# ABCD Spring Meeting
## A deep dive into the semaglutide (Ozempic▼) SUSTAIN programme

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This symposium is organised and funded by Novo Nordisk
Prescribing information and adverse event reporting is available at the end of this presentation

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# Disclosures

- Senior clinical academic since 1993; since that time, reports having received honoraria, teaching and research sponsorship/grants from the following: Abbott, AstraZeneca, Boehringer Ingelheim, BMS, Cellnovo, Diartis, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, Servier and Takeda
- Received funding for the development of educational programmes from Cardiff University, Doctors.net, Elsevier, Onmedica, Omnia-Med and Medscape
- Owns a share of Glycosmedia, which carries sponsorship declared on-site
- Provided expert advice to the All-Wales Medicines Strategy Group and the UK National Institute for Health and Care Excellence

# Agenda

1. SUSTAIN 1–5 and 7 outcomes, including by baseline disease duration
2. Recently published data: SUSTAIN 9 & 10
3. SUSTAIN 6 by baseline CV risk
4. Q&As

SUSTAIN; Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes, CV; cardiovascular

# Semaglutide indication

- Semaglutide 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

Ozempic® Summary of Product Characteristics, Novo Nordisk A/S, Bagsværd, Denmark.

# Overview: semaglutide sc phase 3 programme

| Drug-naïve | 1–3 OADs | Insulin users |
|---|---|---|
| **SUSTAIN 1**[1] vs. placebo | **SUSTAIN 2**[2] vs. sitagliptin (DPP-4i) | **SUSTAIN 5**[5] vs. placebo (add-on to basal insulin) |
| | **SUSTAIN 4**[4] vs. IGlar (basal insulin) | |
| | **SUSTAIN 8**[8] vs. canagliflozin (SGLT2i) | |
| | **SUSTAIN 10**[10] vs. liraglutide (OD GLP-1RA) | |
| | **SUSTAIN 3**[3] vs. exenatide OW (OW GLP-1RA) | |
| | **SUSTAIN 7**[7] vs. dulaglutide (OW GLP-1RA) | |
| | **SUSTAIN 9**[9] vs. placebo (add-on to SGLT2i) | |

**SUSTAIN 6**[6] **(CVOT) vs. placebo**

Recently completed trials

**Why carry out *post hoc* analyses?**

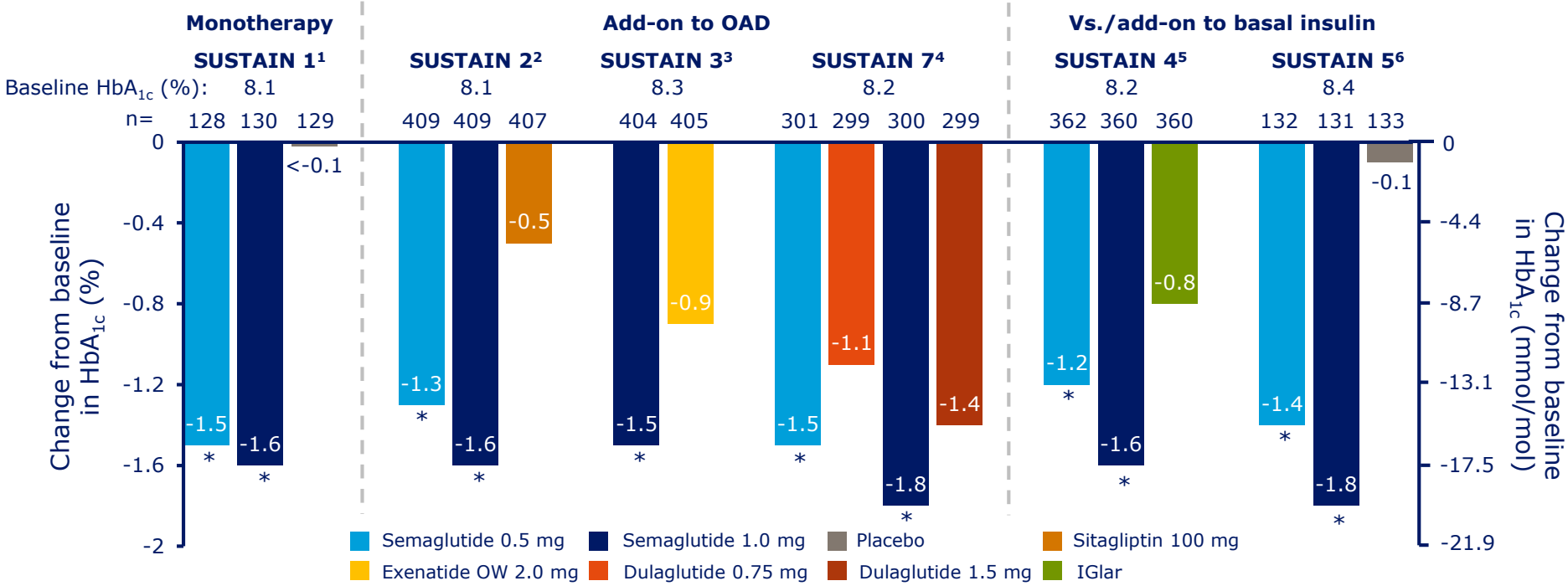
- 10,078 participants included across the SUSTAIN programme
- Vast amount of data collected
- Explores consistency and robustness of results
- Can help translate endpoints to support clinical practice

Drug-naïve, OADs and insulin users refer to background medication. CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; IGlar, insulin glargine; OAD, oral antidiabetic drug; OD, once daily; OW, once weekly; sc, subcutaneous; SLGT2i, sodium-glucose cotransporter-2 inhibitor

1. Sorli *et al. Lancet Diabetes Endocrinol* 2017;5:251–60; 2. Ahrén *et al. Lancet Diabetes Endocrinol* 2017;5:341–54; 3. Ahmann *et al. Diabetes Care* 2018;41:258–66; 4. Aroda *et al. Lancet Diabetes Endocrinol* 2017;5:355–66; 5. Rodbard *et al. J Clin Endo Metab* 2018;103:2291–301; 6. Marso *et al. N Engl J Med* 2016;375:1834–44; 7. Pratley *et al. Lancet Diabetes Endocrinol* 2018;6:275–86; 8. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT03136484; 9. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT03086330; 10. Capehorn M *et al. Diabetes UK Annual Conference.* 2019 (Abstract and poster P439)

# $HbA_{1c}$ changes in SUSTAIN 1–5 and 7

## CHANGE FROM BASELINE IN $HbA_{1c}$

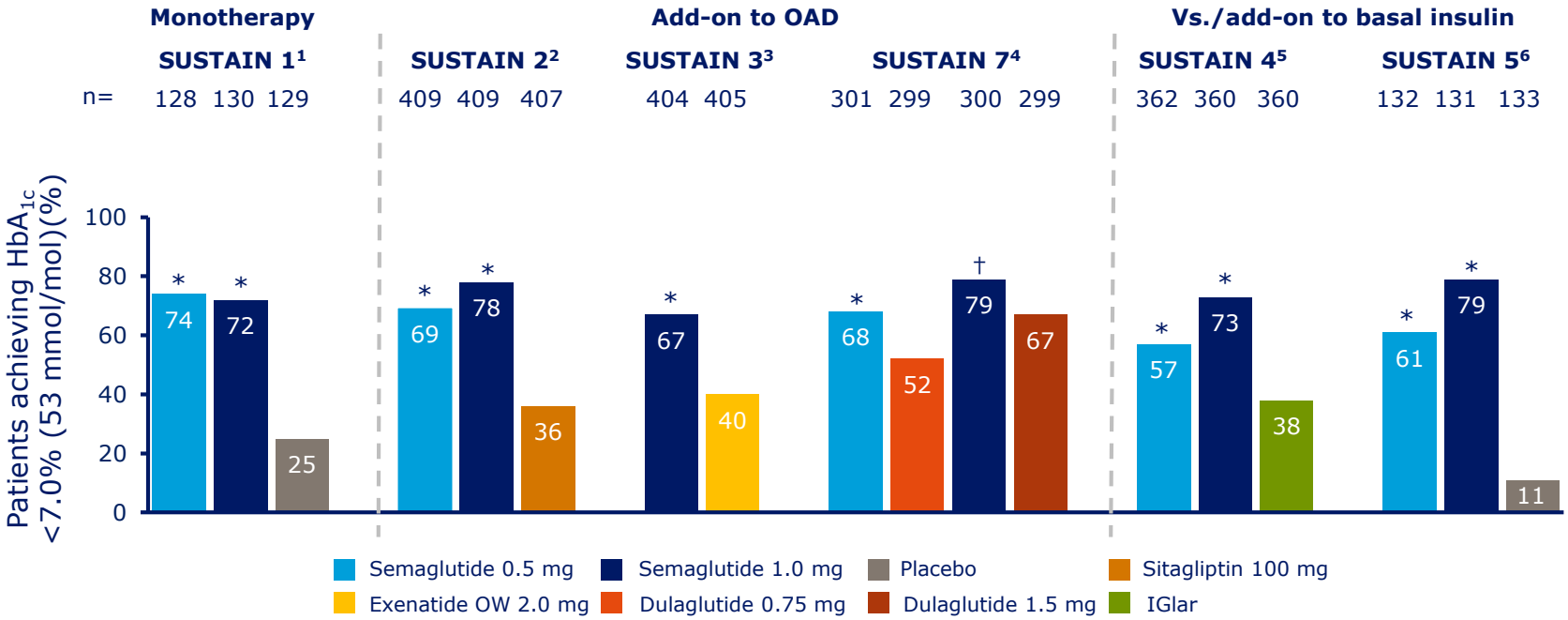



*$p$<0.0001 vs. comparator. IGlar, insulin glargine; OAD, oral antidiabetic drug; OW, once weekly

1. Sorli *et al. Lancet Diabetes Endocrinol* 2017;5:251–60; 2. Ahrén *et al. Lancet Diabetes Endocrinol* 2017;5:341–54; 3. Ahmann *et al. Diabetes Care* 2018;41:258–66; 4. Pratley *et al. Lancet Diabetes Endocrinol* 2018;6:275–86; 5. Aroda *et al. Lancet Diabetes Endocrinol* 2017;5:355–66; 6. Rodbard *et al. J Clin Endocrinol Metab* 2018;103:2291–301

# $HbA_{1c}$ changes in SUSTAIN 1–5 and 7

## PATIENTS ACHIEVING $HbA_{1c}$ <7.0% (53 mmol/mol)

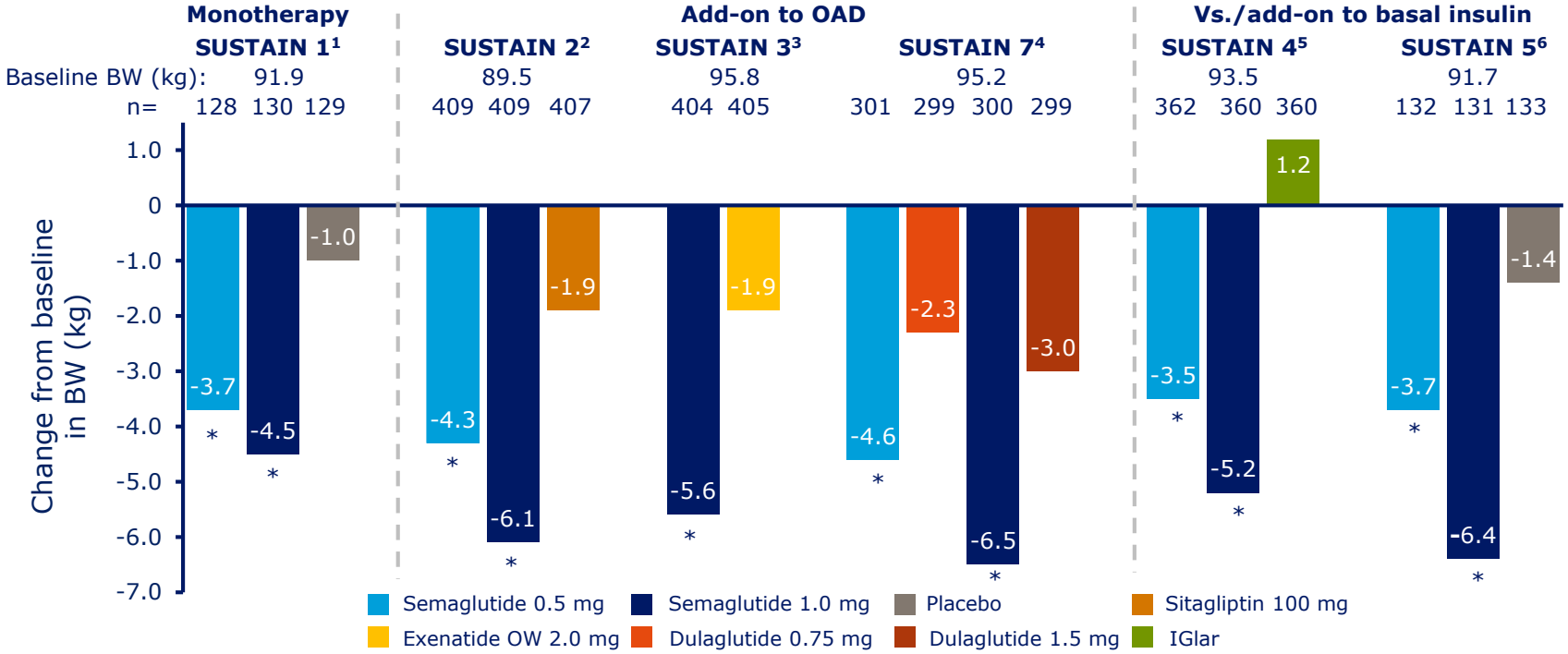



*$p$<0.0001 vs. comparator; †$p$<0.005 vs. comparator. Patients achieving $HbA_{1c}$ <7% was a secondary endpoint. IGlar, insulin glargine; OAD, oral antidiabetic drug; OW, once weekly

