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Contents

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Presentation schedule

Oral presentations

- TUESDAY 17 SEPTEMBER 2019
- WEDNESDAY 18 SEPTEMBER 2019
- THURSDAY 19 SEPTEMBER 2019

Poster presentations

- TUESDAY 17 SEPTEMBER 2019
- WEDNESDAY 18 SEPTEMBER 2019
- THURSDAY 19 SEPTEMBER 2019

Presentation schedule

Oral presentations

TUESDAY 17 SEPTEMBER 2019

OP 03 Addressing limitations of insulin therapy Ochoa Hall

11:15 AM–11:30 AM

17	Lane	Efficacy and safety of fast-acting insulin aspart compared with insulin aspart, both with insulin degludec with or without metformin, in adults with type 2 diabetes

OP 09 Semaglutide: ingested or injected Ochoa Hall

2:30 PM–2:45 PM

49	Haluzík	Efficacy of oral semaglutide according to diabetes duration: an exploratory subgroup analysis of the PIONEER trial programme

2:45 PM–3:00 PM

50	Dahl	Oral semaglutide improves postprandial glucose and lipid metabolism and delays first-hour gastric emptying in subjects with type 2 diabetes

3:00 PM–3:15 PM

51	Meier	Efficacy of oral semaglutide according to baseline HbA_{1c}: an exploratory subgroup analysis of the PIONEER trial programme

3:15 PM–3:30 PM

52	Lingvay	Once-weekly semaglutide vs. canagliflozin in type 2 diabetes: results of the SUSTAIN 8 trial

3:30 PM–3:45 PM

54	McCrimmon	Effects of once-weekly semaglutide vs. canagliflozin on body composition in type 2 diabetes: a substudy of the SUSTAIN 8 trial

3:45 PM–4:00 PM

53	Capehorn	Efficacy and safety of semaglutide 1.0 mg once weekly vs. liraglutide 1.2 mg once daily as add-on to 1–3 oral glucose-lowering drugs in subjects with type 2 diabetes (SUSTAIN 10)

WEDNESDAY 18 SEPTEMBER 2019

OP 14 New insights on early onset type 2 diabetes Vilanova Hall

11:30 AM–11:45 AM

84	Barrett	Efficacy and safety of liraglutide vs. placebo in children and adolescents with type 2 diabetes: the ellipse randomised trial results

OP 15 Clinical aspects of hypoglycaemia Ochoa Hall

11:30 AM–11:45 AM

90	Philis-Tsimikas	Reduced risk of hypoglycaemia and lower HbA_{1c} with degludec compared to glargine U300 in insulin-treated patients with type 2 diabetes

THURSDAY 19 SEPTEMBER 2019

OP 31 Innovative insulin therapy Joslin Hall

3:30 PM–3:45 PM

185	Sesti	DUAL VIII: more patients met treatment targets with IDegLira (insulin degludec/liraglutide) vs. IGlar U100 by Week 26 in a 104-week randomised trial mirroring clinical practice

3:45 PM–4:00 PM

186	Aroda	DUAL VIII: longer time to intensification with insulin degludec/liraglutide (IDegLira) vs. insulin glargine in a 104-week randomised trial mirroring clinical practice

Poster presentations

TUESDAY 17 SEPTEMBER 2019

12:00 PM–1:00 PM PS 055 Extra-glycaemic effects of GLP-1 receptor agonists Poster Hall

753	Blundell (Gibbons)	Oral semaglutide reduces appetite and energy intake and improves control of eating in subjects with type 2 diabetes
754	Wilding	Weight loss induced by semaglutide once weekly contributes to improved health-related quality of life and treatment satisfaction
756	Leiter	Liraglutide and semaglutide improve cardiovascular and renal outcomes across baseline BP categories: analysis of LEADER and SUSTAIN 6
757	Bain	The effect of once-weekly semaglutide on MACE, blood pressure and lipids by race and ethnicity: a SUSTAIN 6 *post hoc* analysis
758	Zinman	Impact of microvascular disease on cardiorenal outcomes in type 2 diabetes: an analysis from the LEADER and SUSTAIN 6 clinical trials

1:15 PM–2:15 PM PS 062 Making diabetes care more cost-effective Poster Hall

821	Löndahl	Cost-effectiveness of once-weekly semaglutide versus empagliflozin in people with type 2 diabetes and inadequate glycaemic control in Sweden

WEDNESDAY 18 SEPTEMBER 2019

1:15 PM–2:15 PM PS 004 Additional spotlights on cardiovascular disease Poster Hall

302	Buse	Outcomes of type 2 diabetes clustering replicated in the DEVOTE trial

12:00 PM–1:00 PM PS 057 Incretin-based therapies: clinical studies Poster Hall

770	Rea	Liraglutide as add-on to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes: a 26-week, randomised, double-blind, placebo-controlled trial
773	Viljoen	Efficacy and safety of semaglutide by baseline BMI in SUSTAIN 1–5 and 7
775	Pratley	Efficacy and safety of once-weekly semaglutide low dose 0.5 mg vs. once-weekly dulaglutide high dose 1.5 mg in type 2 diabetes: a post hoc analysis of SUSTAIN 7
776	Ludvik	Efficacy and safety of semaglutide by background sodium-glucose cotransporter-2 inhibitor: a post hoc analysis of SUSTAIN 9
777	Overgaard	Similar efficacy and gastrointestinal tolerability versus exposure for oral and subcutaneous semaglutide

1:15 PM–2:15 PM PS 070 The potential of new basal insulins Poster Hall

893	Jendle	Real-world cost-effectiveness of insulin degludec in type 1 and type 2 diabetes in a Swedish setting
894	Ericsson	Cost-effectiveness of insulin degludec vs. insulin glargine U100 in type 1 diabetes in a Swedish setting after one year

1:15 PM–2:15 PM PS 082 Promising therapeutic options for diabetic kidney disease Poster Hall

998	Perkovic	Estimated GFR (eGFR) loss with glucagon-like peptide-1 (GLP-1) analogue treatment: data from SUSTAIN 6 and LEADER

1:15 PM–2:15 PM PS 100 Treatment of cardiovascular disease Poster Hall

1164	Verma (Leiter)	Liraglutide and semaglutide improve cardiovascular and renal outcomes across most BMI categories in type 2 diabetes: results of the LEADER and SUSTAIN 6 trials

Poster presentations

THURSDAY 19 SEPTEMBER 2019

12:00 PM–1:00 PM PS 035 The obesity battle Poster Hall

575	Dicker	Effect of liraglutide 3.0 mg on glycaemic parameters in adults with overweight/obesity and type 2 diabetes treated with basal insulin: SCALE insulin trial
576	Mingrone	Efficacy and safety of liraglutide 3.0 mg in individuals with overweight or obesity and type 2 diabetes treated with basal insulin: the SCALE insulin trial

