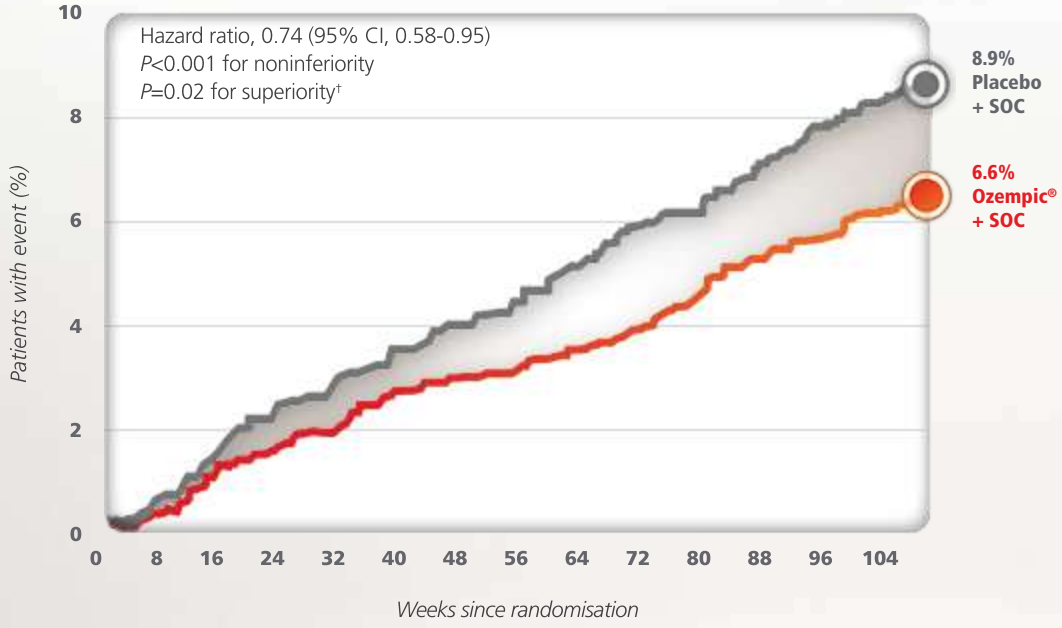
CLINICALLY MEANINGFUL



In patients with type 2 diabetes at high CV risk

Ozempic® reduced the risk of CV events within 2 years[1,5]

Time to first confirmed major adverse CV event (MACE)[5]



WHEN ADDED TO STANDARD OF CARE‡

26%

C RIS REDUCTION

VS PLACEBO[5]

Components of the composite primary outcome (MACE)[1,5]

- **Nonfatal stroke=–39%**
  [HR=0.61 (95% CI, 0.38-0.99; *P*=0.04)]
- **Nonfatal MI=–26%**
  [HR=0.74 (95% CI, 0.51-1.08; *P*=0.12)]
- **CV death=–2%**
  [HR=0.98 (95% CI, 0.65-1.48; *P*=0.92)]

CV=cardiovascular; CI=confidence interval; SOC=standard of care; MI=myocardial infarction.
*When added to SOC.[1]
†Testing for superiority for the primary outcome was not prespecified.[5]
‡SOC included oral antidiabetic treatments, insulin, antihypertensives, diuretics and lipid-lowering therapies.[8]

In patients with type 2 diabetes at high CV risk

Ozempic® reduced the risk of CV events within 2 years[1,5]

CV DISEASE IS THE #1 CAUSE OF DEATH

AND DISABILITY IN TYPE 2 DIABETES WORLDWIDE[15]

PATIENTS WITH TYPE 2 DIABETES HAVE

UP TO 4X GREATER **RISK**

OF CORONARY ARTERY DISEASE AND STROKE

THAN THOSE WITHOUT TYPE 2 DIABETES[16]

CV=cardiovascular.

CV RISK | TRIAL DETAILS | MORE DATA | CVOTs | GUIDANCE

‡SOC included oral antidiabetic treatments, insulin, antihypertensives, diuretics and lipid-lowering therapies.[8]

In patients with type 2 diabetes at high CV risk

*Ozempic® reduced the risk of CV events within 2 years[1,5]**

Key results from CAPTURE[6,7]

1/3

of patients with T2D have established CVD[6]

9 OUT OF 10

patients with T2D and established CVD have ASCVD[6]*

***And yet*...ONLY 2 IN 10**

patients with T2D are prescribed a glucose-lowering treatment with a proven CVD benefit[7†]

T2D=type 2 diabetes; CVD=cardiovascular disease; ASCVD=atherosclerotic cardiovascular disease; GLP-1 RA=glucon-like peptide-1 receptor agonist; SGLT2i=sodium-glucose co-transporter-2 inhibitor.

*ASCVD includes deseases of the heart, brain and periphery.

†Glucose-lowering treatments with proven CV benefit include certain GLP-1 RA and SGLT-2i therapies.

CV RISK | TRIAL DETAILS | MORE DATA | CVOTs | GUIDANCE

‡SOC included oral antidiabetic treatments, insulin, antihypertensives, diuretics and lipid-lowering therapies.[8]

In patients with type 2 diabetes at high CV risk

*Ozempic® reduced the risk of CV events within 2 years[1,5]**

CAPTURE is the first global, noninterventional study to examine key aspects of CVD and its relationship to T2D[6,7]

Primary and secondary analyses within CAPTURE explored the following in patients with T2D:[6,7]

- The prevelence of different types of CVD and risks for CVD
- The clinical management of CVD risk

CAPTURE studied nearly 10,000 people with T2D in 13 countries across 5 continents:[6]

Who was the typical CAPTURE patient?[6]

- Average HbA_{1c} level: 7,3%
- Average years living with T2D: 10,7
- Average age: 64 years

CVD=cardiovascular disease; T2D=type 2 diabetes.

‡SOC included oral antidiabetic treatments, insulin, antihypertensives, diuretics and lipid-lowering therapies.[8]

In patients with type 2 diabetes at high CV risk

Ozempic® reduced the risk of CV events within 2 years[1,5]

SUSTAIN 6: A 2-year CVOT for Ozempic®[1]

3297 PATIENTS[1,5]

Inclusion criteria:

T2D, HbA_{1c} ≥7%

Age ≥60 years with at least 1 CV risk factor

OR

Age ≥50 years with established CV disease

1:1:1:1 randomisation[1]

- Ozempic® 1 mg
- Ozempic® 0.5 mg
- Placebo 1 mg
- Placebo 0.5 mg

\+ Diabetes and CV SOC

Treatment duration: 2 years

Primary composite outcome[1,5]

Randomisation to first occurrence of:

- CV death
- Nonfatal MI
- Nonfatal stroke

CVOT=cardiovascular outcomes trial; T2D=type 2 diabetes; CV=cardiovascular; SOC=standard of care; MI=myocardial infarction.

‡SOC included oral antidiabetic treatments, insulin, antihypertensives, diuretics and lipid-lowering therapies.[8]

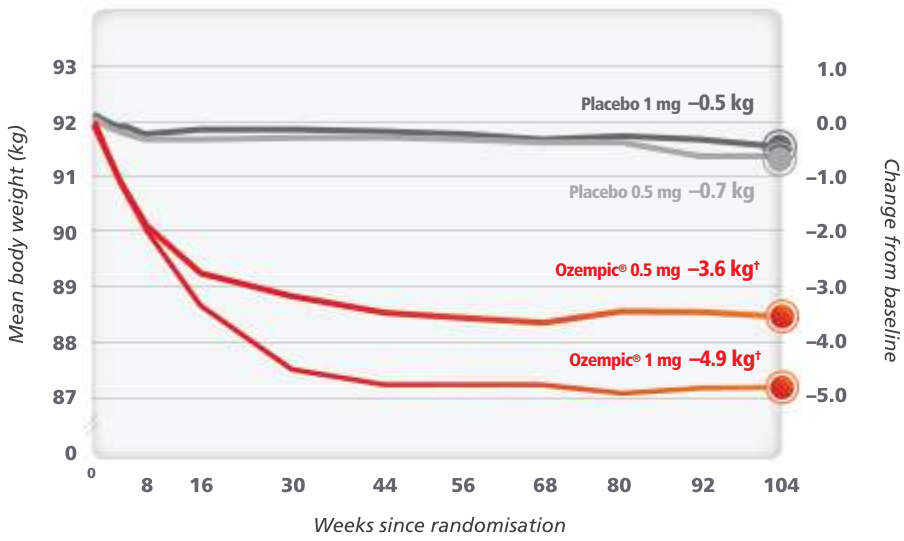
In patients with type 2 diabetes at high CV risk

Ozempic® reduced the risk of CV events within 2 years[1,5]

Ozempic®—clinically meaningful weight loss and glycaemic control at 2 years[5]

*Weight reductions from baseline over 2 years[5]**

†*P*<0.001



Mean body weight at baseline: 92.1 kg

–1.4%

Patients also experienced significant HbA_{1c} reductions at 2 years[5]

At 2 years, Ozempic® 1 mg* provided an HbA_{1c} reduction of up to 1.4% vs 0.4% for placebo* (*P*<0.001)

EVENT HISTORY

*When added to standard of care.[1,5]

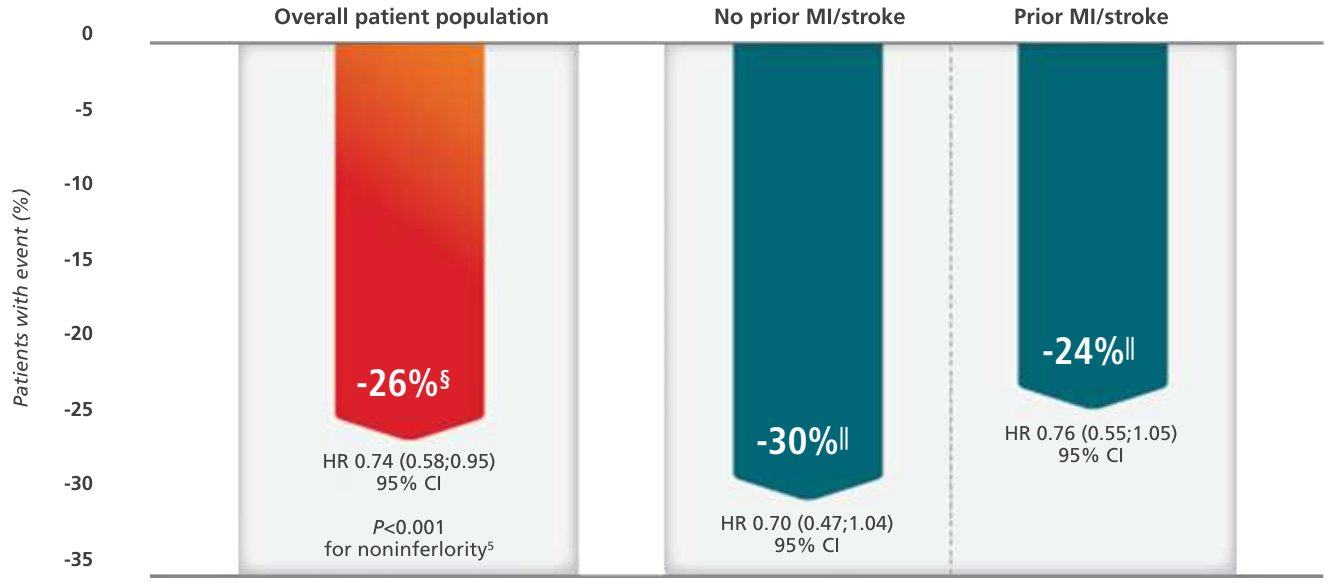
†SOC included oral antidiabetic treatments, insulin, antihypertensives, diuretics and lipid-lowering therapies.[8]

In patients with type 2 diabetes at high CV risk

Ozempic® reduced the risk of CV events within 2 years[1,5]*

Ozempic® has demonstrated consistent reduction in CV risk regardless of event history[32]

SUSTAIN 6: MACE risk reduction in patients with type 2 diabetes and high CV risk[32]



POST HOC ANALYSIS STUDY DESIGN: In SUSTAIN 6, a post hoc subgroup analysis was performed, dividing the population into 2 CV risk levels at baseline: prior MI or stroke(yes/no).[32]

MI=myocardial infarction; HR=hazard ratio; CVD=cardiovascular disease.
§Prespecified analysis: primary endpoint.
‖Post hoc analysis: prior MI/stroke (yes/no). *P*=0.75, subgroup interaction *P* value.