1. Sorli *et al. Lancet Diabetes Endocrinol* 2017;5:251–60; 2. Ahrén *et al. Lancet Diabetes Endocrinol* 2017;5:341–54; 3. Ahmann *et al. Diabetes Care* 2018;41:258–66; 4. Pratley *et al. Lancet Diabetes Endocrinol* 2018;6:275–86; 5. Aroda *et al. Lancet Diabetes Endocrinol* 2017;5:355–66; 6. Rodbard *et al. J Clin Endocrinol Metab* 2018;103:2291–301

# Body weight in SUSTAIN 1–5 and 7

## CHANGE FROM BASELINE IN BODY WEIGHT

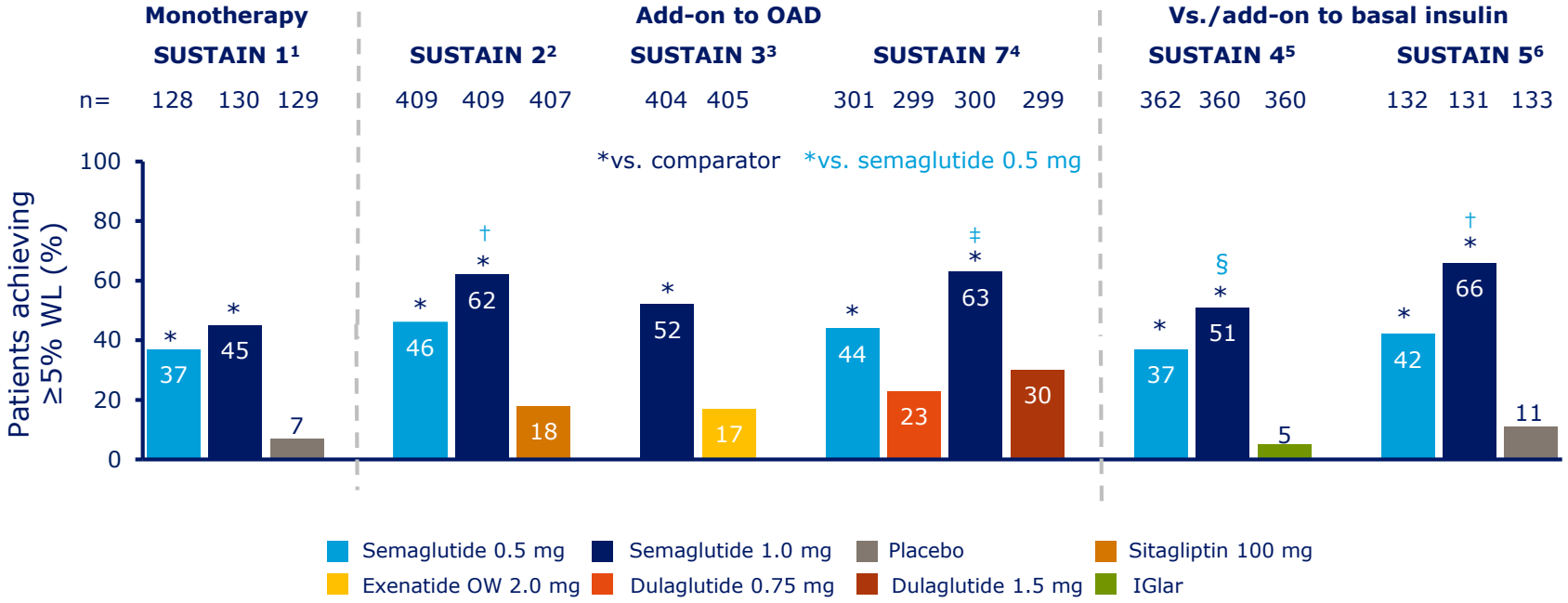



*$p$<0.0001 vs. comparator. Change from baseline in BW was a secondary endpoint. BW, body weight; IGlar, insulin glargine; OAD, oral antidiabetic drug; OW, once weekly

1. Sorli *et al. Lancet Diabetes Endocrinol* 2017;5:251–60; 2. Ahrén *et al. Lancet Diabetes Endocrinol* 2017;5:341–54; 3. Ahmann *et al. Diabetes Care* 2018;41:258–66; 4. Pratley *et al. Lancet Diabetes Endocrinol* 2018;6:275–86; 5. Aroda *et al. Lancet Diabetes Endocrinol* 2017;5:355–66; 6. Rodbard *et al. J Clin Endocrinol Metab* 2018;103:2291–301

# Body weight in SUSTAIN 1–5 and 7

## PATIENTS ACHIEVING ≥5% WEIGHT LOSS (%)

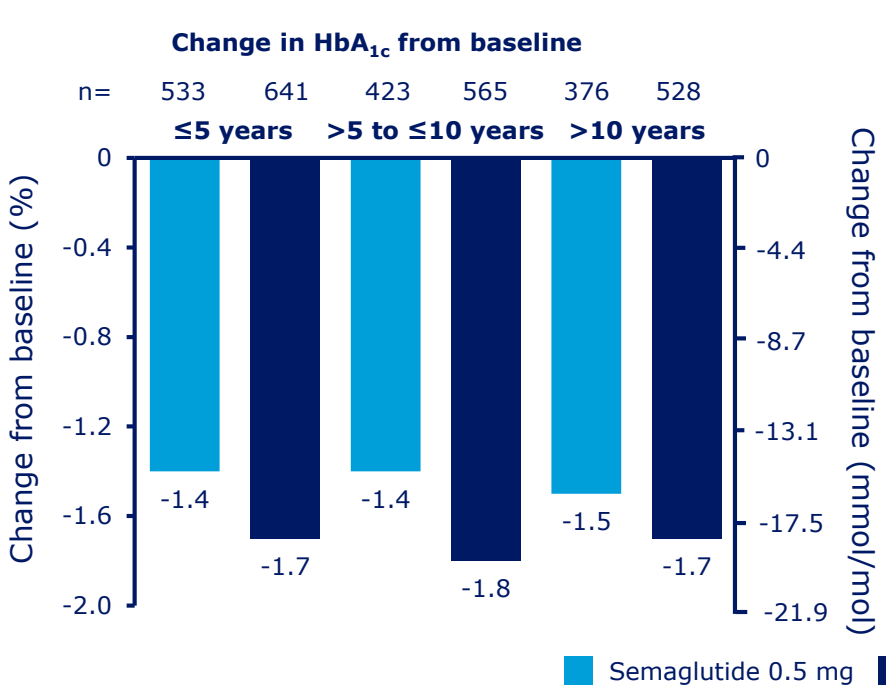


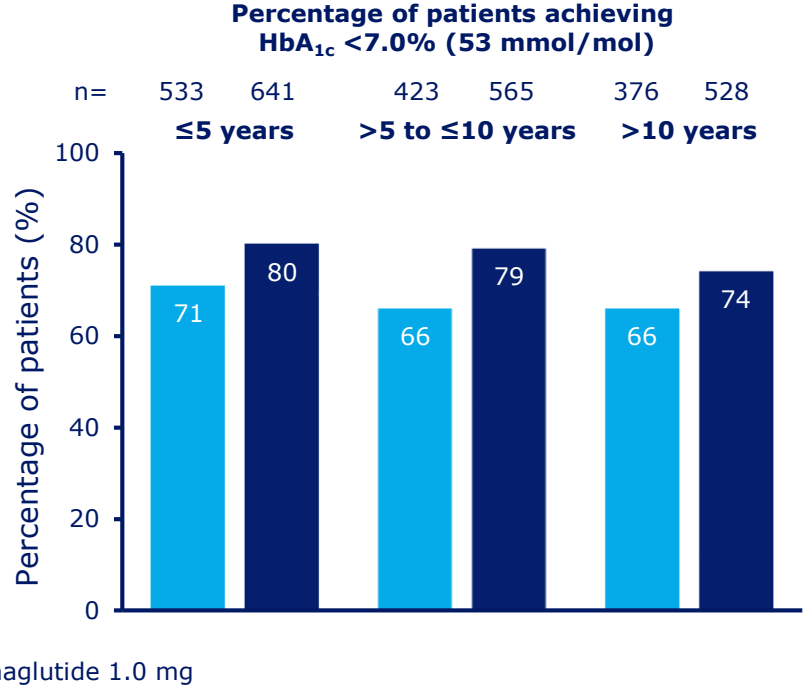

*$p$<0.0001 vs. comparator; †$p$<0.0001, ‡$p$=0.0003 and §$p$=0.002 vs. semaglutide 0.5 mg. *P*-values for semaglutide 0.5 mg vs. 1.0 mg from refs 7 and 8. Patients achieving ≥5% WL was a secondary endpoint. IGlar, insulin glargine; OAD, oral antidiabetic drug; OW, once weekly; WL, weight loss

1. Sorli *et al. Lancet Diabetes Endocrinol* 2017;5:251–60; 2. Ahrén *et al. Lancet Diabetes Endocrinol* 2017;5:341–54; 3. Ahmann *et al. Diabetes Care* 2018;41:258–66; 4. Pratley *et al. Lancet Diabetes Endocrinol* 2018;6:275–86; 5. Aroda *et al. Lancet Diabetes Endocrinol* 2017;5:355–66; 6. Rodbard *et al. J Clin Endocrinol Metab* 2018;103:2291–301

# Differences in glycaemic control by baseline diabetes duration

## SUSTAIN 1–5 and 7



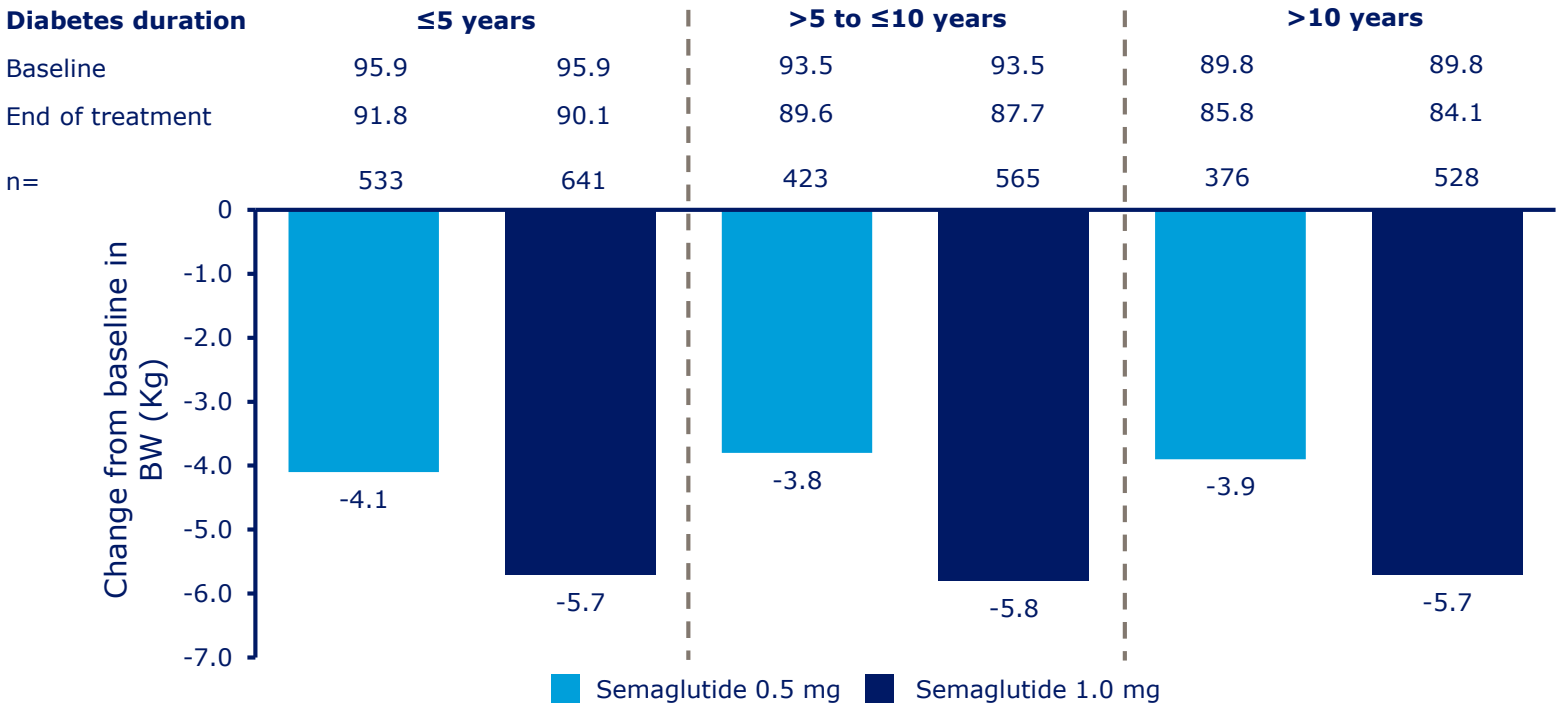




Semaglutide 0.5 mg Semaglutide 1.0 mg

Data presented are estimated change from baseline to week 30 or week 40 based on a meta-analysis of data from the six trials. n, number of subjects in the full analysis set
Adapted from: Rosenstock *et al. Diabetes* 2018; 67(Suppl. 1):A287 (abstract and poster 1081-P)