12:00 PM–1:00 PM PS 059 Modern insulin therapy Poster Hall

793	Feher	Hypoglycaemia, irrespective of the definition used, is reduced when switching to insulin degludec from other basal insulins in routine clinical care: the ReFLeCT study

1:15 PM–2:15 PM PS 060 Applying new technologies in diabetes Poster Hall

795	Hartvig	Improved insulin adherence after introduction of a smart connected insulin pen
796	Kaas	Increased time in range observed after introduction of a connected insulin pen

1:15 PM–2:15 PM PS 066 Consequences of hypoglycaemia Poster Hall

860	Heller	Non-severe hypoglycaemia predicts increased risk of subsequent severe events in patients with type 2 diabetes

Insulin degludec

Oral presentation 90

A Philis-Tsimikas, DC Klonoff, K Khunti, HS Bajaj, LA Leiter, D Tutkunkardas, L Nørgård Troelsen, BA Bak, SR Heller, TR Pieber

Reduced risk of hypoglycaemia and lower HbA_{1c} with degludec compared to glargine U300 in insulin-treated patients with type 2 diabetes

Poster presentation 302

JB Buse, AR Kahkoska, E Hachmann-Nielsen, KR Klein, KG Kongsbak, K Kvist

Outcomes of type 2 diabetes clustering replicated in the DEVOTE trial

Poster presentation 793

MD Feher, GP Fadini, T Krarup Hansen, J Jendle, Á Merchante, MM Koefoed, E Parvaresh Rizi, E Zimmermann, HW de Valk

Hypoglycaemia, irrespective of the definition used, is reduced when switching to insulin degludec from other basal insulins in routine clinical care: the ReFLeCT study

Poster presentation 893

JH Jendle, M Thunander, S Sjoberg, B Ekman, A-C Mardby, J Da Rocha Fernandes, J Gundgaard, A Ericsson

Real-world cost-effectiveness of insulin degludec in type 1 and type 2 diabetes in a Swedish setting

Poster presentation 894

A Ericsson, A-C Mardby

Cost-effectiveness of insulin degludec vs. insulin glargine U100 in type 1 diabetes in a Swedish setting after one year

Oral presentation 90

Reduced risk of hypoglycaemia and lower HbA_{1c} with degludec compared to glargine U300 in insulin-treated patients with type 2 diabetes

A PHILIS-TSIMIKAS[1], DC KLONOFF[2], K KHUNTI[3], HS BAJAJ[4], LA LEITER[5], D TUTKUNKARDAS[6], L NØRGÅRD TROELSEN[6], BA BAK[6], SR HELLER[7], TR PIEBER[8]

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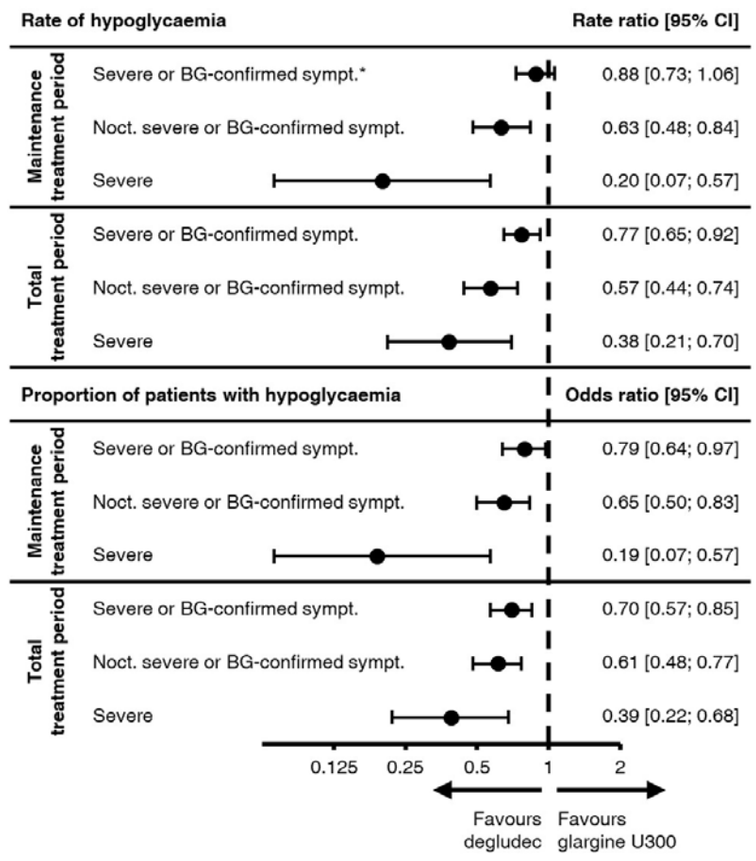
Background and aims: Minimising hypoglycaemia is an important aim of insulin therapy. Long-acting basal insulins, degludec and glargine U300 have been shown to have a lower risk of hypoglycaemia than glargine U100. A head-to-head trial was conducted to evaluate the risk of hypoglycaemia with degludec compared with glargine U300 in insulin-treated patients with type 2 diabetes (T2D).

Materials and methods: This randomised (1:1) open-label, treat-to-target, multinational trial, included T2D patients ≥18 years with HbA_{1c} ≤9.5% and BMI ≤45 kg/m². Patients were previously treated with basal insulin ± oral antidiabetic drugs (excluding insulin secretagogues) and fulfilled at least one criterion that placed them at a risk of hypoglycaemia. Both degludec and glargine U300 were similarly titrated to a fasting blood glucose (BG) target of 4.0–5.0 mmol/L. All endpoints related to hypoglycaemia were assessed during a 36-week maintenance treatment period and the total treatment period of up to 88 weeks.

Results: Of 1609 randomised patients, 703 patients in the degludec arm and 706 patients in the glargine U300 arm completed the treatment. Baseline characteristics were comparable between the treatment arms. The rate ratio (RR) of severe or BG-confirmed symptomatic hypoglycaemia with degludec compared to glargine U300 was 0.88 (NS) during the maintenance period and a statistically significant RR of 0.77 was seen during the total treatment period (**Figure**). During the maintenance and total treatment periods, the RR was statistically significant in favour of degludec for severe hypoglycaemia (RR: 0.20 and 0.38, respectively) and for nocturnal hypoglycaemia (RR: 0.63 and 0.57, respectively). The proportions of patients with hypoglycaemia were statistically significant in favour of degludec during both periods for all hypoglycaemic endpoints (**Figure**). The *post hoc* assessed change from baseline to end of treatment in HbA_{1c} was statistically significantly greater in patients treated with degludec compared to glargine U300 (estimated treatment difference [95% CI]: –0.10% –0.18; –0.02]).