SUSTAINED DATA

‡SOC included oral antidiabetic treatments, insulin, antihypertensives, diuretics and lipid-lowering therapies.[8]

In patients with type 2 diabetes at high CV risk

Ozempic® reduced the risk of CV events within 2 years[1,5]

Cardiovascular outcomes trials in type 2 diabetes: An overview

REWIND[12] (dulaglutide vs placebo)	LEADER[25,26] (liraglutide vs placebo)	EMPA-REG[14,27] (empagliflozin vs placebo)	SUSTAIN 6[5] (semaglutide vs placebo)
MACE **12%** RRR *P*=0.026	MACE **13%** RRR *P*=0.01	MACE **14%** RRR *P*=0.004	MACE **26%** RRR *P*<0.001 for noninferiority *P*=0.02 for superiority†
CV death*=–9% [HR=0.91 (95% CI, 0.78-1.06; *P*=0.21)]	CV death=–22% [HR=0.78 (95% CI, 0.66-0.93; *P*=0.007)]	CV death=–38% [HR=0.62 (95% CI, 0.49-0.77; *P*<0.001)]	CV death=–2% [HR=0.98 (95% CI, 0.65-1.48; *P*=0.92)]
Nonfatal stroke=–24% [HR=0.76 (95% CI, 0.61-0.95; *P*=0.017)]	Nonfatal stroke=–11% [HR=0.89 (95% CI, 0.72-1.11; *P*=0.30)]	Nonfatal stroke=24% [HR=1.24 (95% CI, 0.92-1.67; *P*=0.16)]	Nonfatal stroke=–39% [HR=0.61 (95% CI, 0.38-0.99; *P*=0.04)]
Nonfatal MI=–4% [HR=0.96 (95% CI, 0.79-1.16; *P*=0.65)]	Nonfatal MI=–12% [HR=0.88 (95% CI, 0.75-1.03; *P*=0.11)]	Nonfatal MI=–13% [HR=0.87 (95% CI, 0.70-1.09; *P*=0.22)]	Nonfatal MI=–26% [HR=0.74 (95% CI, 0.51-1.08; *P*=0.12)]

Please note that CVOTs are different in trial designs. Therefore, results cannot be used as a head-to-head comparison.

MACE=major adverse cardiovascular event; RRR=relative risk reduction; HR=hazard ratio; CI=confidence interval; MI=myocardial infarction.
*Includes deaths of unknown cause.
†Testing for superiority for the primary outcome was not prespecified.[5]

BASELINE CRITERIA

‡SOC included oral antidiabetic treatments, insulin, antihypertensives, diuretics and lipid-lowering therapies.[8]

In patients with type 2 diabetes at high CV risk

Ozempic® reduced the risk of CV events within 2 years[1,5]

Baseline criteria

	REWIND[11,12] (dulaglutide vs placebo)	LEADER[25,26] (liraglutide vs placebo)	EMPA-REG[14,27] (empagliflozin vs placebo)	SUSTAIN 6[5,8] (semaglutide vs placebo)
CV RISK	31% established CVD	82% established CVD	99% established CVD	83% established CVD
CV HISTORY				
PRIOR MI	16.2%	31%	47%	33%
HEART FAILURE	8.6%	18%	10%	24%
MEAN DIABETES DURATION	9.5 years	13 years	>10 years	14 years
MEAN HbA_{1c}	7.2%	8.7%	8.1%	8.7%
INSULIN USE	24%	44.6%	48%	58%
TRIAL DURATION	5.4 years	Mean 3.8 years	Mean 3.1 years	2 years

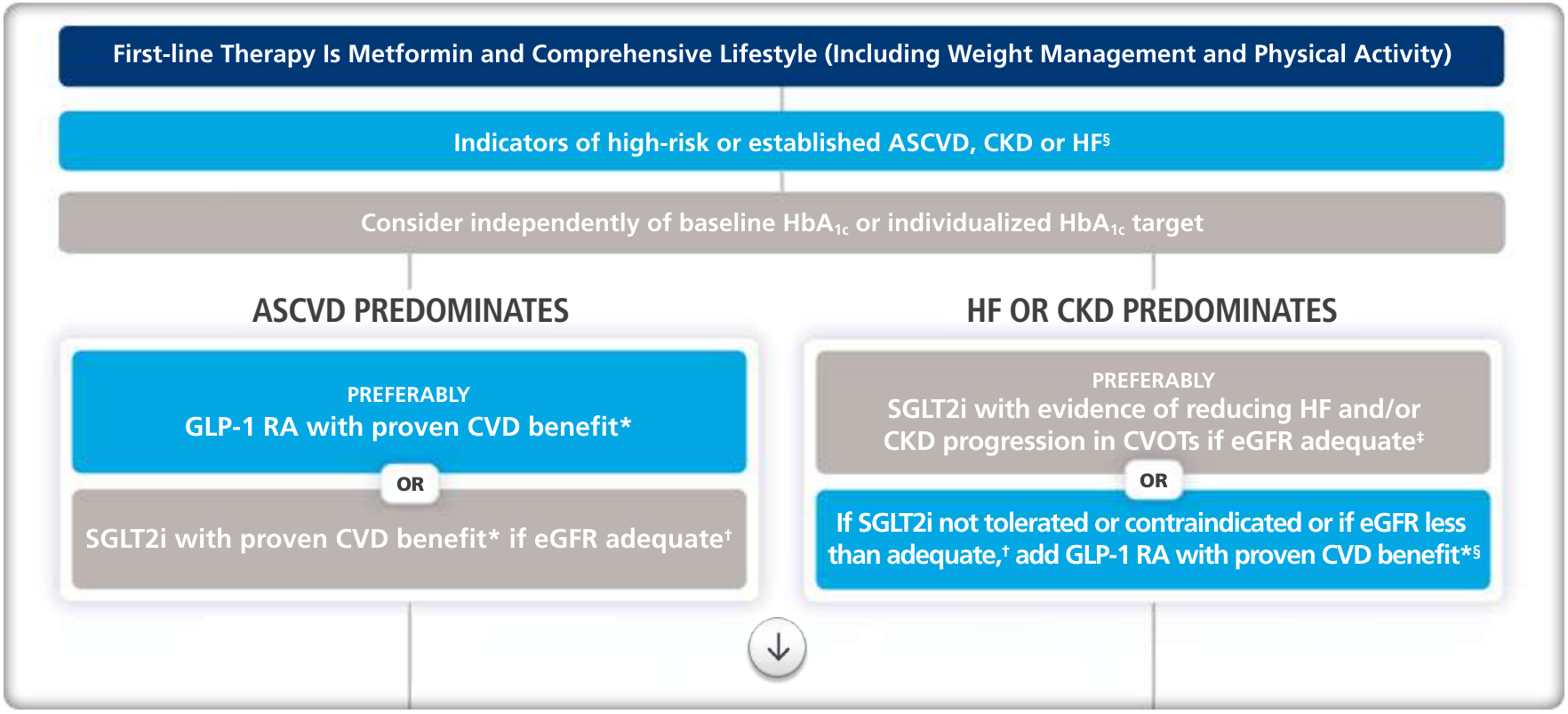
Please note that CVOTs are different in trial designs. Therefore, results cannot be used as a head-to-head comparison.

CVOTs

CV=cardiovascular; CVD=cardiovascular disease; CVOT=cardiovascular outcomes trial.

‡SOC included oral antidiabetic treatments, insulin, antihypertensives, diuretics and lipid-lowering therapies.[8]

2019 update of ADA/EASD consensus report recommends CVD be considered early in treatment[31]



*Proven CVD benefit means it has label indication of reducing CVD events.
†Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
‡Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary heart failure outcome data from DAPA-HF.
§Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
‖Degludec and U100 glargine have demonstrated CVD safety.
¶Low dose may be better tolerated though less well studied for CVD effects.
#Choose later generation SU to lower risk of hypoglycaemia.

2019 update of ADA/EASD consensus report recommends CVD be considered early in treatment[31]

If HbA_{1c} above target

- If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
  - Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
  - DPP-4i if not on GLP-1 RA
  - Basal insulin‖
  - TZD¶
  - SU#

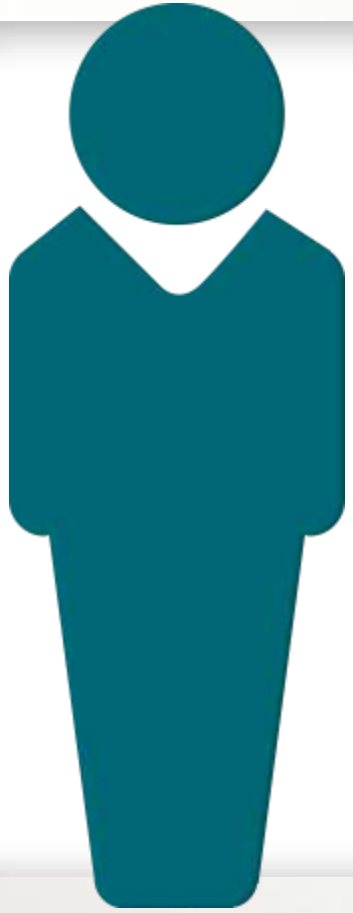
If HbA_{1c} above target

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - Consider adding the other class with proven CVD benefit*
  - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
  - Basal insulin‖
  - SU#

ASCVD=atherosclerotic cardiovascular disease; CKD=chronic kidney disease; HF=heart failure; SGLT2i=sodium-glucose cotransporter 2 inhibitor; eGFR=estimated glomerular filtration rate; CVOT=cardiovascular outcomes trial; DPP-4i=dipeptidyl peptidase-4 inhibitor; SU=sulphonylurea; TZD=thiazolidinedione; ESRD=end-stage renal disease.

*Proven CVD benefit means it has label indication of reducing CVD events.
†Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
‡Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary heart failure outcome data from DAPA-HF.
§Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
‖Degludec and U100 glargine have demonstrated CVD safety.
¶Low dose may be better tolerated though less well studied for CVD effects.
#Choose later generation SU to lower risk of hypoglycaemia.