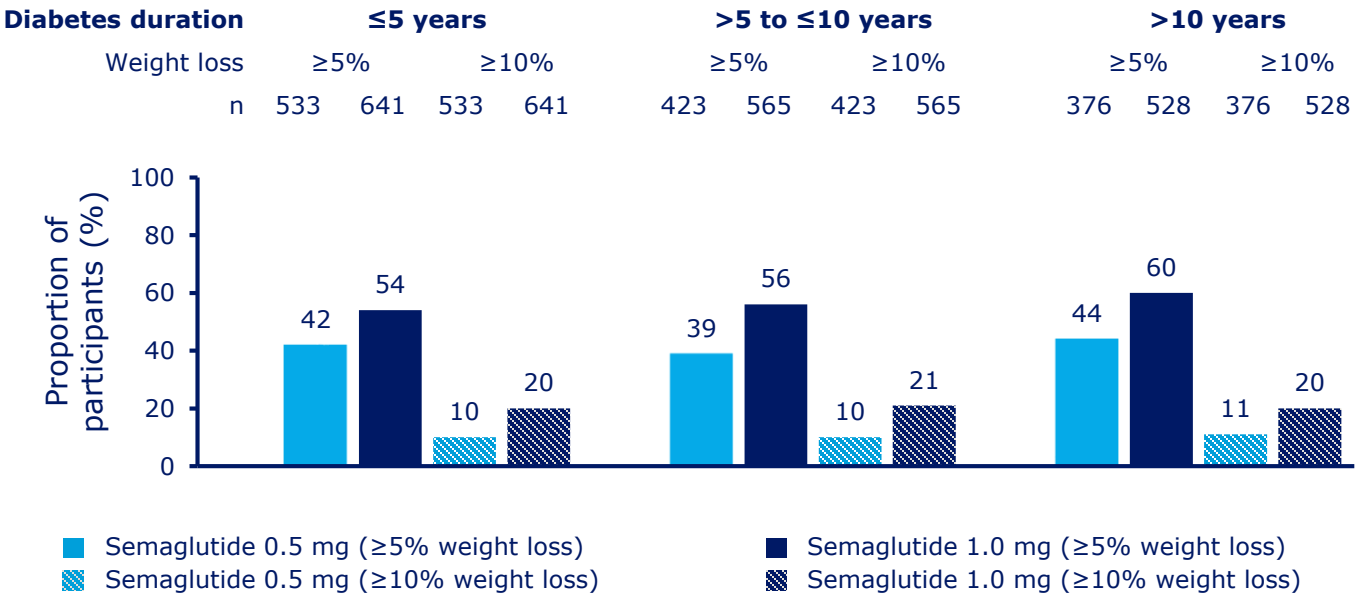
# Change in body weight by diabetes duration

## SUSTAIN 1–5 and 7




Data presented are estimated change from baseline to week 30 or week 40 based on a meta-analysis of data from the six trials. BW, body weight; n, number of subjects in the full analysis set
Adapted from: Rosenstock *et al. Diabetes* 2018; 67(Suppl. 1):A287 (abstract and poster 1081-P)

# Proportion of patients achieving ≥5% and ≥10% weight loss by baseline diabetes duration




Data presented are estimated change from baseline to week 30 or week 40 based on a meta-analysis of data from the six trials. n, number of subjects in the full analysis set
Adapted from: Rosenstock *et al. Diabetes* 2018; 67(Suppl. 1):A287 (abstract and poster 1081-P)

# AEs by baseline diabetes duration

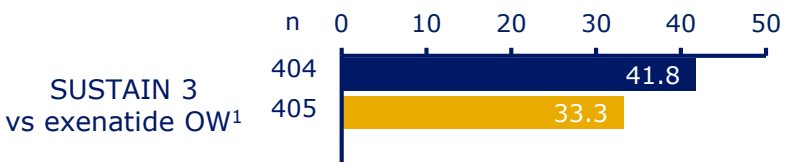
| | Semaglutide 0.5 mg n=1332 n (%) | | | Semaglutide 1.0 mg n=1734 n (%) | | |
|---|---|---|---|---|---|---|
| **Diabetes duration, years** | **≤5** | **>5 to ≤10** | **>10** | **≤5** | **>5 to ≤10** | **>10** |
| AEs (any grade) | 377 (70.4) | 292 (69.0) | 267 (71.0) | 439 (68.6) | 393 (69.5) | 391 (74.1) |
| Serious AEs | 32 (5.9) | 21 (4.9) | 31 (8.2) | 41 (6.4) | 44 (7.7) | 42 (8.1) |
| AEs leading to premature treatment discontinuation | 35 (6.7) | 31 (7.5) | 25 (6.7) | 50 (7.7) | 47 (8.3) | 51 (10.0) |
| Gastrointestinal AEs | 231 (43.3) | 170 (40.5) | 140 (37.4) | 262 (41.1) | 216 (38.2) | 238 (45.5) |

On-treatment data based on all patients randomised and exposed to at least one dose of trial product across SUSTAIN 1–5 and 7. %, proportion of patients with at least one event; AE, adverse event; n, number of patients in the safety analysis set

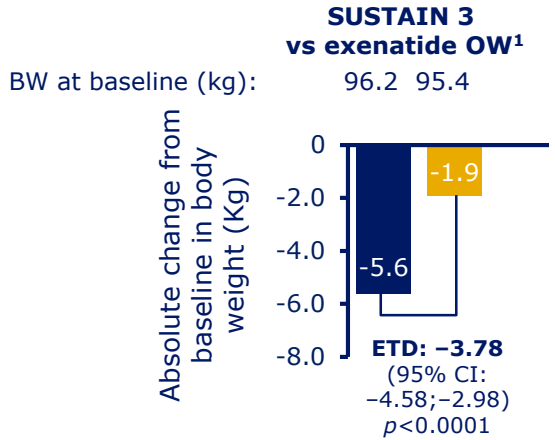
Adapted from: Rosenstock *et al. Diabetes* 2018; 67(Suppl. 1):A287 (abstract and poster 1081-P)

# Link between nausea/vomiting and weight loss with GLP-1RA therapy

**Overall GI AEs (%)**




**Absolute change in body weight from baseline[3]**




Semaglutide 0.5 mg
Semaglutide 1.0 mg
Dulaglutide 1.5 mg
Exenatide OW 2.0 mg
Dulaglutide 0.75 mg

For full safety information, please refer to each product's summary of product characteristics. AE, adverse event; BW, body weight; ETD, estimated treatment difference; GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist; OW, once weekly

Adapted from: Lingvay *et al. Diabetologia* 2018;61(Suppl. 1):S375 (abstract and poster 765)

1. Ahmann *et al. Diabetes Care* 2018;41:258–66; 2. Pratley *et al. Lancet Diabetes Endocrinol* 2018;6:275–86; 3. Lingvay *et al. Diabetologia* 2018;61(Suppl. 1):S375 (abstract and poster 765)

# SUSTAIN 1–5 and 7: summary

Does the efficacy of semaglutide differ across people with different disease duration?

No, semaglutide consistently reduced $HbA_{1c}$ and BW regardless of diabetes duration

Is the effect of semaglutide on weight loss mediated by nausea or vomiting?

No, superior weight loss is due to direct effects of semaglutide rather than nausea or vomiting

BW, body weight

# Agenda

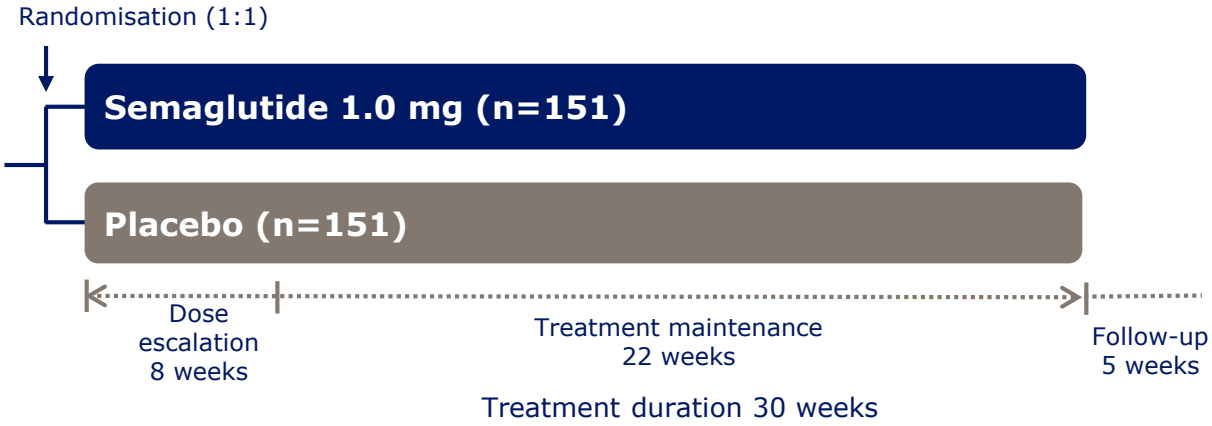
1. SUSTAIN 1–5 and 7 outcomes, including by baseline disease duration
2. Recently published data: SUSTAIN 9 & 10
3. SUSTAIN 6 by baseline CV risk
4. Q&As

CV, cardiovascular

# SUSTAIN 9: trial design

**302 patients with T2D**

- Age ≥18 years
- $HbA_{1c}$ 7.0–10.0% (53 – 86 mmol/mol)
- Stable treatment (90 days) with SGLT-2 inhibitor ± MET or SU
- eGFR ≥60 mL/min/1.73 $m^2$




**Trial information**

- Randomised, double-blind, placebo-controlled, parallel-group, multinational trial
- Semaglutide/placebo fixed dose escalation from starting dose of 0.25 mg for 4 weeks, followed by 0.5 mg for 4 weeks then 1.0 mg ie., the maintenance dose was achieved

eGFR, estimated glomerular filtration rate; MET, metformin; SGLT-2, sodium–glucose cotransporter-2; SU, sulphonylurea.