Conclusion: Degludec showed an overall lower risk of hypoglycaemia compared to glargine U300 accompanied by significantly lower HbA_{1c}.

Figure. Hypoglycaemia endpoints



*Primary endpoint. Severe episodes classified as per the American Diabetes Association definition. BG-confirmed episodes defined as BG <3.1 mmol/L. Nocturnal episodes were between 00:01 and 05:59.
BG: blood glucose; CI: confidence interval; Noct: nocturnal; sympt: symptomatic.

Clinical Trial Registration Number: NCT03078478

Poster presentation 302

Outcomes of type 2 diabetes clustering replicated in the DEVOTE trial

JB BUSE[1], AR KAHKOSKA[1], E HACHMANN-NIELSEN[2], KR KLEIN[1], KG KONGSBAK[2], K KVIST[2]
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Background and aims: T2D is a heterogeneous disease.

Materials and methods: Individuals in the Swedish All New Diabetics in Scania (ANDIS) cohort with newly diagnosed T2D were grouped by 6 demographic and clinical variables to show 4 distinct T2D subtypes with differential risk for nephropathy and retinopathy. We tested the predictive validity of this clustering system for patients with advanced T2D in DEVOTE (a large, global, randomised, double-blind, cardiovascular outcomes trial; median observation time: 1.99 yrs) for major adverse cardiovascular event (MACE)-free survival, severe hypoglycaemia (SH)-free survival and overall survival rates. Subjects (N=7637, mean age=65.0 yrs, mean T2D duration=16.4 yrs, mean HbA_{1c}=8.43%) were assigned to a cluster for which they had the smallest Euclidean distance to the cluster center based on available baseline variables: HbA_{1c}, BMI, age, age at diagnosis. Insulin resistance and sensitivity measures were not available.

Results: The 4 DEVOTE clusters showed baseline characteristics consistent with the original ANDIS clusters, with significant differences in MACE incidence and SH incidence (**Table**). The results were confirmed using data from the LEADER trial (data not shown).

Conclusion: The study suggests that clusters derived from early T2D can be replicated in long-standing T2D. Future work should characterise differences in treatment response across clusters to improve outcomes across the heterogeneous T2D population.

Table: Proportion of subjects with events *p*-values for association between T2D cluster and events over 15125 patient-years of observation (N=7637)

Cluster \ Patient event	MACE	Severe hypoglycaemia	Cardiovascular death	All-cause mortality
Cluster 2: severe insulin-deficient diabetes-like (n=1416, 18.7%)	11.6%	5.9%	4.5%	5.8%
Cluster 3: severe insulin-resistant diabetes-like (n=1789, 23.7%)	8.7%	5.3%	3.9%	5.9%
Cluster 4: mild obesity-related diabetes-like (n=1594, 21.1%)	9.4%	7.3%	3.7%	5.5%
Cluster 5: mild age-related diabetes-like (n=2747, 36.4%)	7.4%	4.9%	3.0%	5.2%
p-value for association	<0.001	0.006	0.076	0.763

Cluster 1: severe autoimmune diabetes (SAID) is not included as it is clinically equivalent to type 1 diabetes and thus not represented in the data.

Clinical Trial Registration Number: NCT01959529

Poster

Poster presentation 793

Hypoglycaemia, irrespective of the definition used, is reduced when switching to insulin degludec from other basal insulins in routine clinical care: the ReFLeCT study

MD FEHER[1,2], GP FADINI[3], T KRARUP HANSEN[4], J JENDLE[5], Á MERCHANTE[6,7], MM KOEFOED[8], E PARVARESH RIZI[8], E ZIMMERMANN[8], HW DE VALK[9]

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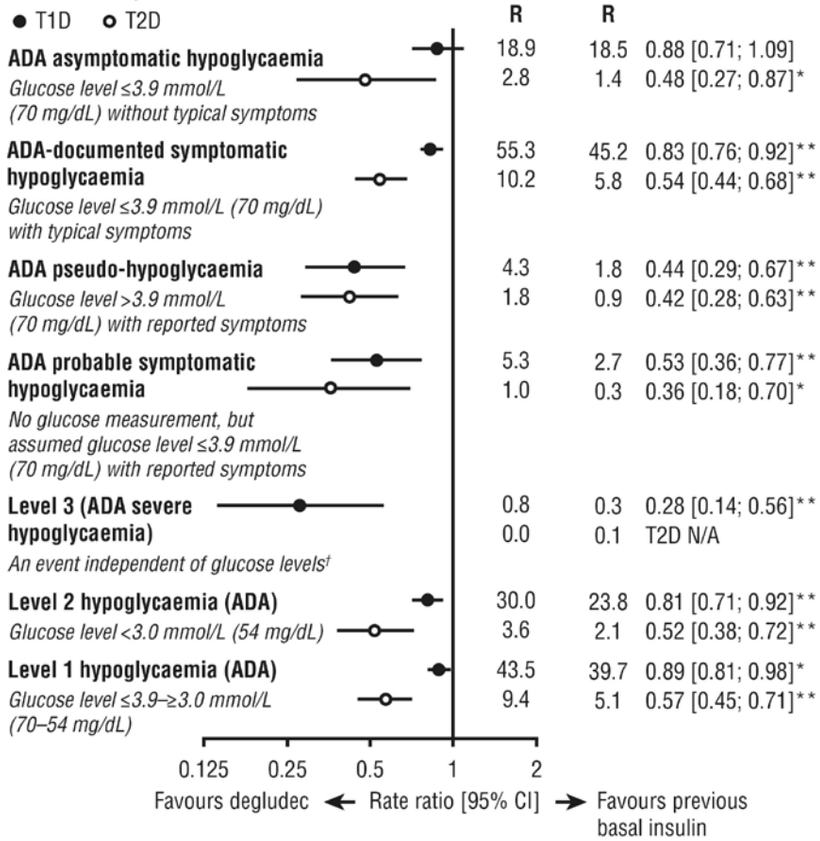
Background and aims: ReFLeCT was a multicentre, prospective, observational study designed to investigate the safety and effectiveness of switching to insulin degludec (degludec) from other basal insulins in patients with type 1 (T1D) or type 2 diabetes (T2D). Few studies had prospectively collected hypoglycaemia data from patient diaries following a switch to degludec in everyday clinical practice. These additional analyses from the ReFLeCT study aimed to assess the effects of switching to degludec according to different hypoglycaemia definitions.