Safety demonstrated across 10 clinical trials, including a 2-year CVOT



No dosage adjustments required in the following special populations[1]

- Patients with mild, moderate or severe renal impairment
- Patients with hepatic impairment
- Patients ≥65 years

GI events[2,17,30]

- GI tolerability comparable with other GLP-1 RAs

Hypoglycaemia[1,2,10,17-20,28-30]

- Low incidence of severe hypoglycaemia* (<3%) across 10 clinical studies

Pancreatitis[2,5,10,17-20,29,30]

- No difference in adverse events related to pancreatitis

Diabetic retinopathy complications[1]

- Caution should be exercised when using Ozempic® in patients with diabetic retinopathy treated with insulin
  - — These patients should be monitored and treated according to clinical guidelines

GI EVENTS | DIABETIC RETINOPATHY COMPLICATIONS

CVOT=cardiovascular outcomes trial; GI=gastrointestinal; GLP-1 RA=glucagon-like peptide-1 receptor agonist.
*Hypoglycaemia defined as severe (requiring the assistance of another person) or symptomatic in combination with a blood glucose <3.1 mmol/L.[1]

Safety demonstrated across 10 clinical trials, including a 2-year CVOT

GI events

Percentage of patients reporting GI adverse events (AEs) in the head-to-head trials[2,17]

	SUSTAIN 7 vs dulaglutide				SUSTAIN 3 vs exenatide ER	
	dulaglutide 0.75 mg (n=299)	Ozempic® 0.5 mg (n=301)	dulaglutide 1.5 mg (n=299)	Ozempic® 1 mg (n=300)	exenatide ER 2 mg (n=405)	Ozempic® 1 mg (n=404)
Nausea	13	23	20	21	12	22
Diarrhoea	8	14	18	14	8	11
Vomiting	4	10	10	10	6	7
Discontinuation rates due to GI AEs	2	5	5	6	3	6

In general, these reactions were mild or moderate in severity and of short duration.[1]

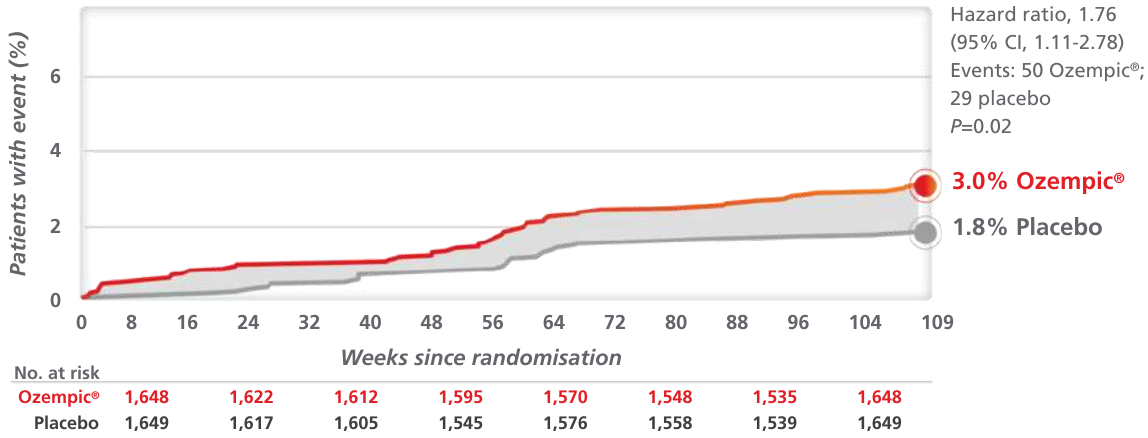
GI=gastrointestinal.

CVOT=cardiovascular outcomes trial; GI=gastrointestinal; GLP-1 RA=glucagon-like peptide-1 receptor agonist.
*Hypoglycaemia defined as severe (requiring the assistance of another person) or symptomatic in combination with a blood glucose <3.1 mmol/L.[1]

Safety demonstrated across 10 clinical trials, including a 2-year CVOT

More information on diabetic retinopathy complications

SUSTAIN 6: Diabetic retinopathy complications[5]



Observed DR complications were consistent with DCCT findings[33]

Patients who developed DR complications predominantly had:[21]

- DR at baseline
- Longer duration of diabetes
- Higher baseline HbA_{1c} vs overall population
- Greater HbA_{1c} reduction vs overall population
- Background insulin therapy

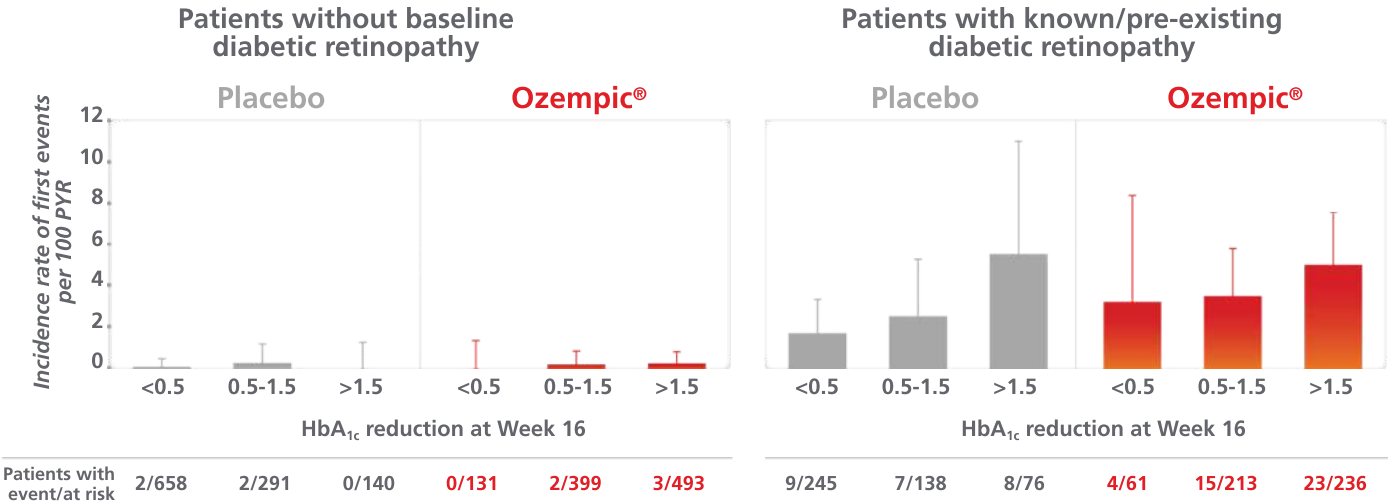
CI=confidence interval; DCCT=Diabetes Control and Complications Trial; DR=diabetic retinopathy.

CVOT=cardiovascular outcomes trial; GI=gastrointestinal; GLP-1 RA=glucagon-like peptide-1 receptor agonist.
*Hypoglycaemia defined as severe (requiring the assistance of another person) or symptomatic in combination with a blood glucose <3.1 mmol/L.[1]

Safety demonstrated across 10 clinical trials, including a 2-year CVOT

More information on diabetic retinopathy complications

Effect of pre-existing diabetic retinopathy (DR) and change in HbA_{1c} on DR complications[21]



Patients with event/at risk	<0.5	0.5-1.5	>1.5	<0.5	0.5-1.5	>1.5
	2/658	2/291	0/140	0/131	2/399	3/493
	9/245	7/138	8/76	4/61	15/213	23/236

Values are observed incidence rates per 100 PYR with error bars representing 95% confidence intervals. PYR=person-years at risk.

CVOT=cardiovascular outcomes trial; GI=gastrointestinal; GLP-1 RA=glucagon-like peptide-1 receptor agonist.
*Hypoglycaemia defined as severe (requiring the assistance of another person) or symptomatic in combination with a blood glucose <3.1 mmol/L.[1]

Safety demonstrated across 10 clinical trials, including a 2-year CVOT

More information on diabetic retinopathy complications

Considerations

- Rapid improvement in glucose has been associated with a temporary worsening of diabetic retinopathy – referred as 'early worsening[34,35]
- Early worsening has been described in patients with T1DM and T2DM, including those receiving various glucose lowering therapies, those who have undergone bariatric surgery, and pregnant women[34,35]
- It does not appear to be agent-specific – it has been described in patients receiving intensive insulin therapy, sulfonylureas, thiazolidinediones and GLP-1 RAs[34,35]
- Caution should be exercised when using Ozempic® in patients with diabetic retinopathy treated with insulin[1]
    - These patients should be monitored and treated according to clinical guidelines

GLP-1 RA=glucagon-like peptide-1 receptor agonist; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus.

CVOT=cardiovascular outcomes trial; GI=gastrointestinal; GLP-1 RA=glucagon-like peptide-1 receptor agonist.
*Hypoglycaemia defined as severe (requiring the assistance of another person) or symptomatic in combination with a blood glucose <3.1 mmol/L.[1]

Getting patients started with flexible once-weekly Ozempic®[1]

Start patients off right with a prescription for 0.25 mg for 4 weeks followed by 0.5 mg for at least another 4 weeks
Then assess whether they need to go up to 1 mg for further glycaemic control

STARTING DOSE
Pen delivers doses of 0.25 mg

ESCALATION & MAINTENANCE DOSE
Pen delivers doses of 0.5 mg

MAXIMUM MAINTENANCE DOSE
Pen delivers doses of 1 mg

1 PACK = 1 MONTH
INCLUDES x4

READY	SET	GO
0.25 mg	0.5 mg	1 mg
for 4 weeks* (starting dose)	for at least 4 weeks (escalation and maintenance dose)	if additional glycemic control is needed after 4 weeks (maximum maintenance dose)

*The starting dose of 0.25 mg is not a maintenance dose and is intended to help patients adjust to treatment.

Ozempic®—initiation begins with a few simple steps[1]

DIAL Dial to the prescribed dose

DOSE Ozempic® can be taken in the abdomen, thigh or upper arm

DONE

THE THINNEST NEEDLE AVAILABLE
WITH A ONCE-WEEKLY GLP-1 RA[22]

NovoFine® Plus 32G 4-mm needle compared with 2 human hairs[23]

HOW-TO-USE VIDEO | SATISFACTION | FLEXTOUCH®

GLP-1 RA=glucagon-like peptide-1 receptor agonist.

4 simple tips for using Ozempic®

The clinical benefits of Ozempic® are accompanied by overall treatment satisfaction[2]

In SUSTAIN 7, there were **no differences in overall treatment satisfaction** for Ozempic® and dulaglutide, suggesting that both treatments were equally suited to patients' day-to-day life.[2]

*Overall treatment satisfaction as measured by DTSQ (Diabetes Treatment Satisfaction Questionnaire) scores ranging from 0 to 36, where higher scores indicate better satisfaction. In all SUSTAIN trials, the DTSQs was completed by patients at randomization and at end of treatment (either planned or at premature discontinuation), preferably before any other trial-related activities. In SUSTAIN 7, DTSQs assessments were also completed at week 16 (corresponding to weeks 12 and 8 after dose-escalation in the 0.5 mg and 1.0 mg semaglutide treatment groups, respectively; there was no dose escalation with dulaglutide).[36]

4 simple tips for using Ozempic®

A user-friendly pen embraced by patients worldwide[24*†]

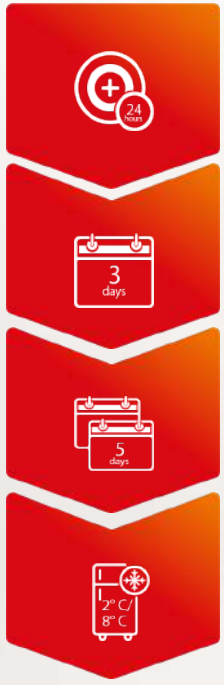
98.5%
FOUND IT EASY TO USE*

1.5 MILLION
PATIENTS USE THE FLEXTOUCH® PEN†

Result do not specifically apply to the Ozempic® pen.

*Data based on a 26-week, multicentre, open-label, randomised, treat-to-target study that included an insulin-naïve patient population and evaluated the pen with insulin using specific device questions.
†The Ozempic® pen is built on the FlexTouch® platform used for other Novo Nordisk products. IQVIA MAT October 2017.

4 simple tips for using Ozempic®



Administer Ozempic® **once weekly at any time of the day**, with or without meals[1]

The day of **weekly administration can be changed, if necessary,** as long as the time between 2 doses is at least **3 days (>72 hours)**[1]

If a dose is missed, administer **Ozempic® as soon as possible within 5 days after the missed dose.** If **more than 5 days have passed**, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their **regular once-weekly** dosing schedule[1]

Storage[1]
Before opening, store in a refrigerator at 2°C to 8°C
After opening, store for 6 weeks at a temperature below 30°C or in a refrigerator at 2°C to 8°C

OZEMPIC®

A **once-weekly** treatment unifying superior efficacy[1-4,28,30] and CV benefits[1,5]

SUPERIOR GLYCAEMIC CONTROL[1,2,28,30*]

SUPERIOR AND SUSTAINED WEIGHT LOSS[1,2,5,28,30*]

PROVEN CV BENEFITS[1,5†]

For adults with type 2 diabetes and established ASCVD or indicators of high ASCVD risk

2019 update of ADA/EASD consensus report recommends GLP-1 RA therapy with proven CVD benefit[31]

ASCVD=atherosclerotic cardiovascular disease; CV=cardiovascular; CVD=cardiovascular disease; ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes; GLP-1 RA=glucagon-like peptide-1 receptor agonist; MI=myocardial infarction.