Zinman B et al. *Lancet Diabetes Endocrinol* 2019;7;5:356-367

# SUSTAIN 9: baseline characteristics

| | Semaglutide 1.0 mg (n=151) | Placebo (n=151) | Total (N=302) |
|---|---|---|---|
| Age (years) | 57.5 (8.9) | 56.6 (10.1) | 57.0 (9.5) |
| Male gender, n (%) | 89 (58.9) | 87 (57.6) | 176 (58.3) |
| $HbA_{1c}$ (%) | 8.0 (0.8) | 8.1 (0.8) | 8.0 (0.8) |
| $HbA_{1c}$ (mmol/mol)* | 64.1 (8.8) | 64.5 (9.1) | 64.3 (9.0) |
| FPG (mmol/L) | 9.1 (2.1) | 8.9 (2.2) | 9.0 (2.1) |
| Diabetes duration (years) | 9.8 (6.3) | 9.6 (5.9) | 9.7 (6.1) |
| Body weight (kg) | 89.6 (19.5) | 93.8 (22.3) | 91.7 (21.0) |
| Systolic blood pressure (mmHg) | 127.2 (14.0) | 128.6 (15.0) | 127.9 (14.5) |
| Diastolic blood pressure (mmHg) | 77.8 (8.0) | 79.9 (9.5) | 78.8 (8.8) |
| eGFR, mL/min/1.73 $m^{2\dagger}$ | 94.5 (15.3) | 96.0 (15.1) | 95.2 (15.2) |

Values are mean (SD) for the full analysis set, unless otherwise stated. *Calculated from percentage values by multiplying by 10.93 and subtracting 23.50.
Zinman B et al. *Lancet Diabetes Endocrinol* 2019;7;5:356-367

# SUSTAIN 9: baseline characteristics

| | Semaglutide 1.0 mg (n=151) | Placebo (n=151) | Total (N=302) |
|---|---|---|---|
| Anti-diabetes medication at screening, n (%) | | | |
| SGLT-2 inhibitor§ | 150 (99.3) | 151 (100) | 301 (99.7) |
| Metformin | 106 (70.2) | 110 (72.8) | 216 (71.5) |
| Sulphonylurea | 19 (12.6) | 20 (13.2) | 39 (12.9) |
| Diabetes complications, n (%) | | | |
| Diabetic retinopathy* | 13 (8.6) | 25 (16.6) | 38 (12.6) |
| Proliferative* | 1 (0.7) | 0 | 1 (0.3) |
| Non-proliferative | 12 (7.9) | 25 (16.6) | 37 (12.3) |

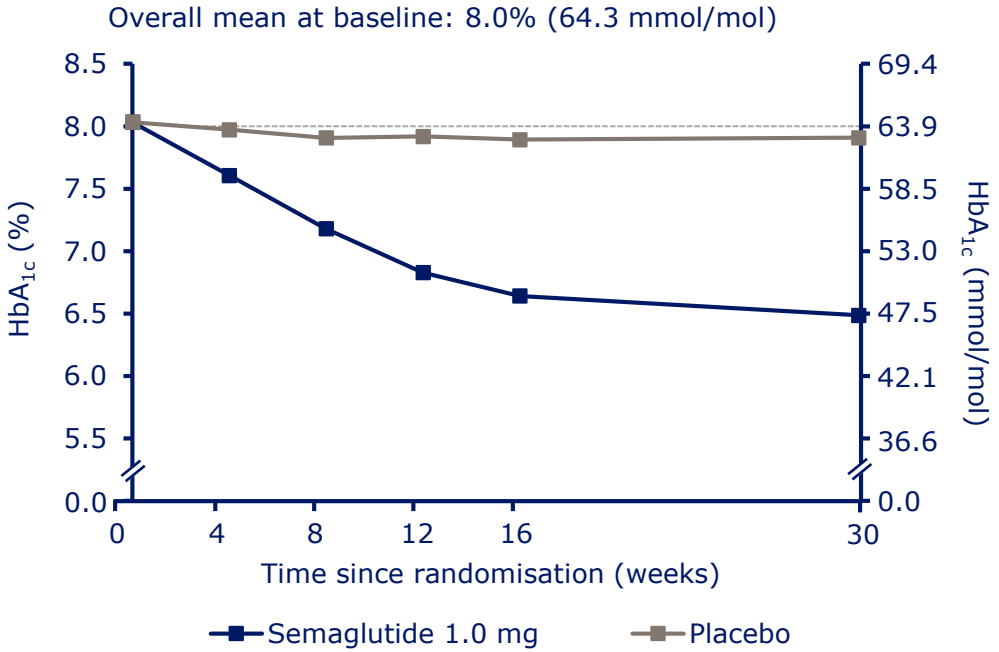
§Includes 68 patients on canagliflozin, 106 on dapagliflozin, 102 on empagliflozin, and 25 on other SGLT-2 inhibitors available only in Japan.

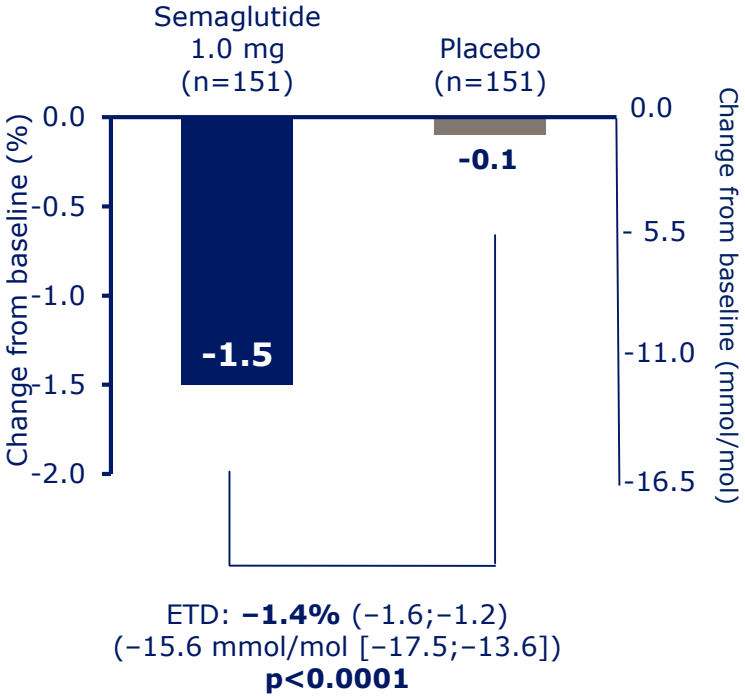
*Patients with proliferative retinopathy or maculopathy requiring acute treatment, verified by fundus photography or dilated fundoscopy within 90 days before randomisation, was an exclusion criterion.

SD, standard deviation; SGLT-2, sodium–glucose cotransporter-2.

Zinman B et al. *Lancet Diabetes Endocrinol* 2019;7;5:356-367

# SUSTAIN 9: change in $HbA_{1c}$ – primary endpoint

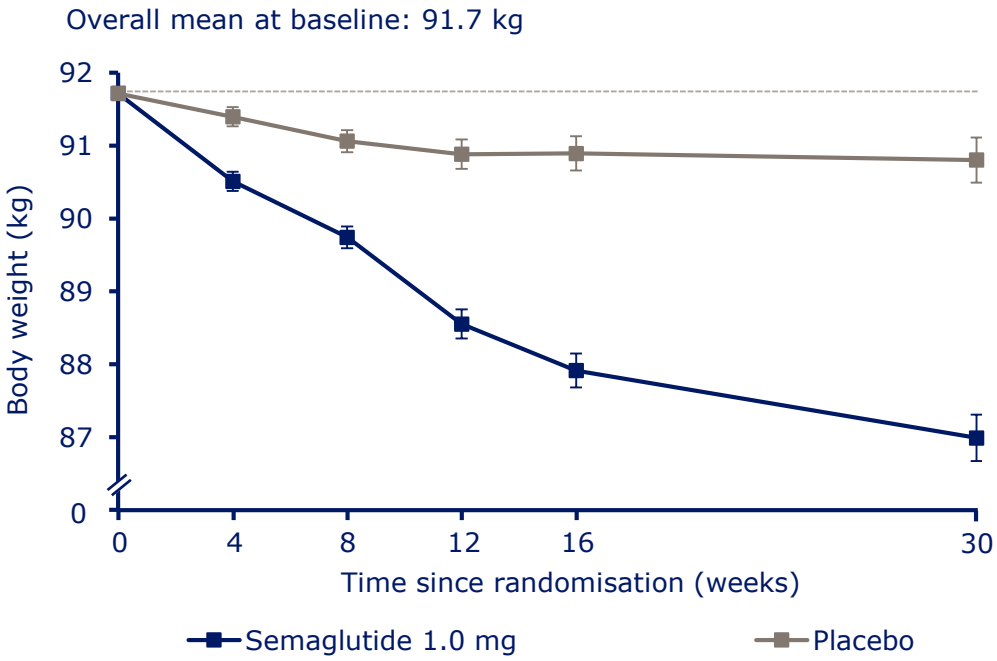


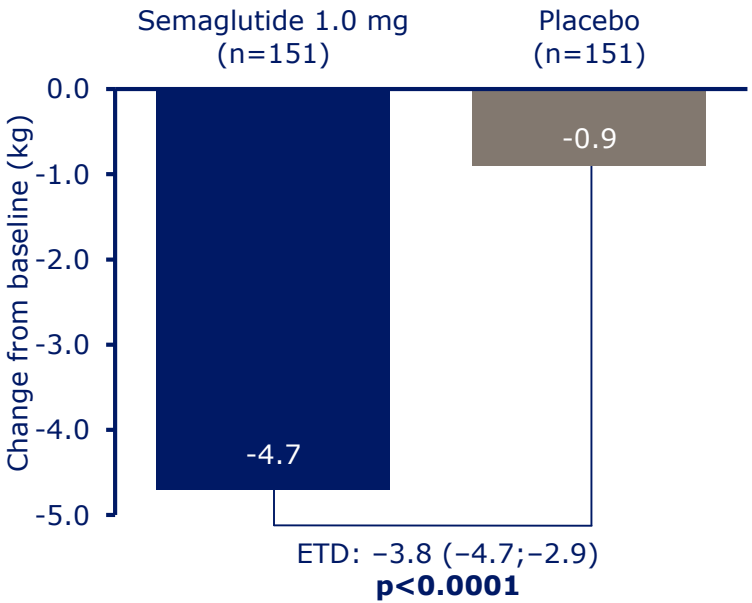




ETD, estimated treatment difference.

Zinman B et al. *Lancet Diabetes Endocrinol* 2019;7;5:356-367

# SUSTAIN 9: body weight

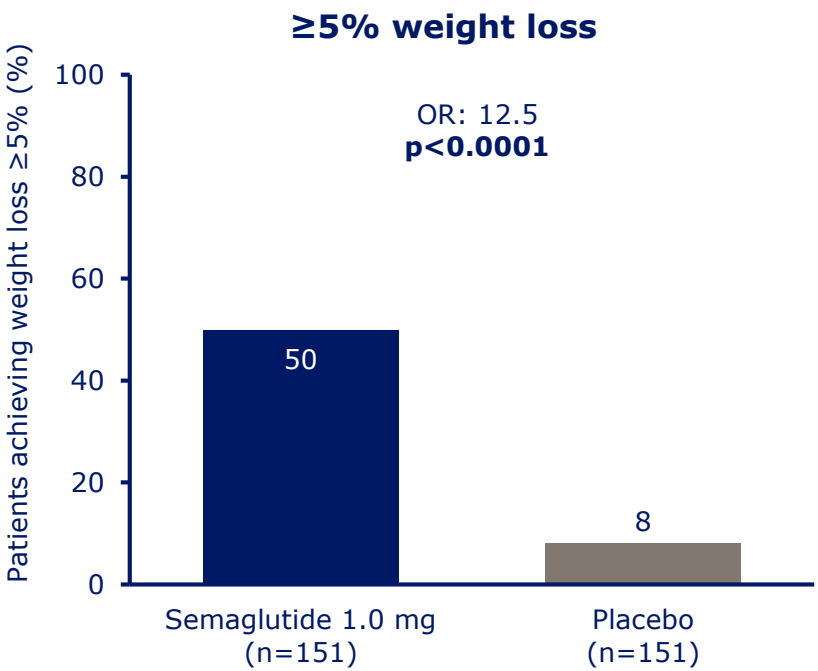


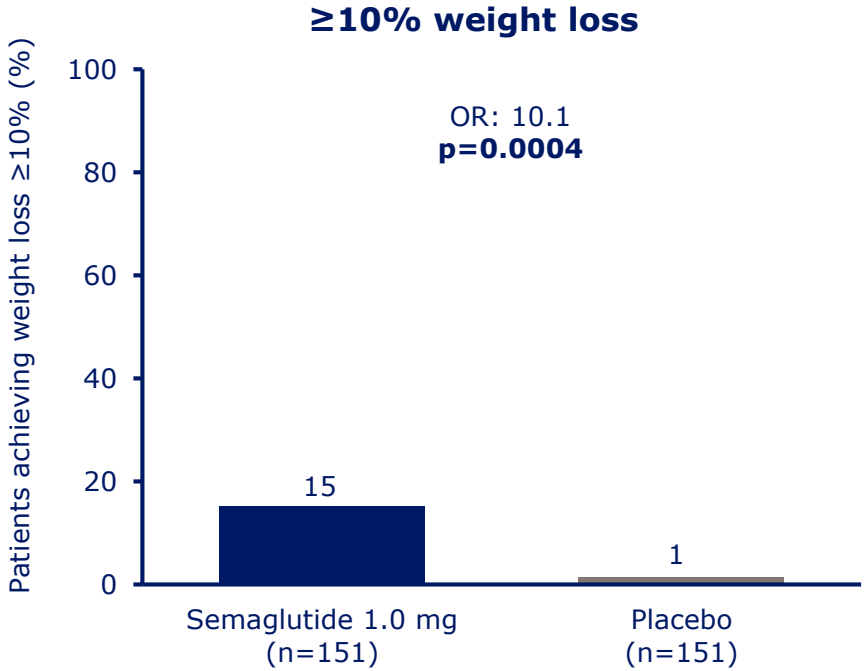




ETD, estimated treatment difference.