Materials and methods: ReFLeCT comprised a 4-week baseline period (pre-switch basal insulin) and a 12-month follow-up period (degludec treatment). The primary endpoint of overall hypoglycaemia reported in patient diaries was reduced during follow-up vs. baseline in T1D and T2D with improvement of glycaemic control, as previously reported. Here, hypoglycaemia data from ReFLeCT were analysed using pre-specified and updated (*post hoc*) American Diabetes Association (ADA) hypoglycaemia definitions. Definitions consisted of: documented asymptomatic and symptomatic, pseudo, probable symptomatic, and Level 1, 2 and 3 (severe) hypoglycaemia (**Fig**). Hypoglycaemic events were analysed using fully adjusted, negative binomial regression models.

Results: In T1D (n=556) and T2D (n=611), estimated rate ratios across the previous and the updated ADA hypoglycaemia definitions were significantly lower during the 12-month follow-up vs. the baseline period, except for asymptomatic hypoglycaemia in T1D and Level 3 hypoglycaemia in T2D (due to a low number of severe hypoglycaemic events, no comparable statistics were performed) (Fig). Event rates per patient year were also lower for all definitions during the 12-month follow-up vs. the baseline period, except for Level 3 hypoglycaemia in T2D, which marginally increased, although this was likely due to the low number of events in this group.

Conclusion: In patients with T1D and T2D, switching to degludec from other basal insulins in routine clinical care is associated with lower rates of hypoglycaemia across a broad range of hypoglycaemia definitions, in combination with improved glycaemic control.

Figure: Adjusted rate ratios of hypoglycaemia according to different hypoglycaemia definitions in patients with T1D or T2D



*, $p<0.05$; **, $p<0.001$. †Severe hypoglycaemia, an episode requiring assistance of another person to actively administer carbohydrate, glucagon or take other corrective actions. All models were adjusted for period (pre/post-switch to degludec), baseline HbA_{1c}, gender, body mass index, duration of diabetes, age and country. For T2D, additional adjustments included bolus insulin (Yes/No) and sulfonylureas + glinides (Yes/No). ADA, American Diabetes Association; CI, confidence interval; N/A, not applicable (due to a low number of severe hypoglycaemic events, no comparable statistics were performed); R, rate of events per patient-year of exposure; T1D, type 1 diabetes; T2D, type 2 diabetes.

Clinical Trial Registration Number: NCT02392117

Poster

Poster presentation 893

Real-world cost-effectiveness of insulin degludec in type 1 and type 2 diabetes in a Swedish setting

JH JENDLE[1], M THUNANDER[2], S SJOBERG[3], B EKMAN[4], A-C MARDBY[5], J DA ROCHA FERNANDES[6], J GUNDGAARD[6], A ERICSSON[5]
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Background and aims: Randomised controlled trials and observational studies have shown lower risk of hypoglycemia in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D) on treatment with insulin degludec (IDeg) vs. insulin glargine 100 units/mL (IGlar). This study assessed cost-effectiveness (C/E) of IDeg vs. insulin treatment before switch to IDeg in a Swedish real-world setting in people with T1D and T2D.

Materials and methods: ReFLeCT is a prospective, observational study in T1D (n=566) and T2D (n=611) in seven European countries and comprised a four-week baseline period (pre-switch basal insulin) and a 12-month follow-up period (IDeg). Data from ReFLeCT was used to assess C/E of IDeg compared with basal insulin treatment prior to switching to IDeg. Basal insulin unit costs were weighted to represent the basal insulin present at baseline (T1D: IGlar 63.8%, Insulin detemir (IDet) 22.7%, other/missing 13.5%. T2D: IGlar 59.1%, IDet 20.8%, other/missing 20.1%). The Swedish original IGlar price was used as base case. IGlar biosimilar price was used in a sensitivity analysis. Where information on basal insulin at baseline was missing, the lowest basal insulin price (insulin NPH) was used as a conservative approach. C/E was analysed over a 1-year time horizon from a Swedish societal perspective (price level 2019). Only differences with $p<0.05$ were included in the analysis.

Results: Basal and bolus insulin doses at baseline were 25.0 IU and 27.3 IU (T1D) and 37.5 IU and 24.4 IU (T2D). At 12 months estimated basal and bolus insulin dose ratios were 0.91 (95% C.I. 0.83–0.91) and 0.87 (0.83–0.91) for T1D and 0.98 (0.95–1.01) and 0.96 (0.94–1.01) for T2D. For T1D risk ratios (RR) for non-severe daytime hypoglycaemia was 0.85 (0.78–0.93), non-severe nocturnal hypoglycaemia 0.63 (0.52–0.76) and severe hypoglycaemia 0.28 (0.14–0.56). Corresponding RR for T2D were 0.56 (0.46–0.69), 0.38 (0.22–0.64) and 2.87 (0.33–24.65). In T1D IDeg was cost-saving compared to previous basal therapy (**Table 1**). In T2D, IDeg was highly cost-effective, with a cost per quality-adjusted life-year (QALY) of SEK 15,000–24,000 (**Table 1**). A treatment is considered cost-effective in Sweden if cost/QALY is below SEK 500,000. Sensitivity analyses showed that the results were robust to changes in efficacy and cost parameters in both T1D and T2D.

Conclusion: In this C/E-analysis, treatment with IDeg was cost-saving (T1D) or highly cost-effective (T2D) relative to the treatment used before switch in a Swedish setting after one year. C/E of IDeg in clinical practice is driven by lower insulin doses (T1D) and reduced risk of hypoglycaemia (T1D and T2D).

Table 1: Cost-effectiveness of IDeg vs treatment before switch of basal insulin.

Diabetes type	Scenario	Cost Difference (SEK)	QALY difference	Cost (SEK) /QALY
T1D	IGlar price: original	-1,249	0.079	Dominant
T1D	IGlar price: biosimilar	-995	0.079	Dominant
T2D	IGlar price: original	560	0.038	14,911
T2D	IGlar price: biosimilar	912	0.038	24,259

SEK: Swedish kronor; QALY: Quality-Adjusted Life-Years; T1D: Type 1 Diabetes; T2D: Type 2 Diabetes; IGlar: Insulin Glargine)

Poster presentation 894

Cost-effectiveness of insulin degludec vs. insulin glargine U100 in type 1 diabetes in a Swedish setting after one year

A ERICSSON, A-C MARDBY
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Background and aims: According to several randomised controlled trials and observational studies, Insulin degludec (IDeg) has a beneficial hypoglycaemia profile compared with insulin glargine U100 (IGlar). Hypoglycaemia is an important cost driver in health economic studies. This analysis was done to assess cost-effectiveness of IDeg vs. original and biosimilar IGlar in a Swedish setting in type 1-diabetes (T1D).

Materials and methods: Data from a double-blinded, randomised, two-period crossover trial in T1D (SWITCH 1) was used to assess the cost-effectiveness of IDeg vs. original and biosimilar IGlar. Cost-effectiveness was analysed over a 1-year time horizon with a societal perspective based on the different rates of hypoglycaemia and actual doses of insulin (price level 2019). Only differences with $p<0.05$ were included in the analysis.