*Results apply to Ozempic® across SUSTAIN trials, which included placebo, sitagliptin, dulaglutide, exenatide extended release, insulin glargine U100, canagliflozin and liraglutide.[1,2,28,30]

†In SUSTAIN 6, Ozempic® reduced CV risk (CV death, nonfatal MI or nonfatal stroke) versus placebo in patients with type 2 diabetes at high CV risk treated with standard of care.[1]

UE21OZM00044, Approval date: September 2021

Consider Ozempic® in patients with T2D when metformin is not enough[1]

FOR PATIENTS WITH THE FOLLOWING RISK FACTORS:

- HbA_{1c} not at target
- Overweight or have obesity
- Risk of CV disease

T2D=type 2 diabetes; CV=cardiovascular.
Models are not actual patients.

Patient Profiles

MoA

...in patients with T2D when metformin is not enough[1]

...H THE FOLLOWING RISK FACTORS:

- HbA_{1c} not at target
- Overweight or have obesity
- Risk of CV disease

T2D=type 2 diabetes; CV=cardiovascular.
Models are not actual patients.

Ozempic®—three key actions that deliver multiple benefits[1]

PANCREAS

Ozempic® reduces blood glucose in a glucose-dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high

BRAIN

Ozempic® helps reduce body weight by regulating appetite and satiety

CARDIOVASCULAR SYSTEM

Ozempic® helps reduce CV risk* by lowering blood pressure and lipid levels and modifying the progression of atherosclerosis†

MOA VIDEO

CV=cardiovascular; MI=myocardial infarction.
*In SUSTAIN 6, Ozempic® reduced CV risk (CV death, nonfatal MI or nonfatal stroke) versus placebo in patients with type 2 diabetes at high CV risk treated with standard of care.[1]
†Shown in animal models.

References

1. Ozempic® [summary of product characteristics].
Bagsværd, Denmark: Novo Nordisk A/S; March 2021.

2. Pratley RE, Aroda VR, Lingvay I, et al.; SUSTAIN 7 Investigators.
Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol. 2018;6(4):275-286.

3. Trulicity® [summary of product characteristics].
Utrecht, The Netherlands: Eli Lilly Nederland B.V. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002825/WC500179470.pdf. Accessed December 9, 2020.

4. Bydureon® [summary of product characteristics].
Södertälje, Sweden: AstraZeneca AB. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002020/WC500108241.pdf. Accessed December 9, 2020.

References

5. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators.
Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834-1844.

6. Mosenzon 0, Alguwaihes A, Arenas Leon JL, et al.
CAPTURE: a cross-sectional study of the contemporary (2019) prevalence of cardiovascular disease in adults with type 2 diabetes across 13 countries. Presented at the 56th Annual Meeting of the European Association of the Study of Diabetes. September 24, 2020 (virtual). Abstract 158.

7. Vencio S, Alguwaihes A, Arenas Leon JL, et al.
Contemporary use of diabetes medications with a cardiovascular indication in adults with type 2 diabetes: a secondary analysis of the multinational CAPTURE study. Presented at the 56th Annual Meeting of the European Association of the Study of Diabetes. September 24, 2020 (virtual). Abstract 945.

8. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators.
Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(suppl 1):S1-S108.

References

9. American Diabetes Association.
Standards of medical care in diabetes—2018. Diabetes Care. 2019. Diabetes Care. 2019;42(suppl 1):S187-S193.

10. Aroda VR, Bain SC, Cariou B, et al.
Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol. 2017;5(5):355-366.

11. Gerstein HC, Colhoun HM, Dagenais GR; REWIND Trial Investigators.
Design and baseline characteristics of participants in the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial on the cardiovascular effects of dulaglutide. Diabetes Obes Metab. 2018;20(1):42-49.

12. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Investigators.
Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193):121-130.

References

13. Rodbard HW, Lingvay I, Reed J, et al.
Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. J Clin Endocrinol Metab. 2018;103(6):2291-2301.

14. Zinman B, Wanner C, Lachin JM, et al.
Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(suppl):1-66.

15. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB.
Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus—mechanisms, management, and clinical considerations. Circulation. 2016;133(24):2459-2502.

16. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, Del Cañizo-Gómez FJ.
Type 2 diabetes and cardiovascular disease: have all risk factors the same strength? World J Diabetes. 2014;5(4):444-470.

References

17. Ahmann AJ, Capehorn M, Charpentier G, et al.
Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care. 2018;41(2):258-266.

18. Sorli C, Harashima S-I, Tsoukas GM, et al.
Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol. 2017;5(4):251-260.

19. Ahrén B, Masmiquel L, Kumar H, et al.
Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol. 2017;5(5):341-354.

20. Rodbard HW, Lingvay I, Reed J, et al.
Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. J Clin Endocrinol Metab. 2018;103(6)(suppl 1):1-28.

References

21. Vilsbøll T, Bain SC, Leiter LA, et al.
Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. Diabetes Obes Metab. 2018;20(4):889-897.

22. GLP-1 agonist medications chart.
Diabetes in Control website. http://www.diabetesincontrol.com/wp-content/uploads/PDF/dic_glp-1_chart_2014-11-06.pdf. Accessed December 9, 2020.

23. Ley B.
Diameter of a human hair. In: Elert G, ed. The Physics Factbook™. http://hypertextbook.com/facts/1999/BrianLey.shtml. Published 1999. Accessed December 9, 2020.

24. Philis-Tsimikas A, Brod M, Niemeyer M, Ocampo Francisco AM, Rothman J.
Insulin degludec once-daily in type 2 diabetes: simple or step-wise titration (BEGIN: once simple use). Adv Ther. 2013;30:607-622.

References

25. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee on behalf of the LEADER Trial Investigators.
Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311-322.

26. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee on behalf of the LEADER Trial Investigators.
Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(suppl):1-68.

27. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators.
Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117-2128.

28. Lingvay I, Catarig AM, Frias JP, et al.
Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol. 2019. doi:10.1016/S2213-8587(19)30311-0.

References

29. Zinman B, Bhosekar V, Busch R, et al.
Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2019;7(5):356-367.

30. Capehorn MS, Catarig AM, Furberg JK, et al.
Efficacy and safety of once-weekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metab. 2019. doi:10.1016/j.diabet.2019.101117.

31. Buse JB, Wexler DJ, Tsapas A, et al.
2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2019. doi:10.2337/dci19-0066.

32. Leiter LA, Bain SC, Hramiak I, et al.
Cardiovascular risk reduction with once-weekly semaglutide in subjects with type 2 diabetes: a post hoc analysis of gender, age, and baseline CV risk profile in the SUSTAIN 6 trial. Cardiovasc Diabetol. 2019;18:73. doi:10.1186/s12933-019-0871-8.

References

33. The Diabetes Control and Complications Trial Research Group.

Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 1998;116:874–86.

34. Bain SC, Klufas MA, Ho A, et al.

Worsening of diabetic retinopathy with rapid improvement in systemic glucose control: A review. Diabetes Obes Metab 2019;21:454–66.

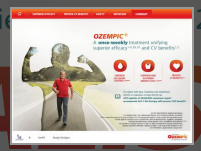
35. Feldman-Billard S, Larger É, Massin P, et al.

Early worsening of diabetic retinopathy after rapid improvement of blood glucose control in patients with diabetes. Diabetes Metab 2018;44:4–14.

36. Jendle J, Birkenfeld AL, Polonsky WH, et al.

Improved treatment satisfaction in patients with type 2 diabetes treated with once-weekly semaglutide in the SUSTAIN trials. Diabetes Obes Metab. 2019 Oct; 21(10): 2315–2326.

SUPERIOR EFFICACY PROVEN CV BENEFITS SAFETY INITIATION SUMMARY



2 diabetes

EASE THE POTENTIAL

Ozempic®—a **once-weekly** treatment unifying superior efficacy[1-4,28,30] and CV benefits[1,5]

SUPERIOR GLYCAEMIC CONTROL[1,2,28,30]*

SUPERIOR AND SUSTAINED WEIGHT LOSS[1,2,5,28,30]*

PROVEN CV BENEFITS[1,5†]

For adults with type 2 diabetes and established ASCVD or indicators of high ASCVD risk

2019 update of ADA/EASD consensus report recommends GLP-1 RA therapy with proven CVD benefit[31]

ASCVD=atherosclerotic cardiovascular disease; CV=cardiovascular; CVD=cardiovascular disease; ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes; GLP-1 RA=glucagon-like peptide-1 receptor agonist.

*Results apply to Ozempic® across SUSTAIN trials, which included placebo, sitagliptin, dulaglutide, exenatide extended release, insulin glargine U100, canagliflozin and liraglutide.[1,2,28,30]

†In SUSTAIN 6, Ozempic® reduced CV risk (CV death, nonfatal myocardial infarction [MI] or nonfatal stroke) versus placebo in patients with type 2 diabetes at high CV risk treated with standard of care.[1]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ozempic 0.25 mg solution for injection in pre-filled pen
Ozempic 0.5 mg solution for injection in pre-filled pen
Ozempic 1 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ozempic 0.25 mg solution for injection
One ml of solution contains 1.34 mg of semaglutide*. One pre-filled pen contains 2 mg semaglutide* in 1.5 ml solution. Each dose contains 0.25 mg of semaglutide in 0.19 ml solution.

Ozempic 0.5 mg solution for injection
One ml of solution contains 1.34 mg of semaglutide*. One pre-filled pen contains 2 mg semaglutide* in 1.5 ml solution. Each dose contains 0.5 mg of semaglutide in 0.37 ml solution.

Ozempic 1 mg solution for injection
One ml of solution contains 1.34 mg of semaglutide*. One pre-filled pen contains 4 mg semaglutide* in 3.0 ml solution. Each dose contains 1 mg of semaglutide in 0.74 ml solution.

*human glucagon-like peptide-1 (GLP-1) analogue produced in *Saccharomyces cerevisiae* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear and colourless or almost colourless, isotonic solution; pH=7.4.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ozempic is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Posology
The starting dose is 0.25 mg semaglutide once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control.

Semaglutide 0.25 mg is not a maintenance dose. Weekly doses higher than 1 mg are not recommended.

When Ozempic is added to existing metformin and/or thiazolidinedione therapy or to a sodium-glucose cotransporter 2 (SGLT2) inhibitor, the current dose of metformin and/or thiazolidinedione or SGLT2 inhibitor can be continued unchanged.

When Ozempic is added to existing therapy of sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see sections 4.4 and 4.8).

Self-monitoring of blood glucose is not needed in order to adjust the dose of Ozempic. Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when Ozempic is started and insulin is reduced. A stepwise approach to insulin reduction is recommended.

Missed dose
If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

Special populations

Elderly
No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited (see section 5.2).

Renal impairment
No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with severe renal impairment is limited. Semaglutide is not recommended for use in patients with end-stage renal disease (see section 5.2).

Hepatic impairment
No dose adjustment is required for patients with hepatic impairment. Experience with the use of Semaglutide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with semaglutide (see section 5.2).

Paediatric population
The safety and efficacy of semaglutide in children and adolescents below 18 years have not yet been established. No data are available.

Method of administration

Ozempic is to be administered once weekly at any time of the day, with or without meals.

Ozempic is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment. Ozempic should not be administered intravenously or intramuscularly.

The day of weekly administration can be changed if necessary as long as the time between two doses is at least 3 days (>72 hours). After selecting a new dosing day, once-weekly dosing should be continued.

For further information on administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Semaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Semaglutide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients whom had rapid discontinuation or dose reduction of insulin when treatment with a GLP-1 receptor agonist is started (see section 4.2).

There is no experience in patients with congestive heart failure NYHA class IV and semaglutide is therefore not recommended in these patients.

Gastrointestinal effects
Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. This should be considered when treating patients, with impaired renal function as nausea, vomiting, and diarrhoea may cause dehydration which could cause a deterioration of renal function (see section 4.8).

Acute pancreatitis
Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, semaglutide should be discontinued; if confirmed, semaglutide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia
Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide (see section 4.8).

Diabetic retinopathy
In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy complications has been observed (see section 4.8). Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded.

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. Semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption.

Paracetamol
Semaglutide delays the rate of gastric emptying as assessed by paracetamol pharmacokinetics during a standardised meal test. Paracetamol $AUC_{0\text{-}60min}$ and C_{max} were decreased by 27% and 23%, respectively, following concomitant use of semaglutide 1 mg. The total paracetamol exposure ($AUC_{0\text{-}5h}$) was not affected. No dose adjustment of paracetamol is necessary when administered with semaglutide.