Zinman B et al. *Lancet Diabetes Endocrinol* 2019;7;5:356-367

# SUSTAIN 9: weight-loss responses




Zinman B et al. *Lancet Diabetes Endocrinol* 2019;7;5:356-367

# SUSTAIN 9: adverse events of clinical interest

| Adverse event | Semaglutide 1.0 mg (n=150) | | | Placebo (n=151) | | |
|---|---|---|---|---|---|---|
| | n (%) | No. of events | Event rate/100 years of exposure | n (%) | No. of events | Event rate/100 years of exposure |
| Hypoglycaemia† | 17 (11.3) | 28 | 30.3 | 3 (2.0) | 4 | 4.2 |
| Severe or blood glucose-confirmed hypoglycaemia | 4 (2.7) | 4 | 4.3 | 0 | – | – |
| Diabetic retinopathy* | 3 (2.0) | 3 | 3.2 | 8 (5.3)‡ | 10 | 10.4 |
| Neoplasms | 4 (2.7) | 4 | 4.0 | 4 (2.6) | 5 | 4.9 |
| Acute renal failure | 1 (0.7) | 1 | 1.1 | 0 | – | – |
| Hypovolaemia | 0 | – | – | 1 (0.7) | 1 | 1.0 |
| Urinary tract infection | 3 (2.0) | 3 | 3.2 | 0 | – | – |
| AEs potentially leading to lower limb amputation§ | 6 (4.0) | 7 | 7.6 | 3 (2.0) | 3 | 3.1 |

*Patients with proliferative retinopathy or maculopathy requiring acute treatment, verified by fundus photography or dilated fundoscopy within 90 days before randomisation, was an exclusion criterion. †ADA classified, including hypoglycaemia episodes classified as severe, documented symptomatic, asymptomatic, probable symptomatic and pseudo-hypoglycaemia.
‡Includes two patients with established diabetic retinopathy at baseline. §Diabetic neuropathy, hypoaesthesia, occlusive peripheral arterial disease, osteonecrosis, paraesthesia, and peripheral neuropathy. This was a predefined Medical Dictionary for Regulatory Activities search.
Zinman B et al. *Lancet Diabetes Endocrinol* 2019;7;5:356-367

# Conclusion:

The addition of semaglutide 1.0 mg appears to be an effective, well tolerated option for patients who have not met their therapeutic goals despite treatment with an SGLT-2 inhibitor

*Stable treatment with SGLT-2 inhibitor was defined as having started SGLT-2 inhibitor treatment at least 90 days before screening.

OAD, oral antidiabetes drug; SGLT-2, sodium–glucose cotransporter-2.

Zinman B et al. *Lancet Diabetes Endocrinol* 2019;7;5:356-367

# SUSTAIN 10

## Efficacy and safety of semaglutide 1.0mg once weekly vs liraglutide 1.2mg once daily as add-on to 1–3 oral antidiabetic drugs in subjects with T2D

Capehorn et al. *Diabetes UK Annual Conference* 2019;P439

# Introduction

- The aim of the SUSTAIN 10 trial was to compare the efficacy and safety of semaglutide vs liraglutide in adults with T2D in an European setting

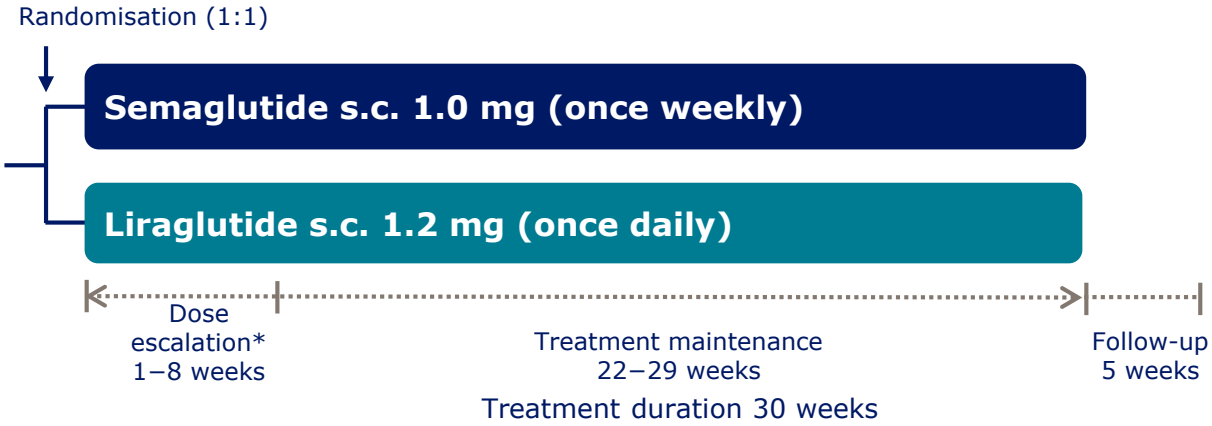
- To reflect the real-world setting, semaglutide 1.0 mg was compared with liraglutide 1.2 mg, which is the most frequently prescribed dose in Europe

Capehorn *et al.* Diabetes UK Professional Conference. 6–8 March 2019, Liverpool, UK (abstract and poster P439)

# Trial design

**577 patients with T2D**

- Age ≥18 years
- $HbA_{1c}$ 53–97 mmol/mol (7.0–11.0%)
- Stable dose of 1–3 OADs (MET ± SU ± SGLT-2i)
- eGFR ≥30 mL/min/1.73 $m^2$




**Trial information**

- Open-label, parallel-group, multicentre trial
- Conducted in 11 European countries
- Randomisation was stratified by background medication of SU ± MET, SGLT-2i ± MET, SU and SGLT-2i ± MET, or MET monotherapy

*Semaglutide dose escalation: from starting dose of 0.25 mg, dose doubled every 4 weeks until trial maintenance dose achieved. Liraglutide dose escalation: from starting dose of 0.6 mg, dose doubled to 1.2 mg after 1 week, except in cases of GI AEs, where escalation could be extended over 2 weeks. AE, adverse event; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; MET, metformin; OAD, oral antidiabetic drug; s.c., subcutaneous; SGLT-2i, sodium–glucose co-transporter-2 inhibitor; SU, sulphonylurea

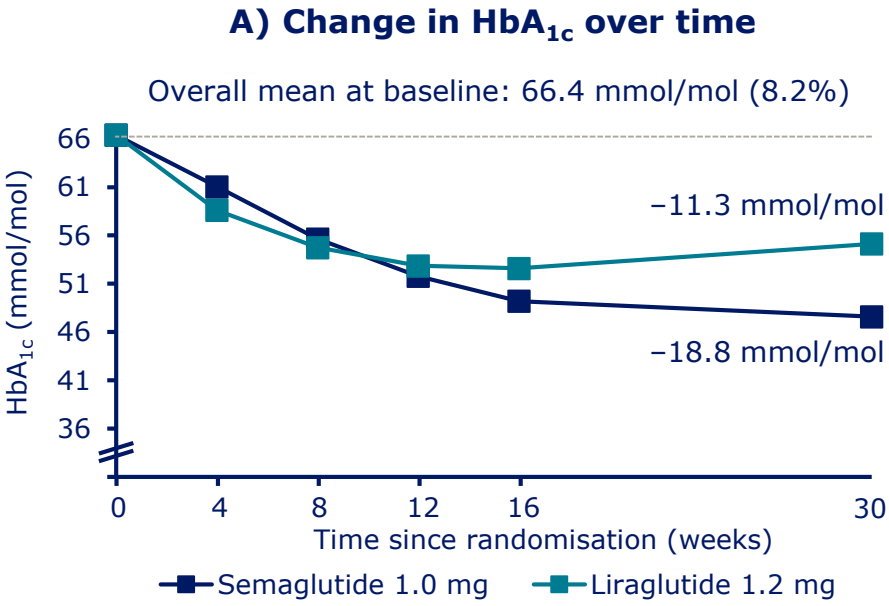
Adapted from Capehorn *et al.* Diabetes UK Professional Conference. 6–8 March 2019, Liverpool, UK (abstract and poster P439)

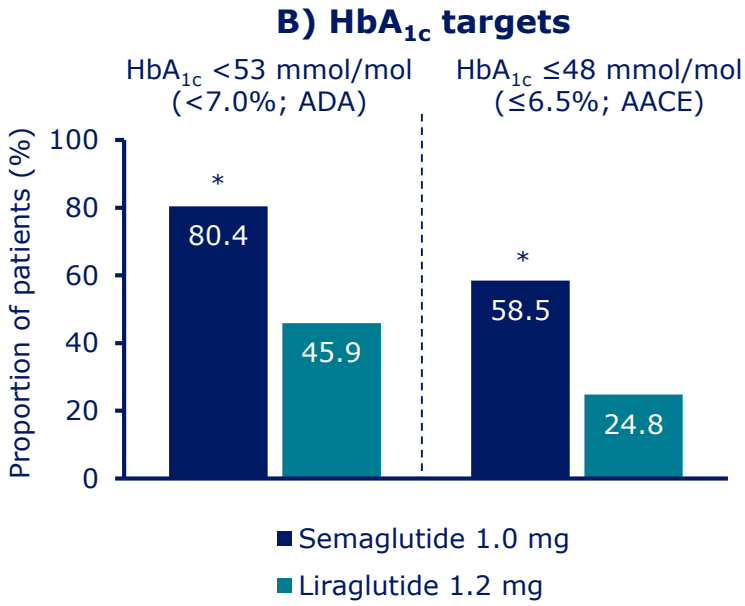
# Baseline characteristics

| | Semaglutide 1.0 mg<br>Mean [min.; max.] | Liraglutide 1.2 mg<br>Mean [min.; max.] | Total<br>Mean [min.; max.] |
|---|---|---|---|
| Age (years) | 60.1 [29; 86] | 58.9 [31; 84] | 59.5 [29; 86] |
| $HbA_{1c}$ (mmol/mol) | 66.0 [47.5; 102.2] | 66.8 [48.6; 95.6] | 66.4 [47.5; 102.2] |
| FPG (mmol/L) | 9.8 [5.3; 19.0] | 9.9 [5.4; 19.3] | 9.9 [5.3; 19.3] |
| Diabetes duration (years) | 9.6 [0.4; 33.1] | 8.9 [0.4; 31.9] | 9.3 [0.4; 33.1] |
| Body weight (kg) | 96.6 [53.3; 190.7] | 97.2 [50.0; 178.0] | 96.9 [50.0; 190.7] |
| BMI ($kg/m^2$) | 33.7 [22.1; 54.1] | 33.7 [20.5; 58.1] | 33.7 [20.5; 58.1] |

Randomised patients
BMI, body mass index; FPG, fasting plasma glucose; max., maximum; min., minimum
Adapted from Capehorn *et al.* Diabetes UK Professional Conference. 6–8 March 2019, Liverpool, UK (abstract and poster P439)

# Glycaemic control



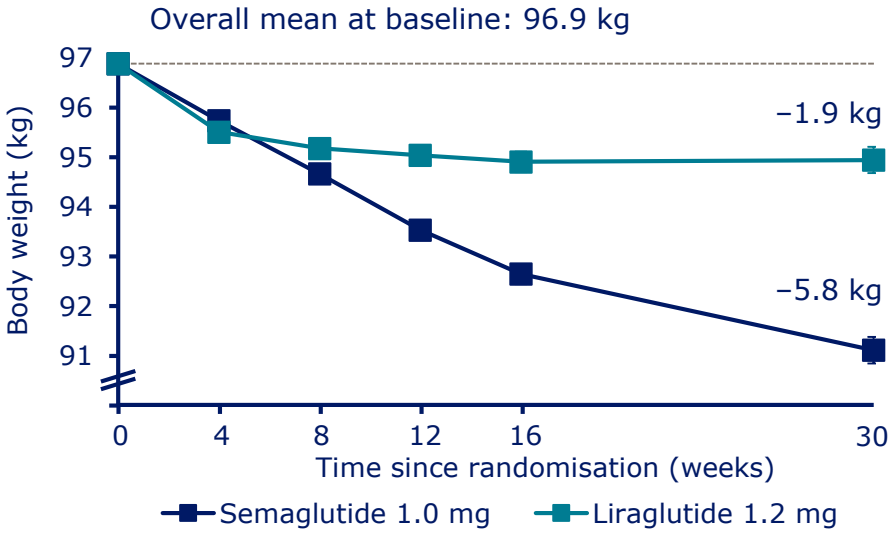

*$p$<0.0001 vs liraglutide 1.2 mg. All figures based on the full analysis set. **Fig. A**. 'On-treatment without rescue medication' data. Mean estimates are from an ANCOVA where missing data were accounted for using multiple imputation (data from patients within the same group defined by randomised treatment). Error bars are ± standard errors of the means. Dashed line indicates the overall average value at baseline. **Fig. B**. 'On-treatment without rescue medication' data, with missing data multiple-imputed using observed data from patients within the same group defined by randomised treatment. After imputation continuous data are dichotomised

AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; ANCOVA, analysis of covariance

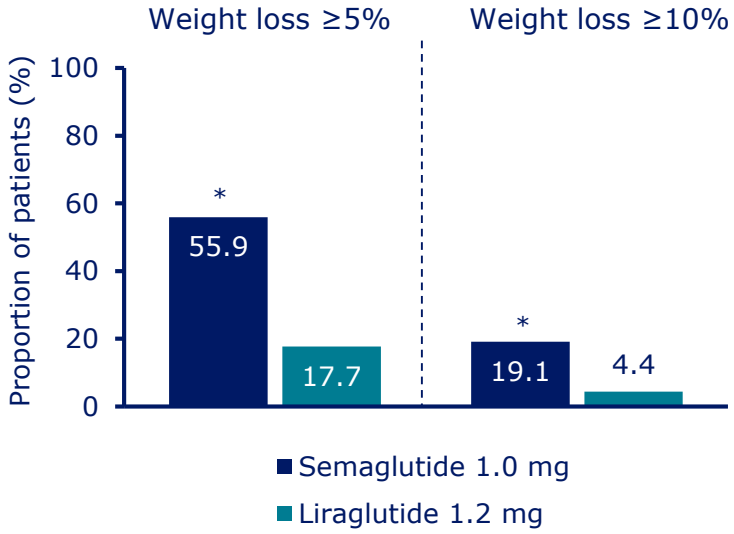
Adapted from Capehorn *et al.* Diabetes UK Professional Conference. 6–8 March 2019, Liverpool, UK (abstract and poster P439)

# Body weight

## A) Change in body weight over time



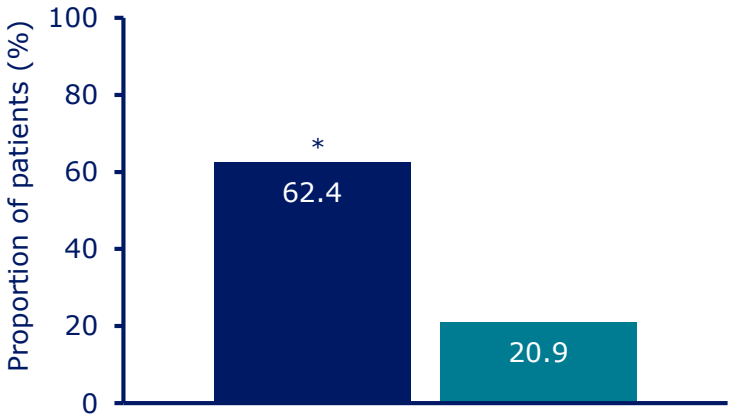

## B) Weight-loss responses



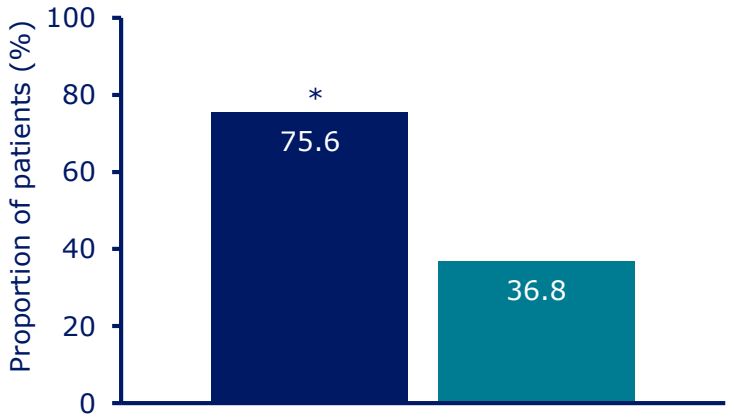

*$p$<0.0001 vs liraglutide 1.2 mg. All figures based on the full analysis set. **Fig. A**. 'On-treatment without rescue medication' data. Mean estimates are from an ANCOVA where missing data were accounted for using multiple imputation (data from patients within the same group defined by randomised treatment). Error bars are ± standard errors of the means. Dashed line indicates the overall average value at baseline. **Fig. B**. 'On-treatment without rescue medication' data, with missing data multiple-imputed using observed data from patients within the same group defined by randomised treatment. After imputation continuous data are dichotomised. All site visits, except screening visits, were to be completed in fasting state
ANCOVA, analysis of covariance
Adapted from Capehorn *et al.* Diabetes UK Professional Conference. 6–8 March 2019, Liverpool, UK (abstract and poster P439)

# Composite endpoints

## $HbA_{1c}$ reduction ≥11 mmol/mol (≥1%) and weight loss ≥3%




## $HbA_{1c}$ <53 mmol/mol (<1%) without weight gain and without severe or BG-confirmed symptomatic hypoglycaemia




■ Semaglutide 1.0 mg ■ Liraglutide 1.2 mg

*$p$<0.0001 vs liraglutide 1.2 mg. All figures based on the full analysis set. 'On-treatment without rescue medication' data, with missing data multiple-imputed ($HbA_{1c}$ and body weight data imputed separately for composite endpoints) using observed data from patients within the same group defined by randomised treatment. After imputation continuous data are dichotomised. All site visits, except screening visits, were to be completed in fasting state. BG, blood glucose

Adapted from Capehorn *et al.* Diabetes UK Professional Conference. 6–8 March 2019, Liverpool, UK (abstract and poster P439)

# Adverse events

| | Semaglutide 1.0 mg | | | | Liraglutide 1.2 mg | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| GI disorders* | **127** | **(43.9)** | **315** | **173.9** | **110** | **(38.3)** | **219** | **119.7** |
| Nausea | 63 | (21.8) | 89 | 49.1 | 45 | (15.7) | 54 | 29.5 |
| Diarrhoea | 45 | (15.6) | 56 | 30.9 | 35 | (12.2) | 44 | 24.0 |
| Vomiting | 30 | (10.4) | 44 | 24.3 | 23 | (8.0) | 33 | 18.0 |
| Constipation | 17 | (5.9) | 17 | 9.4 | 10 | (3.5) | 13 | 7.1 |
| Abdominal pain | 15 | (5.2) | 18 | 9.9 | 6 | (2.1) | 6 | 3.3 |

- Severe or BG-confirmed symptomatic hypoglycaemia was experienced by 1.7% of patients (n=5; 8 events) in the semaglutide group and 2.4% of patients (n=7; 8 events) in the liraglutide group; no patient in either group experienced severe hypoglycaemic episodes (ADA definition)*
- Of the 16 episodes of severe or BG-confirmed symptomatic hypoglycaemia, 15 were in patients receiving background SU

*The GI AEs listed here are those experienced by ≥5% of patients in at least one of the treatment arms. 'On-treatment' data based on the safety analysis set. Please refer to the Summary of Product Characteristics for full safety information. *Severe hypoglycaemia was defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. %, percentage of patients experiencing at least one event; ADA, American Diabetes Association; AE, adverse event; BG, blood glucose; E, number of events; GI, gastrointestinal; N, number of patients experiencing at least one event; R, event rate per 100 exposure-years; SU, sulphonylurea
Adapted from Capehorn *et al.* Diabetes UK Professional Conference. 6–8 March 2019, Liverpool, UK (abstract and poster P439)

# Conclusions

- Semaglutide 1.0 mg was superior to liraglutide 1.2 mg in reducing $HbA_{1c}$ and body weight
- Safety profiles were generally similar with semaglutide vs liraglutide, except for higher rates of GI AEs with semaglutide, and were consistent with those observed in other trials[1–13]
- Semaglutide is an effective and well-tolerated GLP-1RA, with a low risk of hypoglycaemia, for the treatment of adults with T2D

AE, adverse event; GI, gastrointestinal, GLP-1RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes

1. Sorli *et al. Lancet Diabetes Endocrinol* 2017;5:251–60; 2. Ahrén *et al. Lancet Diabetes Endocrinol* 2017;5:341–54; 3. Ahmann *et al. Diabetes Care* 2018;41:258–66; 4. Aroda *et al. Lancet Diabetes Endocrinol* 2017;5:355–66; 5. Rodbard *et al. J Clin Endocrinol Metab* 2018;103:2291–301; 6. Pratley *et al. Lancet Diabetes Endocrinol* 2018;6:275–86; 7. Garber *et al. Lancet* 2009;373:473–81; 8. Marre *et al. Diabet Med* 2009;26:268–78; 9. Nauck *et al. Diabetes Care* 2009;32:84–90; 10. Zinman *et al. Diabetes Care* 2009;32:1224–30; 11. Russell-Jones *et al. Diabetologia* 2009;52:2046–55; 12. Buse *et al. Lancet* 2009;374:39–47; 13. Pratley *et al. Lancet* 2010;375:1447–56
Capehorn *et al.* Diabetes UK Professional Conference. 6–8 March 2019, Liverpool, UK (abstract and poster P439)

# Agenda

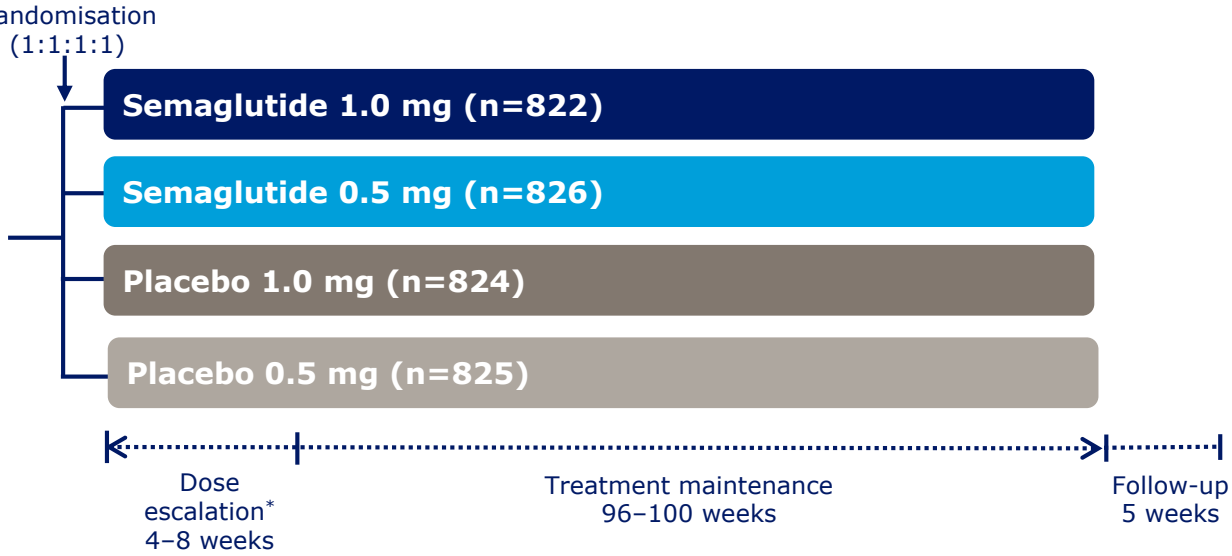
1. SUSTAIN 1–5 and 7 outcomes, including by baseline disease duration
2. Recently published data: SUSTAIN 9 & 10
3. SUSTAIN 6 by baseline CV risk
4. Q&As

CV, cardiovascular

# SUSTAIN 6: CV outcomes trial design

**3297 patients with T2D**

- $HbA_{1c}$ ≥7.0%
- Previously on 0–2 OADs, basal or premix insulin ± 0–2 OADs
- Age ≥50 years with established CVD (prior cardio-, cerebro- or peripheral vascular disease, CHF [NYHA class II–III]), CKD stage 3 or worse or age ≥60 years with at least one CV risk factor