Results: The IGlar basal dose was 40.58 units/day and IDeg/IGlar basal dose ratio was 0.97 [95% confidence interval: 0.94–0.99]. The bolus dose used in the IGlar arm was 31.93 U/day and the bolus dose ratio for the two arms (IDeg/IGlar) 0.97 [0.94–1.01]. Rate ratios (RR) for non-severe daytime hypoglycaemia was 0.98 [0.94–1.03], non-severe nocturnal hypoglycaemia 0.76 [0.69–0.84] and severe hypoglycaemia 0.74 [0.61–0.91)]. IDeg was highly cost-effective compared with IGlar, with an incremental cost-effectiveness ratio of SEK 25,000–52,000. Total cost difference was SEK 575–1,219 (**Table 1**). A treatment is considered cost-effective in Sweden if cost/Quality-Adjusted Life-Year (QALY) is below SEK 500,000. The drivers in the analyses were dose reduction and lower hypoglycaemia for patients treated with IDeg compared with those using IGlar.

Conclusion: The rigorous design of the SWITCH 1 trial, coupled with a representative patient population and a definition of hypoglycaemia that is relevant for patients who prescribers meet in their clinics, makes the results of this trial highly generalisable. This short-term economic analysis estimated that IDeg would be highly cost-effective relative to original and biosimilar IGlar in T1D in a Swedish setting after one year. The result is driven by lower insulin dose and reduced risk of hypoglycaemia.

Table 1: Cost-effectiveness of IDeg vs IGlar U100

Scenario	Cost difference	QALY difference	Cost/ QALY
IGlar price: original	575	0.0232	25,000
IGlar price: biosimilar	1,219	0.0232	52,000

Poster

Oral presentation 185

G Sesti, L Bardtrum, S Daðdelen, N Halladin, M Haluzík, P Örsy, M Rodríguez, VR Aroda

DUAL VIII: more patients met treatment targets with IDegLira (insulin degludec/liraglutide) vs. IGlar U100 by Week 26 in a 104-week randomised trial mirroring clinical practice

Oral presentation 186

VR Aroda, G González-Galvez, M Haluzík, RJ Silver, R Grøn, N Halladin, P Örsy, G. Sesti

DUAL VIII: longer time to intensification with insulin degludec/liraglutide (IDegLira) vs. insulin glargine in a 104-week randomised trial mirroring clinical practice

Oral presentation 185

DUAL VIII: more patients met treatment targets with IDegLira (insulin degludec/liraglutide) vs. IGlar U100 by Week 26 in a 104-week randomised trial mirroring clinical practice

G SESTI[1], L BARDTRUM[2], S DAĐDELEN[3], N HALLADIN[2], M HALUZÍK[4], P ÖRSY[2], M RODRÍGUEZ[5], VR ARODA[6]

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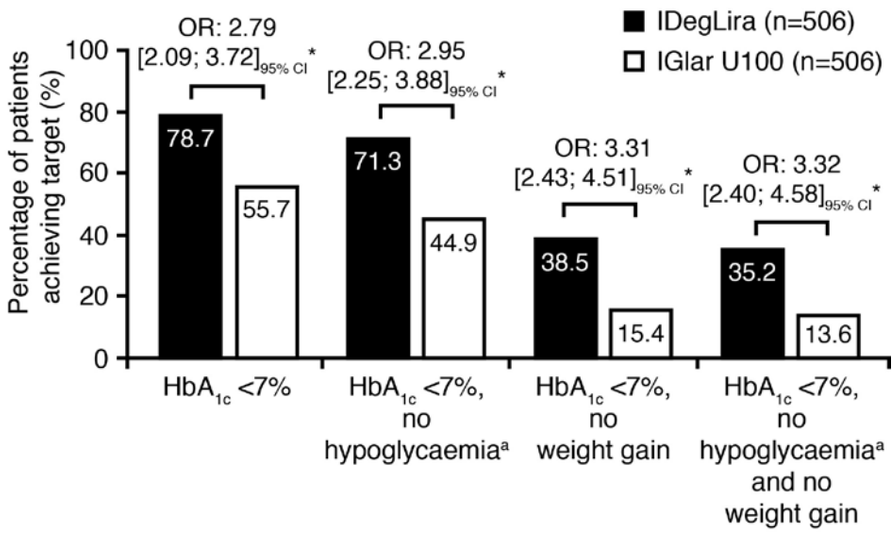
Background and aims: In randomised treat-to-target trials, titration is monitored closely and frequently by trial staff. However, in the 104-week DUAL VIII treat-to-target trial - comparing the durability of glycaemic control beyond 26 weeks of treatment with insulin degludec/liraglutide (IDegLira) vs. insulin glargine 100 units/mL (IGlar U100) in patients with type 2 diabetes (T2D) uncontrolled on oral antidiabetic drugs (OADs) - titration was guided by the investigator over fewer visits, mirroring clinical practice. We report efficacy and safety data at Week 26 to assess whether the benefits of IDegLira over IGlar U100 as an initial injectable therapy are observed in a durability trial resembling recommended routine clinical practice.

Materials and methods: Patients (N=1012) with T2D uncontrolled on a broad range of OADs were randomised 1:1 to open-label IDegLira or IGlar U100. Starting dose was 10 U for both; only IDegLira had a maximum dose (50 U). Patients were instructed to titrate twice weekly to a fasting glucose target of 4–5 mmol/L, and guidance on the prespecified algorithm was at the investigator's discretion. Visits were scheduled at Weeks 1, 2, 4 and 12 and every three months thereafter, as recommended in current guidelines. We report Week 26 data.

Results: Baseline characteristics were similar and representative of patients eligible for basal insulin initiation (overall mean diabetes duration: 10 years, HbA_{1c}: 8.5%, FPG: 10 mmol/L). After 26 weeks, least squares (LS) mean HbA_{1c} reductions were significantly greater with IDegLira versus IGlar U100 (–2.0% vs. –1.5%, estimated treatment difference [ETD], [95% CI]: –0.47% [–0.58; –0.36]), as were the odds of patients achieving HbA_{1c} targets and the composite endpoints of HbA_{1c} targets without weight gain and/or hypoglycaemia after 26 weeks (**Figure**). Daily insulin dose was lower with IDegLira (35.4 U) vs. IGlar U100 (48.4 U). LS mean change from baseline in body weight was 0.5 kg with IDegLira and 2.1 kg with IGlar U100 (ETD: –1.57 kg [–2.00; –1.13]). Hypoglycaemia rates were 44% lower with IDegLira vs. IGlar U100 (rate ratio: 0.56 [0.39; 0.82]). There were no unexpected safety findings.