Oral contraceptives
Semaglutide is not anticipated to decrease the effect of oral contraceptives as semaglutide did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide. Exposure of ethinylestradiol was not affected; an increase of 20% was observed for levonorgestrel exposure at steady state. C_{max} was not affected for any of the compounds.

Atorvastatin
Semaglutide did not change the overall exposure of atorvastatin following a single dose administration of atorvastatin (40 mg). Atorvastatin C_{max} was decreased by 38%. This was assessed not to be clinically relevant.

Digoxin
Semaglutide did not change the overall exposure or C_{max} of digoxin following a single dose of digoxin (0.5 mg).

Metformin
Semaglutide did not change the overall exposure or C_{max} of metformin following dosing of 500 mg twice daily over 3.5 days.

Warfarin
Semaglutide did not change the overall exposure or C_{max} of R- and S-warfarin following a single dose of warfarin (25 mg), and the pharmacodynamic effects of warfarin as measured by the international normalised ratio (INR) were not affected in a clinically relevant manner. However, upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives, frequent monitoring of INR is recommended.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential are recommended to use contraception when treated with semaglutide.

Pregnancy
Studies in animals have shown reproductive toxicity (see section 5.3). There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life (see section 5.2).

Breast-feeding
In lactating rats, semaglutide was excreted in milk. As a risk to a breast-fed child cannot be excluded, semaglutide should not be used during breast-feeding.

Fertility
The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats. In female rats, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss (see section 5.3).

4.7 Effects on ability to drive and use machines

Semaglutide has no or negligible influence on the ability to drive or use machines. When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines (see section 4.4).

4.8 Undesirable effects

Summary of safety profile
In 8 phase 3a trials 4,792 patients were exposed to semaglutide. The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea (very common), diarrhoea (very common) and vomiting (common). In general, these reactions were mild or moderate in severity and of short duration.

Tabulated list of adverse reactions
Table 1 lists adverse reactions identified in all phase 3a trials in patients with type 2 diabetes mellitus (further described in section 5.1). The frequencies of the adverse reactions are based on a pool of the phase 3a trials excluding the cardiovascular outcomes trial (see text below the table for additional details).

The reactions are listed below by system organ class and absolute frequency. Frequencies are defined as: very common: (≥1/10); common: (≥1/100 to <1/10); uncommon: (≥1/1,000 to <1/100); rare: (≥1/10,000 to <1/1,000); very rare: (<1/10,000) and not known: cannot be estimated from available data. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions from long-term controlled phase 3a trials including the cardiovascular outcomes trial

MedDRA system organ class	Very common	Common	Uncommon	Rare	Not known
Immune system disorders			Hypersensitivity[c]	Anaphylactic reaction	
Metabolism and nutrition disorders	Hypoglycaemia[a] when used with insulin or sulfonylurea	Hypoglycaemia[a] when used with other OADs Decreased appetite			
Nervous system disorders		Dizziness	Dysgeusia		
Eye disorders		Diabetic retinopathy complications[b]			
Cardiac disorders			Increased heart rate		
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension	Acute pancreatitis		

		Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Eructation Flatulence			
Hepatobiliary disorders		Cholelithiasis			
Skin and subcutaneous tissue disorders					Angioedema[d]
General disorders and administration site conditions		Fatigue	Injection site reactions		
Investigations		Increased lipase Increased amylase Weight decreased			

[a)] Hypoglycaemia defined as severe (requiring the assistance of another person) or symptomatic in combination with a blood glucose <3.1 mmol/L.
[b)] Diabetic retinopathy complications is a composite of: retinal photocoagulation, treatment with intravitreal agents, vitreous haemorrhage, diabetes-related blindness (uncommon). Frequency based on cardiovascular outcomes trial.
[c)] Grouped term covering also adverse events related to hypersensitivity such as rash and urticaria.
[d)] From post-marketing reports.

2-year cardiovascular outcomes and safety trial
In cardiovascular high risk population the adverse reaction profile was similar to that seen in the other phase 3a trials (described in section 5.1).

Description of selected adverse reactions

Hypoglycaemia
No episodes of severe hypoglycaemia were observed when semaglutide was used as monotherapy. Severe hypoglycaemia was primarily observed when semaglutide was used with a sulfonylurea (1.2% of subjects, 0.03 events/patient year) or insulin (1.5% of subjects, 0.02 events/patient year). Few episodes (0.1% of subjects, 0.001 events/patient year) were observed with semaglutide in combination with oral antidiabetics other than sulfonylureas.

ADA classified hypoglycaemia occurred in 11.3% (0.3 events/patient year) of patients when semaglutide 1.0 mg was added to SGLT2 inhibitor in SUSTAIN 9 compared to 2.0% (0.04 events/patient year) of placebo-treated patients. Severe hypoglycaemia was reported in 0.7% (0.01 events/patient year) and 0% of patients, respectively.

Gastrointestinal adverse reactions
Nausea occurred in 17.0% and 19.9% of patients when treated with semaglutide 0.5 mg and 1 mg, respectively, diarrhoea in 12.2% and 13.3% and vomiting in 6.4% and 8.4%. Most events were mild to moderate in severity and of short duration. The events led to treatment discontinuation in 3.9% and 5% of patients. The events were most frequently reported during the first months on treatment.
Patients with low body weight may experience more gastrointestinal side effects when treated with semaglutide.

In concomitant use with an SGLT2 inhibitor in SUSTAIN 9, constipation and gastro-oesophageal reflux disease occurred in 6.7% and 4% respectively of patients treated with semaglutide 1.0 mg compared to no events for placebo-treated patients. The prevalence of these events did not decrease over time.

Acute pancreatitis
The frequency of adjudication-confirmed acute pancreatitis reported in phase 3a clinical trials was 0.3% for semaglutide and 0.2% for the comparator, respectively. In the 2-year cardiovascular outcomes trial the frequency of acute pancreatitis confirmed by adjudication was 0.5% for semaglutide and 0.6% for placebo (see section 4.4).

Diabetic retinopathy complications
A 2-year clinical trial investigated 3,297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. Systematic evaluation of diabetic retinopathy complication was only performed in the cardiovascular outcomes trial. In clinical trials up to 1 year involving 4,807 patients with type 2 diabetes, adverse events related to diabetic retinopathy were reported in similar proportions of subjects treated with semaglutide (1.7%) and comparators (2.0%).

Discontinuation due to an adverse event
The incidence of discontinuation of treatment due to adverse events was 6.1% and 8.7% for patients treated with semaglutide 0.5 mg and 1 mg, respectively, versus 1.5% for placebo. The most frequent adverse events leading to discontinuation were gastrointestinal.

Injection site reactions
Injection site reactions (e.g. injection site rash, erythema) have been reported by 0.6% and 0.5% of patients receiving semaglutide 0.5 mg and 1 mg, respectively. These reactions have usually been mild.

Immunogenicity
Consistent with the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop antibodies following treatment with semaglutide. The proportion of patients tested positive for anti-semaglutide antibodies at any time point post-baseline was low (1−2%) and no patients had anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect at end-of-trial.

Heart rate increase
Increased heart rate has been observed with GLP-1 receptor agonists. In the phase 3a trials, mean increases of 1 to 6 beats per minute (bpm) from a baseline of 72 to 76 bpm were observed in subjects treated with Ozempic. In a long-term trial in subjects with cardiovascular risk factors, 16% of Ozempic-treated subjects had an increase in heart rate of >10 bpm compared to 11% of subjects on placebo after 2 years of treatment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported adverse reaction was nausea. All patients recovered without complications.

There is no specific antidote for overdose with semaglutide. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of semaglutide of approximately 1 week (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Glucagon-like peptide-1 (GLP-1) analogues, ATC code: A10BJ06

Mechanism of action
Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

GLP--1 is a physiological hormone that has multiple actions in glucose and appetite regulation, and in the cardiovascular system. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain.

Semaglutide reduces blood glucose in a glucose dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion.

Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high fat foods.

GLP-1 receptors are also expressed in the heart, vasculature, immune system and kidneys. Semaglutide had a beneficial effect on plasma lipids, lowered systolic blood pressure and reduced inflammation in clinical studies. In animal studies, semaglutide attenuates the development of atherosclerosis by preventing aortic plaque progression and reducing inflammation in the plaque.

Pharmacodynamic effects
All pharmacodynamic evaluations were performed after 12 weeks of treatment (including dose escalation) at steady state with semaglutide 1 mg once weekly.

Fasting and postprandial glucose
Semaglutide reduces fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with semaglutide 1 mg resulted in reductions in glucose in terms of absolute change from baseline (mmol/L) and relative reduction compared to placebo (%) for fasting glucose (1.6 mmol/L; 22% reduction), 2 hour postprandial glucose (4.1 mmol/L; 37% reduction), mean 24 hour glucose concentration (1.7 mmol/L; 22% reduction) and postprandial glucose excursions over 3 meals (0.6-1.1 mmol/L) compared with placebo. Semaglutide lowered fasting glucose after the first dose.

Beta-cell function and insulin secretion
Semaglutide improves beta-cell function. Compared to placebo, semaglutide improved first- and second-phase insulin response with a 3– and 2–fold increase, respectively, and increased maximal

beta-cell secretory capacity in patients with type 2 diabetes. In addition, semaglutide treatment increased fasting insulin concentrations compared to placebo.

Glucagon secretion
Semaglutide lowers the fasting and postprandial glucagon concentrations. In patients with type 2 diabetes, semaglutide resulted in the following relative reductions in glucagon compared to placebo: fasting glucagon (8–21%), postprandial glucagon response (14–15%) and mean 24 hour glucagon concentration (12%).

Glucose dependent insulin and glucagon secretion
Semaglutide lowered high blood glucose concentrations by stimulating insulin secretion and lowering glucagon secretion in a glucose dependent manner. With semaglutide, the insulin secretion rate in patients with type 2 diabetes was comparable to that of healthy subjects.

During induced hypoglycaemia, semaglutide compared to placebo did not alter the counter regulatory responses of increased glucagon and did not impair the decrease of C-peptide in patients with type 2-diabetes.

Gastric emptying
Semaglutide caused a minor delay of early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.

Appetite, energy intake and food choice
Semaglutide compared to placebo lowered the energy intake of 3 consecutive *ad libitum* meals by 18-35%. This was supported by a semaglutide-induced suppression of appetite in the fasting state as well as postprandially, improved control of eating, less food cravings and a relative lower preference for high fat food.

Fasting and postprandial lipids
Semaglutide compared to placebo lowered fasting triglyceride and very low density lipoproteins (VLDL) cholesterol concentrations by 12% and 21%, respectively. The postprandial triglyceride and VLDL cholesterol response to a high fat meal was reduced by >40%.

Cardiac electrophysiology (QTc)
The effect of semaglutide on cardiac repolarization was tested in a thorough QTc trial. Semaglutide did not prolong QTc intervals at supra-therapeutic dose levels (up to 1.5 mg at steady state).

Clinical efficacy and safety

Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes.

The efficacy and safety of Ozempic 0.5 mg and 1 mg once weekly were evaluated in six randomised controlled phase 3a trials that included 7,215 patients with type 2 diabetes mellitus (4,107 treated with semaglutide). Five trials (SUSTAIN 1–5) had the glycaemic efficacy assessment as the primary objective, while one trial (SUSTAIN 6) had cardiovascular outcome as the primary objective.

In addition a phase 3b trial (SUSTAIN 7) including 1,201 patients was conducted to compare the efficacy and safety of Ozempic 0.5 mg and 1 mg once weekly to dulaglutide 0.75 mg and 1.5 mg once weekly, respectively. A phase 3b trial (SUSTAIN 9), was conducted to investigate the efficacy and safety of semaglutide as add-on to SGLT2 inhibitor treatment.

Treatment with semaglutide demonstrated sustained, statistically superior and clinically meaningful reductions in HbA_{1c} and body weight for up to 2 years compared to placebo and active control treatment (sitagliptin, insulin glargine, exenatide ER and dulaglutide).