**Trial information**

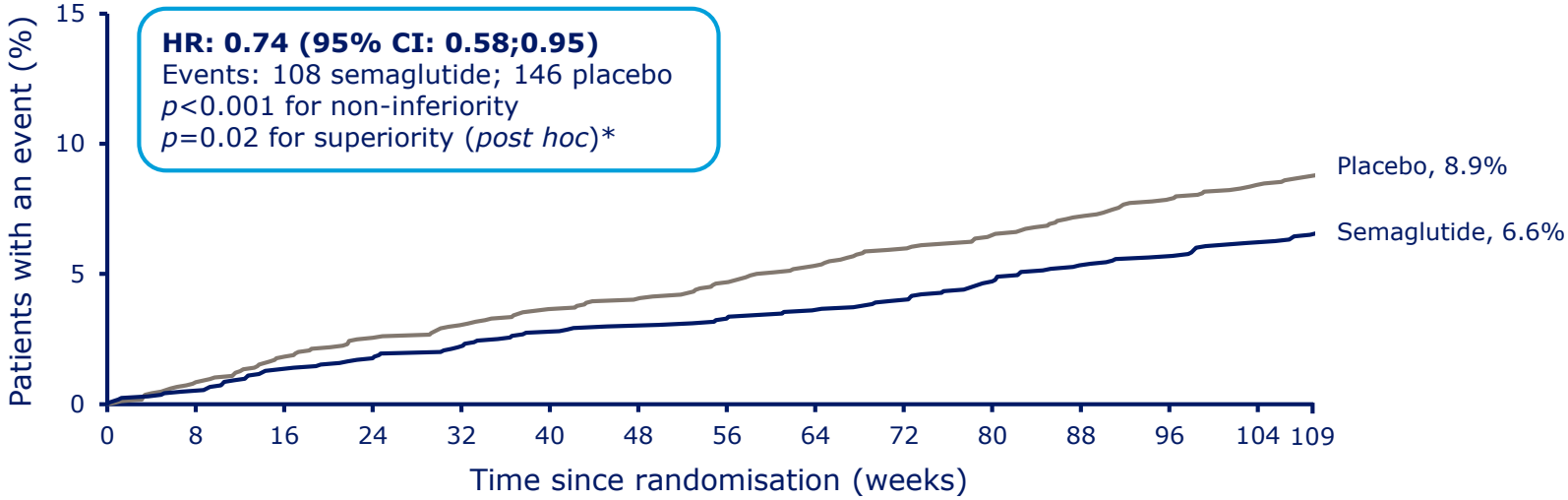
- Randomised, double-blind, placebo-controlled, multicentre, multinational, four-armed trial
- Additional glucose-lowering medication could be added to achieve glycaemic control at the discretion of the investigator

*Starting dose 0.25 mg, dose doubled every 4 weeks until maintenance dose achieved. CHF, chronic heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; NYHA, New York Heart Association; OAD, oral antidiabetic drug

Adapted from: Marso *et al. N Engl J Med* 2016;375:1834–44

# SUSTAIN 6: primary outcome

## TIME TO FIRST OCCURRENCE OF CV DEATH, NONFATAL MI OR NONFATAL STROKE




**Number of patients at risk**

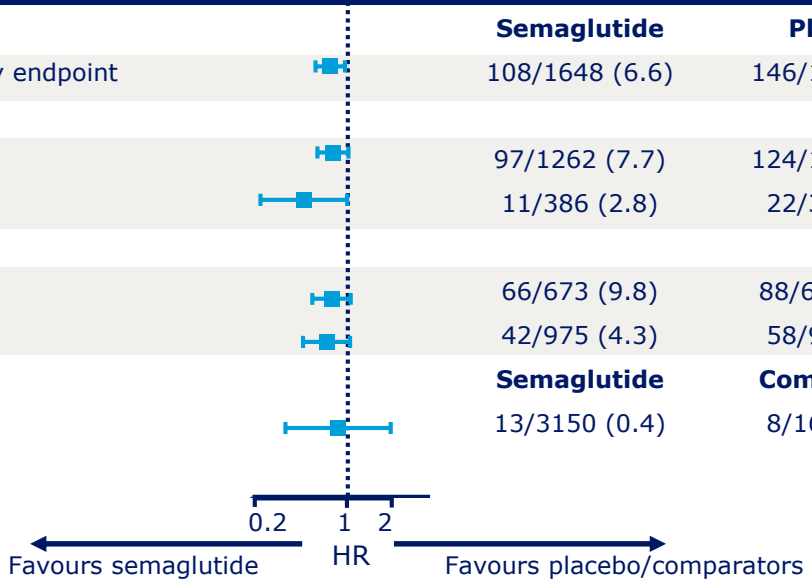
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Semaglutide** | **1648** | **1619** | **1601** | **1584** | **1568** | **1543** | **1524** | **1513** |
| **Placebo** | **1649** | **1616** | **1586** | **1567** | **1534** | **1508** | **1479** | **1466** |

*Not prespecified. Kaplan–Meier plot for first event adjudication committee-confirmed MACE (CV death, nonfatal MI or nonfatal stroke) using 'in-trial' data from subjects in the full analysis set
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction
Adapted from: Marso *et al. N Engl J Med* 2016;375:1834–44

# SUSTAIN 6/phase 3a trials

## RISK OF MACE AND BASELINE CV RISK ANALYSIS

| | No. of participants with an event/total no. of participants (%) | | HR (95% CI) | Interaction *P*-value |
|---|---|---|---|---|
| **SUSTAIN 6** | **Semaglutide** | **Placebo** | | |
| Prespecified analysis: primary endpoint | 108/1648 (6.6) | 146/1649 (8.9) | 0.74 (0.58;0.95) | N/A |
| *Post hoc* analysis: | | | | |
| Established CV disease | 97/1262 (7.7) | 124/1271 (9.8) | 0.78 (0.60;1.01) | 0.2219* |
| CV risk factors | 11/386 (2.8) | 22/378 (5.8) | 0.48 (0.23;0.99) | |
| ***Post hoc* analysis:** | | | | |
| Prior MI/stroke | 66/673 (9.8) | 88/694 (12.7) | 0.76 (0.55;1.05) | 0.7541* |
| No prior MI/stroke | 42/975 (4.3) | 58/955 (6.1) | 0.70 (0.47;1.04) | |
| **SUSTAIN phase 3a trials** | **Semaglutide** | **Comparators** | | |
| *Post hoc* meta-analysis‡ | 13/3150 (0.4) | 8/1657 (0.5) | 0.85 (0.35;2.06) | 0.7258† |

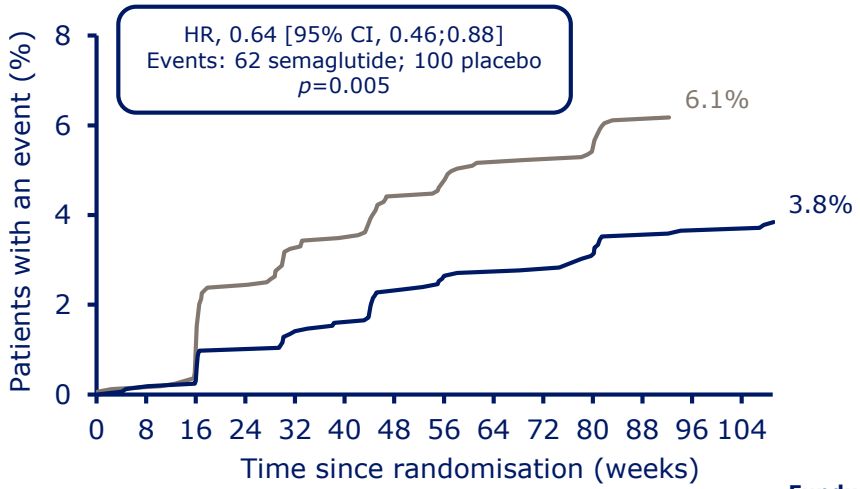



*Subgroup interaction *p*-value for MACE by prior MI/stroke or CV risk factors/established CV disease. †*P*-value for MACE (SUSTAIN phase 3a pool, excluding SUSTAIN 6) semaglutide vs comparators; ‡phase 3a meta-analysis was not stratified by trial. AE, adverse event; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; N/A, not applicable

Adapted from: Bain *et al. Eur Heart J* 2018;39(Suppl.):598 (abstract and poster P2859)

# SUSTAIN 6: microvascular outcomes

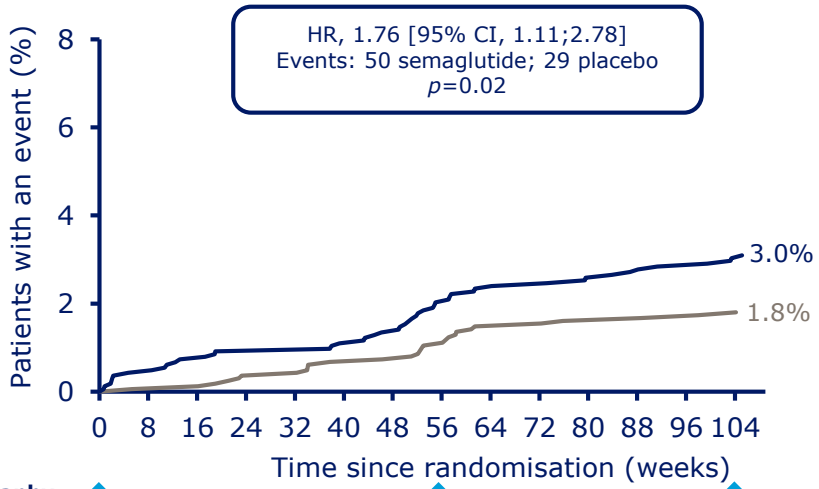
## New or worsening nephropathy




**No. of patients at risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Semaglutide** | **1648** | **1630** | **1605** | **1580** | **1563** | **1541** | **1525** | **1518** |
| **Placebo** | **1649** | **1629** | **1570** | **1545** | **1518** | **1498** | **1471** | **1465** |

## Diabetic retinopathy complications




**Fundus photography or fundoscopy:***

**No. of patients at risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Semaglutide** | **1648** | **1622** | **1612** | **1595** | **1570** | **1548** | **1535** | **1525** |
| **Placebo** | **1649** | **1636** | **1617** | **1605** | **1576** | **1558** | **1539** | **1530** |

Semaglutide Placebo

*Protocol-defined assessments. Additional assessments/eye examinations, which could also identify diabetic retinopathy events, could be performed by other healthcare professionals. Kaplan–Meier plot for time from randomisation to first EAC-confirmed new or worsening nephropathy or diabetic retinopathy complication using 'in-trial' data from patients in the full analysis set. Fundoscopy or fundus photography was performed at baseline, unless undertaken within 90 days prior to randomisation, by the investigator or a local ophthalmologist or optometrist according to local practice. EAC, (external) event adjudication committee. Adapted from: Marso *et al. N Engl J Med* 2016;375:1834–44

# SUSTAIN 6: summary

Is MACE risk reduction with semaglutide impacted by baseline CV risk?

No, MACE risk reduction was greater with semaglutide than placebo, regardless of baseline CV risk

CV, cardiovascular; MACE, major adverse cardiovascular event

# Selected adverse events (AEs) and precautions for use

For full list of adverse events and precautions please refer to the semaglutide SmPC

- The most frequently reported adverse reactions of semaglutide were gastrointestinal disorders including nausea, diarrhoea and vomiting. These were generally mild to moderate in severity and of short duration
- Treatment in combination with SU/insulin may increase the risk of hypoglycaemia. This risk can be lowered by reducing the dose of SU/insulin when initiating treatment
- Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. Such patients should be monitored closely and treated according to clinical guidelines.

Ozempic® Summary of Product Characteristics, Novo Nordisk A/S, Bagsværd, Denmark.

# Semaglutide prescribing information

**Ozempic®** ▼
semaglutide

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

One ml of solution contains 1.34 mg of semaglutide (human glucagon-like peptide-1 (GLP-1)).

**Indication**: 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.

**Posology and administration**: Administered once weekly at any time of the day, with or without meals. Injected subcutaneously in the abdomen, thigh or upper arm. Starting dose: 0.25 mg 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. Children: No data available. Elderly: No dose adjustment, therapeutic experience in patients ≥75 is limited. Renal impairment: No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience in patients with severe renal impairment is limited. Not recommended for use in patients with end-stage renal disease. Hepatic impairment: No dose adjustment is required for patients with hepatic impairment. Experience with severe hepatic impairment is limited. Caution should be exercised when treating these patients with semaglutide.

**Contraindications**: Hypersensitivity to the active substance or to any of the excipients

**Special warnings and Precautions for use**: Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Not a substitute for insulin. There is no experience in patients with congestive heart failure NYHA class IV and is therefore not recommended in these patients. 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. 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.

Use of 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.