Conclusion: After 26 weeks of treatment in a trial set-up resembling recommended clinical practice, more patients met HbA_{1c} targets without weight gain and/or hypoglycaemia with IDegLira vs. IGlar U100, and with a lower insulin dose. These data support the use of IDegLira as a first injectable therapy for patients with T2D eligible for basal insulin initiation.

Percentage of patients achieving treatment targets with IDegLira compared with IGlar U100 at Week 26 of DUAL VIII



%, based on observed data. ORs (IDegLira/IGlar U100) are from a logistic regression model with treatment, baseline HbA_{1c} group, pre-trial OAD and region as factors and baseline HbA_{1c} (and body weight for endpoints including 'without weight gain') as covariate. *Statistically significant difference (in favour of IDegLira). [a]Severe or blood glucose-confirmed (<3.1 mmol/L) symptomatic hypoglycaemia was based on hypoglycaemic episodes during a patient's last 12 weeks of treatment.
IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; OAD, oral antidiabetic drug; OR, odds ratio.

Clinical Trial Registration Number: NCT02501161

Oral presentation 186

DUAL VIII: longer time to intensification with insulin degludec/liraglutide (IDegLira) vs. insulin glargine in a 104-week randomised trial mirroring clinical practice

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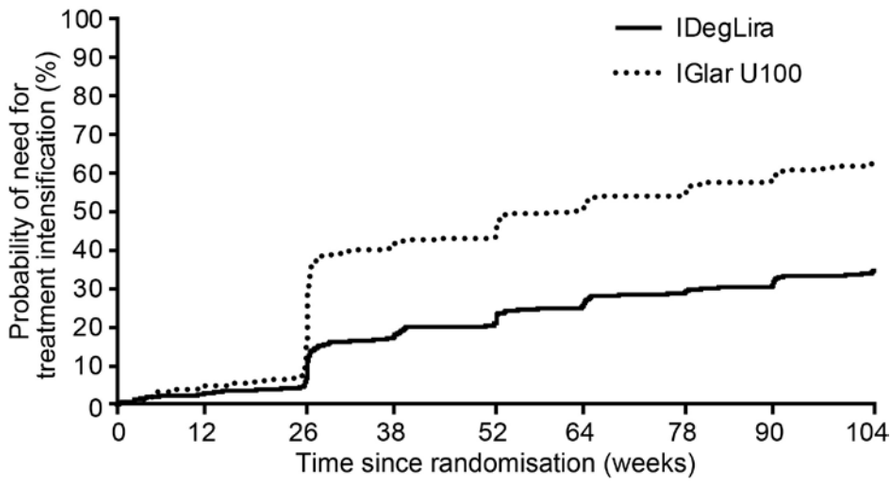
Background and aims: Long-term glycaemic control is key to avoid type 2 diabetes (T2D) complications. Few trials have studied treatment durability and impact on time to intensification, which affects overall maintenance of glycaemic control. The aim of DUAL VIII was to compare the durability of glycaemic control of insulin degludec/liraglutide (IDegLira) vs. insulin glargine 100 units/mL (IGlar U100) in a trial mirroring clinical practice.

Materials and methods: Patients (n=1012) with T2D (HbA_{1c} 7–11%) on oral antidiabetic drugs (OADs) were randomised 1:1 to open-label IDegLira or IGlar U100 in a 104-week trial to assess treatment durability. The primary endpoint was time from randomisation to treatment intensification (HbA_{1c} ≥7.0% at 2 consecutive visits including Week 26); patients who met the primary endpoint discontinued study drug.

Results: Baseline characteristics were similar. Over 104 weeks, fewer patients with IDegLira required intensification vs. IGlar U100 (37.4% vs. 66.2%). Patients treated with IDegLira had a significantly longer time to intensification (median: >2 years/~1 year for IDegLira/IGlar U100; **Figure**). There was a greater effect with IDegLira vs. IGlar U100 after 104 weeks, had patients remained on treatment and intensification not been needed, in terms of: patients achieving HbA_{1c} <7% (55.7 vs. 28.5%), and HbA_{1c} <7% with no weight gain (20.9 vs. 6.3%), lower estimated mean insulin dose (36 vs. 51 U; estimated treatment difference –14.9 U), and 56% lower rate of severe or blood glucose-confirmed symptomatic hypoglycaemia (0.38 vs. 0.86 events/patient-year of exposure), p<0.0001 for all. Safety results were similar.

Conclusion: Improved long-term glycaemic control, evidenced by significantly longer time to treatment intensification, was achieved with IDegLira vs. IGlar U100 in patients previously uncontrolled on OADs.

DUAL VIII trial
Kaplan–Meier curve of time to need for treatment intensification (HbA_{1c} ≥7% at two consecutive visits including Week 26)



IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL
Data based on full analysis set. Patients discontinuing treatment contributed to analyses as having needed treatment intensification from time of discontinuation. The primary analysis used a stratified log-rank test where treatment, baseline HbA_{1c} group (<8.5, ≥8.5%) and previous oral antidiabetic treatment (sulphonylurea/non-sulphonylurea) were included as strata in the model (stratified log-rank test p<0.0001, in favour of IDegLira)

Clinical Trial Registration Number: NCT02501161

Liraglutide diabetes

Oral presentation 84

T Barrett, WV Tamborlane, U Fainberg, H Frimer-Larsen, M Hafez, PM Hale, MY Jalaludin, M Kovarenko, I Libman, PV Rao, N Shehadeh, S Turan, D Weghuber, M Barrientos-Pérez

Efficacy and safety of liraglutide vs. placebo in children and adolescents with type 2 diabetes: the ellipse randomised trial results

Poster presentation 770

R Rea, L Blonde, L Belousova, U Fainberg, PA Garcia-Hernandez, SM Jain, MS Kaltoft, O Mosenzon, J Nafach, MS Palle

Liraglutide as add-on to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes: a 26-week, randomised, double-blind, placebo-controlled trial

Oral presentation 84

Efficacy and safety of liraglutide vs. placebo in children and adolescents with type 2 diabetes: the ellipse randomised trial results