The efficacy of semaglutide was not impacted by age, gender, race, ethnicity, BMI at baseline, body weight (kg) at baseline, diabetes duration and level of renal function impairment.

Detailed information is provided below.

SUSTAIN 1 – Monotherapy
In a 30-week double-blind placebo-controlled trial, 388 patients inadequately controlled with diet and exercise, were randomised to Ozempic 0.5 mg or Ozempic 1 mg once weekly or placebo.

Table 2 SUSTAIN 1: Results at week 30

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Placebo**
Intent-to-Treat (ITT) Population (N)	128	130	129
HbA_{1c} (%)			
Baseline (mean)	8.1	8.1	8.0
Change from baseline at week 30	-1.5	-1.6	0
Difference from placebo [95% CI]	-1.4 [-1.7, -1.1][a]	-1.5 [-1.8, -1.2][a]	-
Patients (%) achieving HbA_{1c} <7%	74	72	25
FPG (mmol/L)			
Baseline (mean)	9.7	9.9	9.7
Change from baseline at week 30	-2.5	-2.3	-0.6
Body weight (kg)			
Baseline (mean)	89.8	96.9	89.1
Change from baseline at week 30	-3.7	-4.5	-1.0
Difference from placebo [95% CI]	-2.7 [-3.9, -1.6][a]	-3.6 [-4.7, -2.4][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 2 – Ozempic vs. sitagliptin both in combination with 1–2 oral antidiabetic drugs (metformin and/or thiazolidinediones)
In a 56-week active-controlled double-blind trial, 1,231 patients were randomised to Ozempic 0.5 mg once weekly, Ozempic 1 mg once weekly or sitagliptin 100 mg once daily, all in combination with metformin (94%) and/or thiazolidinediones (6%).

Table 3 SUSTAIN 2: Results at week 56

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Sitagliptin 100 mg**
Intent-to-Treat (ITT) Population (N)	409	409	407
HbA_{1c} (%)			
Baseline (mean)	8.0	8.0	8.2
Change from baseline at week 56	-1.3	-1.6	-0.5
Difference from sitagliptin [95% CI]	-0.8 [-0.9, -0.6][a]	-1.1 [-1.2, -0.9][a]	-
Patients (%) achieving HbA_{1c} <7%	69	78	36
FPG (mmol/L)			
Baseline (mean)	9.3	9.3	9.6
Change from baseline at week 56	-2.1	-2.6	-1.1
Body weight (kg)			
Baseline (mean)	89.9	89.2	89.3
Change from baseline at week 56	-4.3	-6.1	-1.9
Difference from sitagliptin [95% CI]	-2.3 [-3.1, -1.6][a]	-4.2 [-4.9, -3.5][a]	-

[a]p <0.0001 (2-sided) for superiority

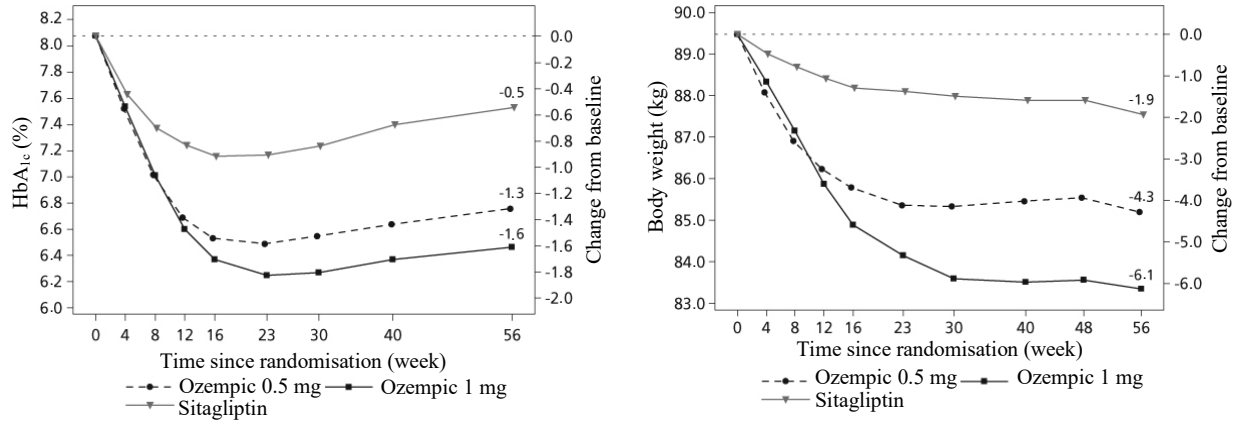


Figure 1 Mean change in HbA_{1c} (%) and body weight (kg) from baseline to week 56

SUSTAIN 7 – Ozempic vs. dulaglutide both in combination with metformin
In a 40-week, open-label trial, 1,201 patients on metformin were randomised 1:1:1:1 to once weekly Ozempic 0.5 mg, dulaglutide 0.75 mg , Ozempic 1 mg or dulaglutide 1.5 mg, respectively .
The trial compared 0.5 mg of Ozempic to 0.75 mg of dulaglutide and 1 mg of Ozempic to 1.5 mg of dulaglutide.

Gastrointestinal disorders were the most frequent adverse events, and occurred in similar proportion of patients receiving Ozempic 0.5 mg (129 patients [43%]), Ozempic 1 mg (133 [44%]), and dulaglutide 1.5 mg (143 [48%]); fewer patients had gastrointestinal disorders with dulaglutide 0.75 mg (100 [33%]).
At week 40, the increase in pulse rate for Ozempic (0.5 mg and 1 mg) and dulaglutide (0.75 mg and 1.5 mg) was 2.4, 4.0, and 1.6, 2.1, beats/min, respectively.

Table 4 SUSTAIN 7: Results at week 40

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Dulaglutide 0.75 mg**	**Dulaglutide 1.5 mg**
Intent-to-Treat (ITT) Population(N)	301	300	299	299
HbA_{1c} (%)				
Baseline (mean)	8.3	8.2	8.2	8.2
Change from baseline at week 40	-1.5	-1.8	-1.1	-1.4
Difference from dulaglutide [95% CI]	-0.4[b] [-0.6, -0.2][a]	-0.4[c] [-0.6, -0.3][a]	-	-
Patients (%) achieving HbA_{1c} <7%	68	79	52	67
FPG (mmol/L)				
Baseline (mean)	9.8	9.8	9.7	9.6
Change from baseline at week 40	-2.2	-2.8	-1.9	-2.2
Body weight (kg)				
Baseline (mean)	96.4	95.5	95.6	93.4
Change from baseline at week 40	-4.6	-6.5	-2.3	-3.0
Difference from dulaglutide [95% CI]	-2.3[b] [-3.0, -1.5][a]	-3.6[c] [-4.3, -2.8][a]	-	-

[a]p <0.0001 (2-sided) for superiority
[b] Ozempic 0.5 mg vs dulaglutide 0.75 mg
[c] Ozempic 1 mg vs dulaglutide 1.5 mg

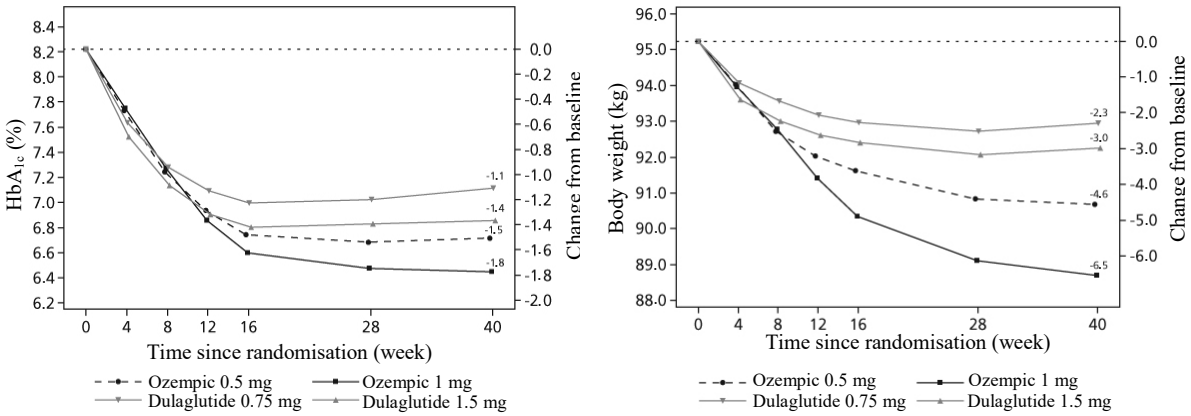


Figure 2 Mean change in HbA_{1c} (%) and body weight (kg) from baseline to week 40

SUSTAIN 3 – Ozempic vs. exenatide ER both in combination with metformin or metformin with sulfonylurea

In a 56-week open-label trial, 813 patients on metformin alone (49%), metformin with sulfonylurea (45%) or other (6%) were randomised to Ozempic 1 mg or exenatide ER 2 mg once weekly.

Table 5 SUSTAIN 3: Results at week 56

	Semaglutide 1 mg	**Exenatide ER 2 mg**
Intent-to-Treat (ITT) Population (N)	404	405
HbA_{1c} (%)		
Baseline (mean)	8.4	8.3
Change from baseline at week 56	-1.5	-0.9
Difference from exenatide [95% CI]	-0.6 [-0.8, -0.4][a]	-
Patients (%) achieving HbA_{1c} <7%	67	40
FPG (mmol/L)		
Baseline (mean)	10.6	10.4
Change from baseline at week 56	-2.8	-2.0
Body weight (kg)		
Baseline (mean)	96.2	95.4
Change from baseline at week 56	-5.6	-1.9
Difference from exenatide [95% CI]	-3.8 [-4.6, -3.0][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 4 – Ozempic vs. insulin glargine both in combination with 1–2 oral antidiabetic drugs (metformin or metformin and sulfonylurea)

In a 30-week open-label comparator trial 1,089 patients were randomised to Ozempic 0.5 mg once weekly, Ozempic 1 mg once weekly, or insulin glargine once-daily on a background of metformin (48%) or metformin and sulfonylurea (51%).

Table 6 SUSTAIN 4: Results at week 30

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Insulin Glargine**
Intent-to-Treat (ITT) Population (N)	362	360	360
HbA_{1c} (%)			
Baseline (mean)	8.1	8.2	8.1
Change from baseline at week 30	-1.2	-1.6	-0.8
Difference from insulin glargine [95% CI]	-0.4 [-0.5, -0.2][a]	-0.8 [-1.0, -0.7][a]	-
Patients (%) achieving HbA_{1c} <7%	57	73	38
FPG (mmol/L)			

Baseline (mean)	9.6	9.9	9.7
Change from baseline at week 30	-2.0	-2.7	-2.1
Body weight (kg)			
Baseline (mean)	93.7	94.0	92.6
Change from baseline at week 30	-3.5	-5.2	+1.2
Difference from insulin glargine [95% CI]	-4.6 [-5.3, -4.0][a]	-6.34 [-7.0, -5.7][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 5 – Ozempic vs. placebo both in combination with basal insulin

In a 30-week double-blind placebo-controlled trial, 397 patients inadequately controlled with basal insulin with or without metformin were randomised to Ozempic 0.5 mg once weekly, Ozempic 1 mg once weekly or placebo.

Table 7 SUSTAIN 5: Results at week 30

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Placebo**
Intent-to-Treat (ITT) Population (N)	132	131	133
HbA_{1c} (%)			
Baseline (mean)	8.4	8.3	8.4
Change from baseline at week 30	-1.4	-1.8	-0.1
Difference from placebo [95% CI]	-1.4 [-1.6, -1.1][a]	-1.8 [-2.0, -1.5][a]	-
Patients (%) achieving HbA_{1c} <7%	61	79	11
FPG (mmol/L)			
Baseline (mean)	8.9	8.5	8.6
Change from baseline at week 30	-1.6	-2.4	-0.5
Body weight (kg)			
Baseline (mean)	92.7	92.5	89.9
Change from baseline at week 30	-3.7	-6.4	-1.4
Difference from placebo [95% CI]	-2.3 [-3.3, -1.3][a]	-5.1 [-6.1, -4.0][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 9 – Ozempic vs. placebo as add-on to SGLT2 inhibitor ± metformin or SU

In a 30-week double-blind placebo-controlled trial, 302 patients inadequately controlled with SGLT2 inhibitor with or without metformin or SU were randomised to semaglutide 1.0 mg once weekly or placebo.