In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy complications has been observed. 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. When semaglutide is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

**Fertility, pregnancy and lactation**: Women of childbearing potential are recommended to use contraception when treated with semaglutide. Should not be used during pregnancy or breast-feeding. Discontinue at least 2 months before a planned pregnancy. Effect on fertility unknown.

**Undesirable effects**: The Summary of Product Characteristics should be consulted in relation to other adverse reactions. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

*Very common (≥1/10);* Hypoglycaemia when used with insulin or sulfonylurea, nausea, diarrhoea *Common: (≥1/100 to <1/10);* Hypoglycaemia when used with other OADs, decreased appetite, dizziness, diabetic retinopathy complications, vomiting, abdominal pain, abdominal distension, constipation, dyspepsia, gastritis, gastro-oesophageal reflux disease, eructation, flatulence, cholelithiasis, fatigue, increased lipase, increased amylase, weight decreased. U*ncommon: (≥1/1,000 to <1/100);* Dysgeusia, increased heart rate, injection site reactions. *Rare: (≥1/10,000 to <1/1,000)* Anaphylactic reaction.

**MA numbers and Basic NHS Price**:

Ozempic® 0.25 mg pre-filled pen EU/1/17/1251/002 £73.25;
Ozempic® 0.5 mg pre-filled pen EU/1/17/1251/003 £73.25;
Ozempic® 1 mg pre-filled pen EU/1/17/1251/005 £73.25

**Legal Category**: POM.

**Further prescribing information can be obtained from**: Novo Nordisk Limited, 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA.

**Marketing Authorisation Holder**: Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark.

**Date last revised**: July 2018

**Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Novo Nordisk Limited (Telephone Novo Nordisk Customer Care Centre 0845 6005055). Calls may be monitored for training purposes.**

# Liraglutide prescribing information

**Victoza®** Liraglutide.

Victoza® 6 mg/ml pre-filled pen

1 ml of solution contains 6 mg of liraglutide. One pre-filled pen contains 18 mg liraglutide in 3 ml.

**Indication:** 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 SmPC sections 4.4, 4.5 and 5.1.

**Posology and administration**: Victoza® is administered once daily by subcutaneous injection and at any time independent of meals however it is preferable to inject around the same time of day. Victoza® should not be administered intravenously or intramuscularly. Recommended starting dose is 0.6 mg daily, after at least one week, the dose should be increased to a maintenance dose of 1.2 mg. Based on clinical response, after at least one week the dose can be increased to 1.8 mg. Daily doses higher than 1.8 mg are not recommended. When Victoza® is added to sulfonylurea or insulin, a reduction in dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia. Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when Victoza® therapy is started and insulin is reduced. A stepwise approach to insulin dose reduction is recommended. Victoza® can be used in the elderly (>65 years) without dose adjustment. No dose adjustment for patients with mild, moderate or severe renal impairment. There is no therapeutic experience in patients with end-stage renal disease. No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Victoza® is not recommended for use in patients with end-stage renal disease, patients with severe hepatic impairment or children and adolescents <18 years.

**Contraindications:** Hypersensitivity to the active substance or any of the excipients.

**Special warnings and Precautions for use**: Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Victoza® is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin. No experience in patients with New York Heart Association (NYHA) IV and Victoza® is not recommended for use in these patients. Due to limited experience Victoza® is not recommended in patients with inflammatory bowel disease and diabetic gastroparesis since it is associated with transient gastrointestinal (GI) adverse reactions, including nausea, vomiting and diarrhoea. Acute pancreatitis has been observed with the use of GLP-1 receptor agonists; patients should be informed of symptoms of acute pancreatitis. If pancreatitis is suspected, Victoza® should be discontinued. If acute pancreatitis is confirmed, Victoza® should not be restarted. Thyroid adverse events, such as goitre have been reported in clinical trials particularly in patients with pre-existing thyroid disease and Victoza® should be used with caution. Risk of dehydration in relation to GI side effects; take precautions to avoid fluid depletion. Victoza® has no or negligible influence on the ability to drive and use machines. Patients advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Victoza® is used in combination with sulfonylurea or insulin. In the absence of compatibility studies Victoza® must not be mixed with other medicinal products.

**Fertility, pregnancy and lactation:** If a patient wishes to become pregnant, pregnancy occurs or is breast feeding, treatment with Victoza® should be discontinued. Apart from a slight decrease in number of live implants in animal studies no harmful effects on fertility observed.

**Undesirable effects:** The most frequently observed adverse reactions from long term phase 3a controlled trials, the LEADER trial (a long-term cardiovascular outcome trial) and spontaneous (post-marketing) reports were: Very common (≥1/10): nausea, diarrhoea, hypoglycaemia when used in combination with sulfonylureas. Common (≥1/100 to <1/10): vomiting, constipation, abdominal pain, discomfort and distension, dyspepsia, gastritis, flatulence, gastroesophageal reflux disease, increased heart rate, toothache, headache, dizziness, nasopharyngitis, bronchitis, hypoglycaemia, anorexia, appetite decreased, fatigue, rash, injection site reactions, increased lipase, increased amylase; GI adverse reactions are more frequent at start of therapy but are usually transient. Patients >70 years or with mild and moderate renal impairment (CrCl 60-90 ml/min and 30-59 ml/min, respectively) may experience more GI effects. Few cases of cholelithiasis and cholecystitis have been reported in phase 3a clinical trials. Dehydration, renal impairment, acute renal failure and malaise were uncommonly reported (≥1/1,000 to <1/100) and intestinal obstruction reported rarely (≥1/10,000 to <1/1,000). Consistent with medicinal products containing proteins/peptides, patients may develop anti-liraglutide antibodies following treatment but this has not been associated with reduced efficacy of Victoza®. Few cases of: angioedema (0.05%), acute pancreatitis (<0.2%), injection site reactions (usually mild, approx. 2%). Allergic reactions (including urticaria, rash and pruritus) and a few cases of anaphylactic reactions (with additional symptoms such as hypotension, palpitations, dyspnoea and oedema) have been reported from marketed use of Victoza®. The Summary of Product Characteristics should be consulted for a full list of side effects.

**MA numbers and Basic NHS Price:**

2 x 3 ml pre-filled pens EU/1/09/529/002 £78.48;

3 x 3 ml pre-filled pens EU/1/09/529/003 £117.72.

**Legal Category**: POM.

**Further prescribing information can be obtained from**:

Novo Nordisk Limited, 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA.

**Marketing Authorisation Holder**: Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark.

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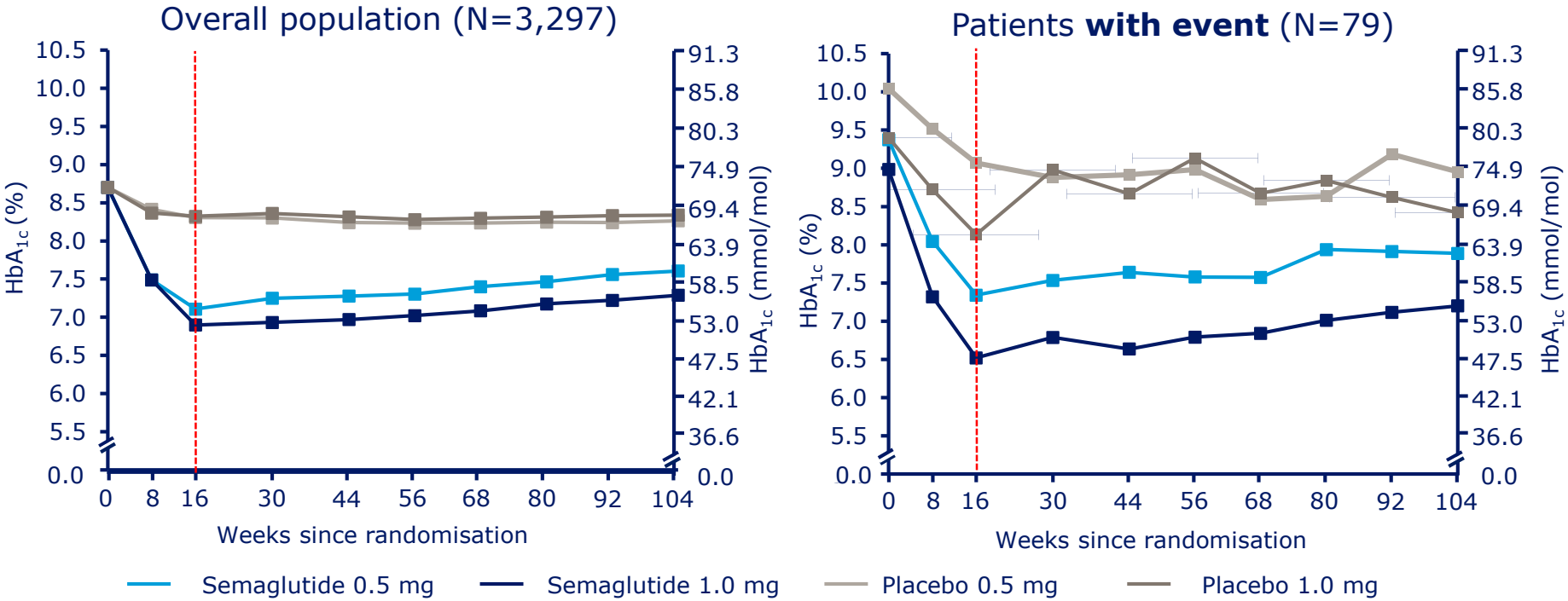
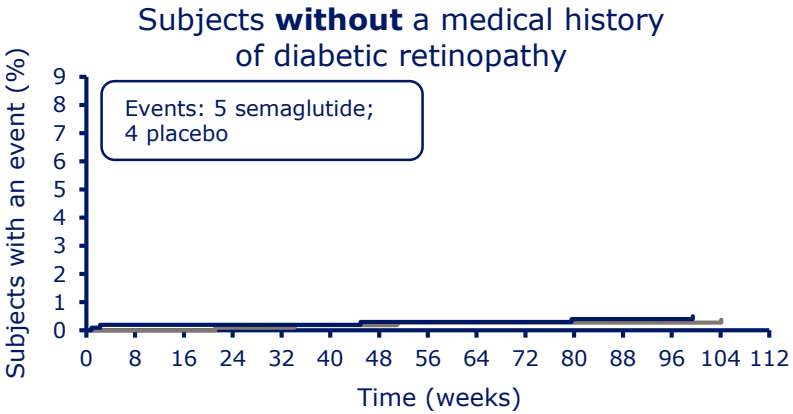
**Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.**
**Adverse events should also be reported to Novo Nordisk Limited (Telephone Novo Nordisk Customer Care Centre 0845 6005055). Calls may be monitored for training purposes.**

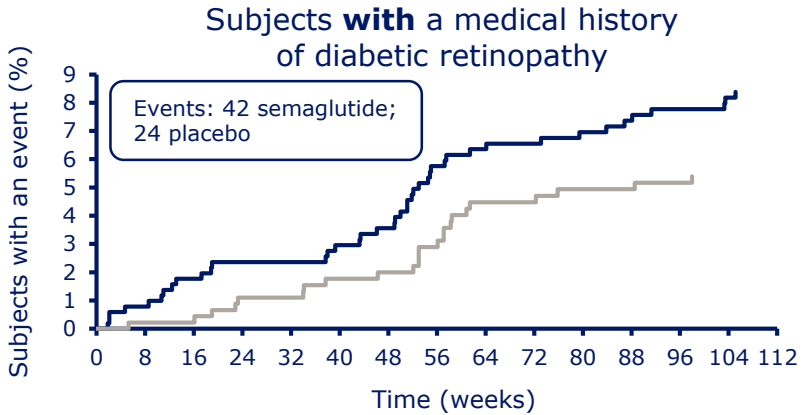
# SUSTAIN 6: early $HbA_{1c}$ reduction and diabetic retinopathy complication events




Adapted from: Vilsbøll T *et al. Diabetes Obes Metab* 2018; 20:889–897.

# SUSTAIN 6: risk of diabetic retinopathy complications in patients with medical history of diabetic retinopathy




Number of subjects at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Semaglutide | 1023 | 1015 | 1011 | 1005 | 999 | 985 | 978 | 116 |
| Placebo | 1089 | 1083 | 1073 | 1071 | 1058 | 1045 | 1035 | 119 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Semaglutide | 510 | 498 | 492 | 483 | 466 | 460 | 454 | 54 |
| Placebo | 459 | 453 | 445 | 437 | 421 | 417 | 410 | 43 |

Semaglutide Placebo

Four subjects' history of diabetic retinopathy was unknown at baseline. CI, confidence interval; HR, hazard ratio.
Adapted from: Vilsbøll T *et al. Diabetes Obes Metab* 2018; 20:889–897.