T BARRETT[1], WV TAMBORLANE[2], U FAINBERG[3], H FRIMER-LARSEN[3], M HAFEZ[4], PM HALE[5], MY JALALUDIN[6], M KOVARENKO[7], I LIBMAN[8], PV RAO[9], N SHEHADEH[10], S TURAN[11], D WEGHUBER[12], M BARRIENTOS-PÉREZ[13]
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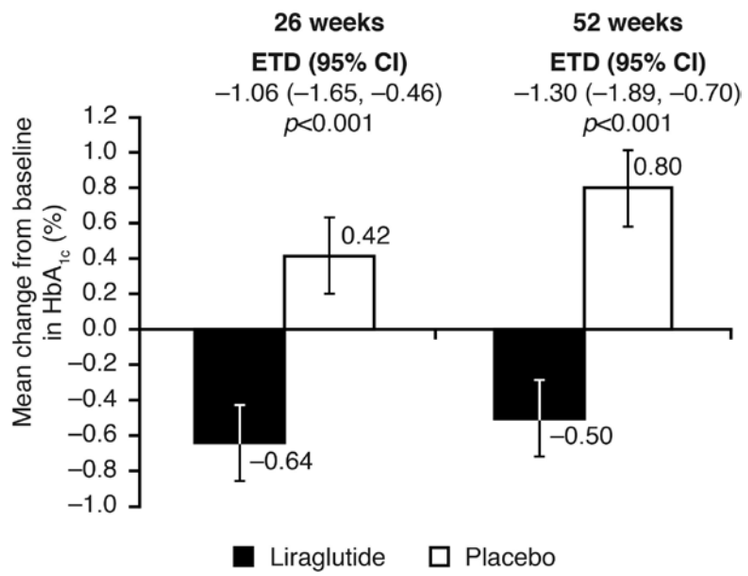
Background and aims: Despite the T2D burden in children and adolescents, metformin and insulin are the only agents currently approved for this age group. The ellipse trial assessed the efficacy and safety of liraglutide vs. placebo when added to metformin, with or without basal insulin, as a new treatment option for youth with T2D.

Materials and methods: In ellipse, children aged 10 to <17 years were randomised 1:1 to liraglutide up to 1.8 mg/day (or max. tolerated dose) or placebo for a 26-week, double-blind period, followed by a 26-week open label extension for additional data collection (total 52 weeks). Inclusion criteria: BMI >85th percentile of the general age- and gender-matched population; HbA_{1c} ≥7.0% and ≤11% if diet- and exercise-treated or ≥6.5% and ≤11% if treated with metformin and/or basal insulin. Primary endpoint: HbA_{1c} change from baseline at 26 weeks. Secondary endpoints included change in fasting plasma glucose (FPG). Safety was assessed throughout the trial.

Results: Of 135 children randomised, 134 were exposed to treatment (liraglutide 66; placebo 68). Mean age: 14.6 yrs (SD: 1.7 yrs; range: 10.0–16.9 yrs; 30% aged 10–14 yrs), 62% were female. Demographics were similar in both groups. At 26 weeks (primary endpoint), HbA_{1c} decreased from 7.87% to 7.13% with liraglutide and increased from 7.69% to 8.19% with placebo (estimated treatment difference [ETD]: –1.06%; 95% CI 1.65, 0.46; p<0.001; **Figure**). Similarly, after 52 weeks, HbA_{1c} decreased with liraglutide and increased with placebo (ETD: –1.30%; 95% CI 1.89, –0.70; p<0.001; **Figure**). Liraglutide also decreased FPG at 26 and 52 weeks (–1.1 and –1.0 mmol/L, respectively) versus increases with placebo (+0.8 and +0.8 mmol/L respectively). The percentage of children who reported an adverse event (AE) was similar in both groups (84.8% vs. 80.9% with liraglutide vs. placebo, respectively). Gastrointestinal AEs were more frequent with liraglutide (33.3%) than placebo (13.2%).

Conclusion: Liraglutide at doses up to 1.8 mg/day (when added to metformin ± basal insulin) offers a new, efficacious and durable treatment option, with an acceptable safety profile, for children and adolescents with T2D in need of improved glycaemic control.

Figure. Mean change from baseline in HbA_{1c}, estimate from primary analysis



Error bars represent standard error. ETD, estimated treatment difference

Clinical Trial Registration Number: NCT01541215

Poster presentation 770

Liraglutide as add-on to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes: a 26-week, randomised, double-blind, placebo-controlled trial

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Background and aims: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) reduce HbA_{1c}, but randomised controlled trial data on their combined use are limited. The LIRA-ADD2SGLT2i trial compared the effect on glycaemic control of liraglutide 1.8 mg/day (a GLP-1 analogue) vs. placebo as add-on to SGLT2i ± metformin in patients with type 2 diabetes (T2D).

Materials and methods: In this phase 3b trial, patients with T2D on a stable dose of SGLT2i ± metformin and with HbA_{1c} 7.0-9.5% were randomised 2:1 to add either liraglutide 1.8 mg/day or placebo. Exclusion criteria included a history of diabetic ketoacidosis (DKA) while treated with SGLT2i and/or estimated GFR <60 mL/min/1.73 m^2. The primary endpoint was HbA_{1c} change from baseline at 26 weeks; also assessed after 26 weeks were change in body weight, proportion of patients achieving HbA_{1c} <7% and safety. All were analysed regardless of premature trial product discontinuation or initiation of glucose lowering rescue medication.

Results: Overall, 412 patients were screened, 303 were randomised and 280 (92.4%) completed treatment (92.1% with liraglutide, 93.0% with placebo). Baseline characteristics were balanced between treatment groups: mean HbA_{1c} 8.0%, mean body weight 91.1 kg, mean diabetes duration 9.9 years. At week 26, the mean HbA_{1c} change from baseline with liraglutide was –0.98% (n=203) vs. –0.30% with placebo (n=100) (estimated treatment difference [ETD]: –0.68%; 95% CI: –0.89, –0.48; p<0.001). The mean change in body weight from baseline with liraglutide was –2.81 kg vs. –1.99 kg with placebo (ETD: –0.82 kg; 95% CI: –1.73, 0.09; p=0.077). In the liraglutide group, 51.8% of patients achieved HbA_{1c} <7.0% vs. 23.2% in the placebo group (odds ratio: 5.1; 95% CI: 2.67, 9.87; p<0.001). A higher proportion of patients in the liraglutide group reported ≥1 treatment-emergent adverse events (AEs) than in the placebo group (66.3% vs. 47.0%). Nausea was the most frequent AE, occurring in 26.2% of the liraglutide group and 6.0% of the placebo group, and it generally had early onset (initial 4 weeks) and was transient. Similar incidences of hypoglycaemic episodes were reported in both groups (8.9% with liraglutide vs. 8.0% with placebo); none was severe. The proportion of patients reporting serious AEs was low in both groups (liraglutide 2.5% vs. placebo 1.0%). No fatalities occurred in either group and there were no reports of acute renal failure, DKA, diabetic foot ulcers or amputations with liraglutide in combination with SGLT-2i.

Conclusion: In patients with T2D, the addition of liraglutide to SGLT2i therapy (± metformin) provided superior glycaemic control vs. ≥ placebo, and had a safety profile consistent with the known safety profile of both drug classes.