Table 8 SUSTAIN 9: Results at week 30

	Semaglutide 1 mg	**Placebo**
Intent-to-Treat (ITT) Population (N)	151	151
HbA_{1c} (%)		
Baseline (mean)	8.0	8.1
Change from baseline at week 30	-1.5	-0.1
Difference from placebo [95% CI]	-1.4 [-1.6, -1.2][a]	-
Patients (%) achieving HbA_{1c} <7%	78.7	18.7
FPG (mmol/L)		
Baseline (mean)	9.1	8.9
Change from baseline at week 30	-2.2	0.0
Body weight (kg)		
Baseline (mean)	89.6	93.8
Change from baseline at week 30	-4.7	-0.9
Difference from placebo [95% CI]	-3.8 [-4.7, -2.9][a]	-

[a]$p < 0.0001$ (2-sided) for superiority, adjusted regarding multiplicity based on hierarchical testing of the HbA1c value and body weight

Combination with sulfonylurea monotherapy
In SUSTAIN 6 (see subsection Cardiovascular disease) 123 patients were on sulfonylurea monotherapy at baseline. HbA_{1c} at baseline was 8.2%, 8.4% and 8.4% for Ozempic 0.5 mg, Ozempic 1 mg, and placebo, respectively. At week 30, the change in HbA_{1c} was -1.6%, -1.5% and 0.1% for Ozempic 0.5 mg, Ozempic 1 mg, and placebo, respectively.

Combination with premix insulin ± 1–2 OADs
In SUSTAIN 6 (see subsection Cardiovascular disease) 867 patients were on premix insulin (with or without OAD(s)) at baseline. HbA_{1c} at baseline was 8.8%, 8.9% and 8.9% for Ozempic 0.5 mg, Ozempic 1 mg, and placebo, respectively. At week 30, the change in HbA_{1c} was -1.3%, -1.8% and -0.4% for Ozempic 0.5 mg, Ozempic 1 mg, and placebo, respectively.

Cardiovascular disease
In a 104-week double-blind trial (SUSTAIN 6), 3,297 patients with type 2 diabetes mellitus at high cardiovascular risk were randomised to either Ozempic 0.5 mg once weekly, Ozempic 1 mg once weekly or corresponding placebo in addition to standard-of-care hereafter followed for 2 years. In total 98% of the patients completed the trial and the vital status was known at the end of the trial for 99.6% of the patients.

The trial population was distributed by age as: 1,598 patients (48.5%) ≥65 years, 321 (9.7%) ≥75 years, and 20 (0.6%) ≥85 years. There were 2,358 patients with normal or mild renal impairment, 832 with moderate and 107 with severe or end stage renal impairment. There were 61% males, the mean age was 65 years and mean BMI was 33 kg/m^2. The mean duration of diabetes was 13.9 years.

The primary endpoint was time from randomisation to first occurrence of a major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The total number of primary component MACE endpoints was 254, including 108 (6.6%) with semaglutide and 146 (8.9%) with placebo. See figure 4 for results on primary and secondary cardiovascular endpoints. Treatment with semaglutide resulted in a 26% risk reduction in the primary composite outcome of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke. The total numbers of cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes were 90, 111, and 71, respectively, including 44 (2.7%), 47 (2.9%), and 27 (1.6%), respectively, with semaglutide (figure 4). The risk reduction in the primary composite outcome was mainly driven by decreases in the rate of non-fatal stroke (39%) and non-fatal myocardial infarction (26%) (figure 3).

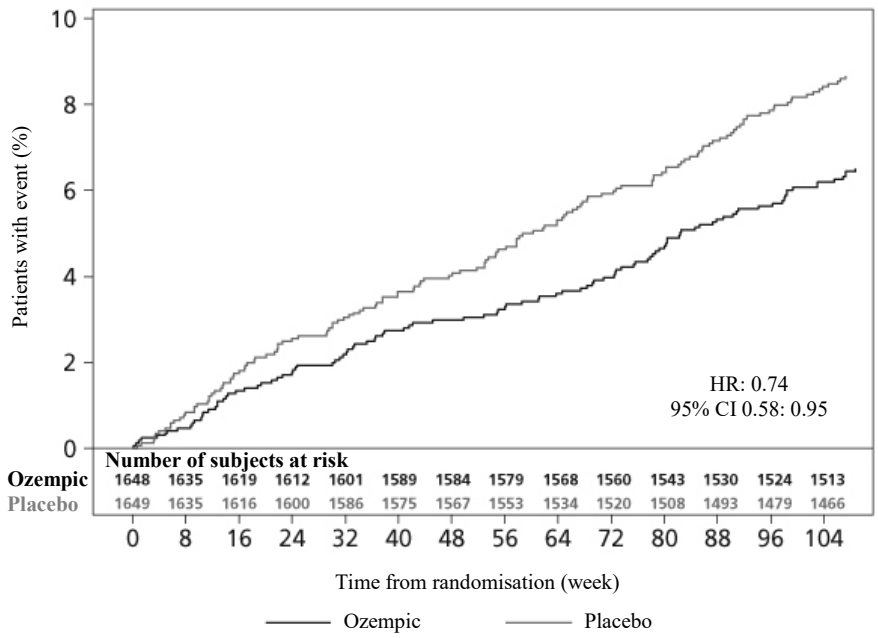


Figure 3 Kaplan-Meier plot of time to first occurrence of the composite outcome: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (SUSTAIN 6)

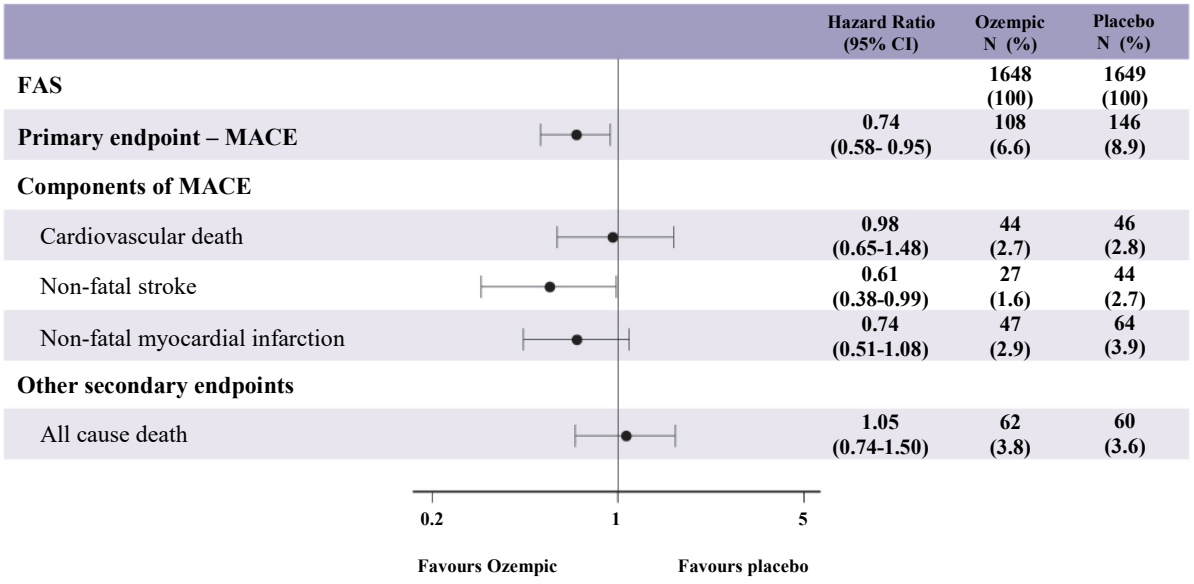


Figure 4 Forest plot: analyses of time to first occurrence of the composite outcome, its components and all cause death (SUSTAIN 6)

There were 158 events of new or worsening nephropathy. The hazard ratio [95% CI] for time to nephropathy (new onset of persistent macroalbuminuria, persistent doubling of serum creatinine, need for continuous renal replacement therapy and death due to renal disease) was 0.64 [0.46; 0.88] driven by new onset of persistent macroalbuminuria.

Body weight

After one year of treatment, a weight loss of ≥5% and ≥10% was achieved for more subjects with Ozempic 0.5 mg (46% and 13%) and 1 mg (52 – 62% and 21 – 24%) compared with the active comparators sitagliptin (18% and 3%) and exenatide ER (17% and 4%).

In the 40-week trial versus dulaglutide a weight loss of ≥5% and ≥10% was achieved for more subjects with Ozempic 0.5 mg (44% and 14%) compared with dulaglutide 0.75 mg (23% and 3%) and Ozempic 1 mg (up to 63% and 27%) compared with dulaglutide 1.5 mg (30% and 8%).

A significant and sustained reduction in body weight from baseline to week 104 was observed with Ozempic 0.5 mg and 1 mg vs placebo 0.5 mg and 1 mg, in addition to standard-of-care (-3.6 kg and -4.9 kg vs -0.7 kg and -0.5 kg , respectively) in SUSTAIN 6.

Blood pressure
Significant reductions in mean systolic blood pressure were observed when Ozempic 0.5 mg (3.5-5.1 mmHg) and 1 mg (5.4–7.3 mmHg) were used in combination with oral antidiabetic medicinal products or basal insulin. For diastolic blood pressure, there were no significant differences between semaglutide and comparators.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with semaglutide in one or more subsets of the paediatric population in type 2 diabetes (see section 4.2).

5.2 Pharmacokinetic properties

Compared to native GLP-1, semaglutide has a prolonged half-life of around 1 week making it suitable for once weekly subcutaneous administration. The principal mechanism of protraction is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilised against degradation by the DPP-4 enzyme.

Absorption
Maximum concentration was reached 1 to 3 days post dose. Steady state exposure was achieved following 4–5 weeks of once weekly administration. In patients with type 2 diabetes, the mean steady state concentrations following subcutaneous administration of 0.5 mg and 1 mg semaglutide were approximately 16 nmol/L and 30 nmol/L, respectively. Semaglutide exposure increased in a dose proportional manner for doses of 0.5 mg and 1 mg. Similar exposure was achieved with subcutaneous administration of semaglutide in the abdomen, thigh, or upper arm. Absolute bioavailability of subcutaneous semaglutide was 89%.

Distribution
The mean volume of distribution of semaglutide following subcutaneous administration in patients with type 2 diabetes was approximately 12.5 L. Semaglutide was extensively bound to plasma albumin (>99%).

Metabolism/Biotransformation
Prior to excretion, semaglutide is extensively metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain. The enzyme neutral endopeptidase (NEP) is expected to be involved in the metabolism of semaglutide.

Elimination
In a study with a single subcutaneous dose of radiolabelled semaglutide, it was found that the primary excretion routes of semaglutide-related material were via urine and faeces; approximately 2/3 of semaglutide-related material were excreted in urine and approximately 1/3 in faeces. Approximately 3% of the dose was excreted as intact semaglutide via urine. In patients with type 2 diabetes clearance of semaglutide was approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 weeks after the last dose.

Special population

Elderly
Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3a studies including patients of 20–86 years of age.

Gender, race and ethnicity
Gender, race (White, Black or African-American, Asian) and ethnicity (Hispanic or Latino, non-Hispanic or -Latino) had no effect on the pharmacokinetics of semaglutide.

Body weight
Body weight has an effect on the exposure of semaglutide. Higher body weight results in lower exposure; a 20% difference in body weight between individuals will result in an approximate 16% difference in exposure. Semaglutide doses of 0.5 mg and 1 mg provide adequate systemic exposure over a body weight range of 40–198 kg.

Renal impairment
Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown with a single dose of 0.5 mg semaglutide for patients with different degrees of renal impairment (mild, moderate, severe or patients in dialysis) compared with subjects with normal renal function. This was also shown for subjects with type 2 diabetes and with renal impairment based on data from phase 3a studies, although the experience in patients with end-stage renal disease was limited.

Hepatic impairment
Hepatic impairment did not have any impact on the exposure of semaglutide. The pharmacokinetics of semaglutide were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function in a study with a single-dose of 0.5 mg semaglutide.

Paediatric population
Semaglutide has not been studied in paediatric patients.

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity.

Non-lethal thyroid C-cell tumours observed in rodents are a class effect for GLP-1 receptor agonists. In 2-year carcinogenicity studies in rats and mice, semaglutide caused thyroid C-cell tumours at clinically relevant exposures. No other treatment-related tumours were observed. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. The relevance for humans is considered to be low, but cannot be completely excluded.

In fertility studies in rats, semaglutide did not affect mating performance or male fertility. In female rats, an increase in oestrous cycle length and a small reduction in *corpora lutea* (ovulations) were observed at doses associated with maternal body weight loss.

In embryo-foetal development studies in rats, semaglutide caused embryotoxicity below clinically relevant exposures. Semaglutide caused marked reductions in maternal body weight and reductions in embryonic survival and growth. In foetuses, major skeletal and visceral malformations were observed, including effects on long bones, ribs, vertebrae, tail, blood vessels and brain ventricles. Mechanistic evaluations indicated that the embryotoxicity involved a GLP-1 receptor mediated impairment of the nutrient supply to the embryo across the rat yolk sac. Due to species differences in yolk sac anatomy and function, and due to lack of GLP-1 receptor expression in the yolk sac of non-human primates,

this mechanism is considered unlikely to be of relevance to humans. However, a direct effect of semaglutide on the foetus cannot be excluded.

In developmental toxicity studies in rabbits and *cynomolgus* monkeys, increased pregnancy loss and slightly increased incidence of foetal abnormalities were observed at clinically relevant exposures. The findings coincided with marked maternal body weight loss of up to 16%. Whether these effects are related to the decreased maternal food consumption as a direct GLP-1 effect is unknown.

Postnatal growth and development were evaluated in *cynomolgus* monkeys. Infants were slightly smaller at delivery, but recovered during the lactation period.

In juvenile rats, semaglutide caused delayed sexual maturation in both males and females. These delays had no impact upon fertility and reproductive capacity of either sex, or on the ability of the females to maintain pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dihydrate
Propylene glycol
Phenol
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.
In-use shelf life: 6 weeks.

After first use: Store below 30°C or in a refrigerator (2°C to 8°C). Do not freeze Ozempic and do not use Ozempic if it has been frozen. Keep the pen cap on when the pen is not in use in order to protect it from light.

Always remove the injection needle after each injection and store the pen without a needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

6.4 Special precautions for storage

Before first use: Store in a refrigerator (2°C to 8°C). Keep away from the cooling element.
Do not freeze Ozempic and do not use Ozempic if it has been frozen.

For storage conditions after first opening of the medicinal product, see section 6.3.

Keep the pen cap on in order to protect from light.

6.5 Nature and contents of container

1.5 ml or 3 ml glass cartridge (type I glass) closed at the one end with a rubber plunger (chlorobutyl) and at the other end with an aluminium cap with a laminated rubber sheet (bromobutyl/polyisoprene) inserted. The cartridge is assembled into a disposable pre-filled pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene.

Pack sizes:
Ozempic 0.25 mg solution for injection: Each pre-filled pen contains 1.5 ml of solution, delivering 4 doses of 0.25 mg.
1 pre-filled pen and 4 disposable NovoFine Plus needles

Ozempic 0.5 mg solution for injection: Each pre-filled pen contains 1.5 ml of solution, delivering 4 doses of 0.5 mg.
1 pre-filled pen and 4 disposable NovoFine Plus needles
3 pre-filled pens and 12 disposable NovoFine Plus needles

Ozempic 1 mg solution for injection: Each pre-filled pen contains 3 ml of solution, delivering 4 doses of 1 mg.
1 pre-filled pen and 4 disposable NovoFine Plus needles
3 pre-filled pens and 12 disposable NovoFine Plus needles

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The patient should be advised to discard the injection needle after each injection and store the pen without an injection needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing. Needles and other waste material should be disposed of in accordance with local requirements.

The pen is for use by one person only.
Ozempic should not be used if it does not appear clear and colourless or almost colourless.
Ozempic should not be used if it has been frozen.

Ozempic can be administered with needles up to a length of 8 mm. The pen is designed to be used with NovoFine or NovoTwist disposable needles. NovoFine Plus needles are included in the package.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBERS

EU/1/17/1251/002
EU/1/17/1251/003
EU/1/17/1251/004
EU/1/17/1251/005
EU/1/17/1251/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 February 2018

10. DATE OF REVISION OF THE TEXT

03/2021

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

STUDY DESIGNS

SUSTAIN 1: Monotherapy vs placebo[1,18]

A 30-week, randomised, double-blind, placebo-controlled, parallel-group, multicentre trial to evaluate the efficacy and safety of Ozempic® vs placebo. A total of 388 patients with type 2 diabetes inadequately controlled with diet and exercise were randomised to receive once-weekly Ozempic® 0.5 mg (n=128), Ozempic® 1 mg (n=130) or placebo (n=129). The primary endpoint was change in HbA_{1c} at Week 30, and the secondary endpoint was change in mean body weight at Week 30.

SUSTAIN 2: Head-to-head vs sitagliptin[1,19]

A 56-week, randomised, double-blind, double-dummy, active-controlled, parallel-group, multicentre trial to compare the efficacy and safety of Ozempic® vs sitagliptin. A total of 1231 patients with type 2 diabetes inadequately controlled on metformin and/or thiazolidinediones were randomised to receive once-weekly Ozempic® 0.5 mg (n=409), once-weekly Ozempic® 1 mg (n=409) or once-daily sitagliptin 100 mg (n=407). The primary endpoint was change in HbA_{1c} at Week 56, and the secondary endpoint was change in mean body weight at Week 56.

SUSTAIN 3: Head-to-head vs exenatide ER[1,17]

A 56-week, randomised, open-label, active-controlled, parallel-group, multicentre trial to compare the efficacy and safety of Ozempic® vs exenatide ER. A total of 813 patients with type 2 diabetes inadequately controlled on metformin, metformin and sulphonylurea or thiazolidinediones were randomised to receive once-weekly Ozempic® 1 mg (n=404) or exenatide ER 2 mg (n=405). The primary endpoint was change in HbA_{1c} at Week 56, and the secondary endpoint was change in mean body weight at Week 56.

SUSTAIN 4: Head-to-head vs insulin glargine U100[1,10]

A 30-week, randomised, open-label, active-controlled, parallel-group, multicentre trial to compare the efficacy and safety of Ozempic® vs insulin glargine U100. A total of 1089 insulin-naïve patients with type 2 diabetes inadequately controlled on metformin alone or in combination with a sulphonylurea were randomised to receive once-weekly Ozempic® 0.5 mg (n=362), once-weekly Ozempic® 1 mg (n=360) or once-daily insulin glargine U100 with a starting dose of 10 IU (n=360). The primary endpoint was change in HbA_{1c} at Week 30, and the secondary endpoint was change in mean body weight at Week 30.

SUSTAIN 5: As add-on to basal insulin vs placebo[1,13]

A 30-week, randomised, double-blind, placebo-controlled, parallel-group, multicentre trial to demonstrate the superiority of Ozempic® in combination with basal insulin vs placebo. A total of 397 patients inadequately controlled on basal insulin with or without metformin were randomised to once-weekly Ozempic® 0.5 mg (n=132), Ozempic® 1 mg (n=131) or placebo (n=133). Randomisation was stratified according to HbA_{1c} at screening. Patients with HbA_{1c} ≤8% at screening reduced the insulin dose by 20% at start of trial to reduce the risk of hypoglycaemia. The primary endpoint was change in HbA_{1c} at Week 30, and the secondary endpoint was change in mean body weight at Week 30.

SUSTAIN 6: CV outcomes[1,5,8]

A 2-year, randomised, double-blind, placebo-controlled, parallel-group trial to evaluate CV and other long-term outcomes of Ozempic®. A total of 3297 patients with type 2 diabetes and high risk of CV events were randomised based on evidence of CV disease, insulin treatment and renal impairment to once-weekly Ozempic® 0.5 mg (n=826), Ozempic® 1 mg (n=822) or placebo (n=1649) in addition to standard of care treatments such as oral antidiabetic treatments, insulin, antihypertensives, diuretics and lipid-lowering therapies at investigator discretion. The primary endpoint was time from randomisation to first occurrence of a major adverse CV event (MACE) defined as CV death, nonfatal myocardial infarction or nonfatal stroke. Secondary endpoints included first occurrence from baseline to Week 104 of the individual components of the composite outcomes; nephropathy and diabetic retinopathy complications; change from baseline to Week 104 in body weight and HbA_{1c}.

Inclusion criteria were HbA_{1c} ≥7%; previously on 0-2 oral antidiabetic drugs (OADs), basal or pre-mix insulin ± 0-2 OADs; ≥50 years with established CV disease (≥1 coexisting condition); ≥60 years with at least 1 CV risk factor as determined by the investigator. Exclusion criteria were treatment with a dipeptidyl peptidase-4 inhibitor within 30 days before screening or with a GLP-1 receptor agonist or insulin other than basal or pre-mixed within 90 days before screening; a history of an acute coronary or cerebrovascular event within 90 days before randomisation; planned revascularisation of a coronary, carotid or peripheral artery; or long-term dialysis.

SUSTAIN 7: Head-to-head vs dulaglutide[1,2]

A 40-week, randomised, open-label, active-controlled, parallel-group, multicentre, multinational, four-armed trial to compare the efficacy and safety of Ozempic® vs dulaglutide. A total of 1199 patients with type 2 diabetes inadequately controlled on metformin were randomised to receive Ozempic® 0.5 mg (n=301), Ozempic® 1 mg (n=300), dulaglutide 0·75 mg (n=299) or dulaglutide 1.5 mg (n=299) once weekly. The primary endpoint was change in HbA_{1c} at Week 40, and the secondary endpoint was change in mean body weight at Week 40.

SUSTAIN 8: Head-to-head vs canagliflozin[28]

A 52-week, confirmatory, randomised (1:1), double-blind, double-dummy, active-controlled, parallel-group trial to compare (pairwise) the efficacy and safety of once-weekly Ozempic® 1·0 mg vs once-daily oral canagliflozin 300 mg, both in combination with metformin. 784 adults with type 2 diabetes inadequately controlled with metformin were randomised. The primary endpoint was change in HbA_{1c} at Week 52, and the key secondary endpoint was change in body weight at Week 52.

SUSTAIN 9: As add-on to SGLT-2i vs placebo[29]

A randomised, double-blind, parallel-group trial to compare the efficacy and safety of Ozempic® as add-on to SGLT-2i monotherapy or in combination with either metformin or sulphonylurea vs placebo. 302 patients with type 2 diabetes and inadequate glycaemic control, despite ≥90 days treatment with an SGLT-2i, were randomly assigned (1:1) to receive Ozempic® 1.0 mg or volume-matched placebo once weekly for 30 weeks. Existing antidiabetic medications, including SGLT-2i treatment, were continued during the trial. The primary outcome was change in HbA_{1c} from baseline at Week 30, with confirmatory secondary outcome of change in body weight.

SUSTAIN 10: Head-to-head vs liraglutide[30]

An open-label, parallel-group, multicentre trial conducted in 11 European countries to compare the efficacy and safety of Ozempic® vs liraglutide in 577 adults with type 2 diabetes, on 1 to 3 oral antidiabetic drugs. Patients were randomised 1:1 to Ozempic® 1.0 mg once weekly or liraglutide 1.2 mg once daily. Randomisation was stratified by background medication of sulphonylureas ± metformin, SGLT-2i ± metformin, SU and SGLT-2i ± metformin or metformin monotherapy. Primary and secondary endpoints were change from baseline to Week 30 in HbA_{1c} and body weight.