Clinical Trial Registration Number: NCT02964247

Poster

Poster presentation 575

D Dicker, AL Birkenfeld, T Garvey, G Mingrone, SD Pedersen, A Satylganova, D Skovgaard, D Sugimoto, N Zeuthen, O Mosenzon

Effect of liraglutide 3.0 mg on glycaemic parameters in adults with overweight/obesity and type 2 diabetes treated with basal insulin: SCALE insulin trial

Poster presentation 576

G Mingrone, T Garvey, AL Birkenfeld, D Dicker, SD Pedersen, A Satylganova, DC Skovgaard, D Sugimoto, N Zeuthen, O Mosenzon

Efficacy and safety of liraglutide 3.0 mg in individuals with overweight or obesity and type 2 diabetes treated with basal insulin: the SCALE insulin trial

Poster presentation 575

Effect of liraglutide 3.0 mg on glycaemic parameters in adults with overweight/obesity and type 2 diabetes treated with basal insulin: SCALE insulin trial

D DICKER[1], AL BIRKENFELD[2], T GARVEY[3], G MINGRONE[4], SD PEDERSEN[5], A SATYLGANOVA[6], D SKOVGAARD[6], D SUGIMOTO[7], N ZEUTHEN[6], O MOSENZON[8]
[1]D Hasharon Hospital, Petah Tikva, Israel; [2]Universitätsklinikum, Dresden, Germany; [3]University of Alabama, Birmingham, AL, USA; [4]UCSC, Rome, Italy; [5]C-ENDO Diabetes & Endocrinology Clinic, Calgary, AB, Canada; [6]Novo Nordisk, Søborg, Denmark; [7]Cedar Crosse Research Center, Chicago, IL, USA; [8]Hadassah Hebrew University Hospital, Jerusalem, Israel

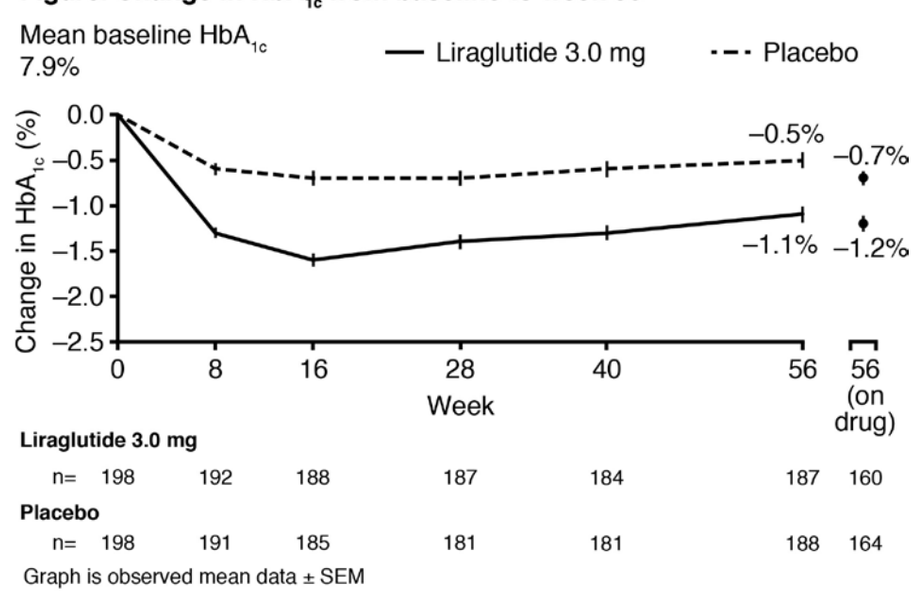
Background and aims: Liraglutide at doses ≤1.8 mg once-daily with basal insulin is an established treatment for T2D. The SCALE Insulin trial investigated the efficacy and safety of liraglutide 3.0 mg for weight management in adults with obesity and T2D on basal insulin; here we report the glycaemic effects.

Materials and methods: This 56-week double-blind trial randomised adults with T2D (HbA_{1c} 6–10%) and overweight/obesity (BMI ≥27 kg/m^2) to liraglutide 3.0 mg (n=198) or placebo (n=198), both as adjunct to intensive behaviour therapy (IBT). All patients were on basal insulin and ≤2 oral antidiabetic drugs at baseline (BL). Patients on sulphonylurea (SU) were stratified between arms. Insulin doses were titrated weekly in both arms to achieve the same fasting plasma glucose (FPG) targets. Week 56 outcomes were assessed using all observed values regardless of treatment status at Week 56 and a jump-to-reference (placebo at 56 weeks) multiple imputation approach for missing data.

Results: Mean characteristics at randomisation: 57 years old, 48% male, BMI 36 kg/m^2, HbA_{1c} 7.9%, FPG 8.0 mmol/L, diabetes duration 12 years, 34% on SU. 195 and 197 participants, respectively, were exposed to liraglutide 3.0 mg and placebo, with 166 (83.8%) and 168 (84.8%) on drug at week 56. Mean ΔHbA_{1c} at 56 weeks was –1.09% vs. –0.55% with liraglutide vs. placebo, respectively (estimated treatment difference [ETD] –0.53; p<0.0001) (**Figure**). Mean ΔFPG was –1.02 vs. –0.64 mmol/L (ETD –0.39, p=0.1502), respectively. At Week 56, the 7-point self-measured blood glucose profile showed improved postprandial glucose control (Δmean daytime value: liraglutide, –2.2 mmol/L; placebo, –1.5 mmol/L) (ETD –0.69; p=0.0032). Mean total insulin dose increased by 2.8U vs. 17.8U (ETD –15U, p<0.0001) with liraglutide vs. placebo, respectively, from BL mean of 38U. Proportion of individuals achieving the composite endpoint of HbA_{1c} <7.0% + ≥5% weight loss (WL) with liraglutide and placebo was 39.0% and 13.9% (OR 3.94, p<0.0001), respectively, and for HbA_{1c} <7.0% + ≥5% WL + no documented symptomatic hypoglycaemia (DSH) was 17.8% and 6.2% (OR 3.28, p=0.0006), respectively. DSH (on drug) occurred at rates of 4.25 vs. 2.99 events/patient-year with liraglutide vs. placebo, respectively, in patients taking SU at BL, and 2.90 vs. 4.75 events/patient-year in patients not taking SU at BL.

Conclusion: In insulin-treated patients with T2D and overweight/obesity, liraglutide 3.0 mg + IBT achieved better glycaemic control vs. placebo + IBT (based on ΔHbA_{1c}), in addition to clinically relevant WL, with need for less basal insulin and no increase in risk of hypoglycaemia.

Figure. Change in HbA_{1c} from baseline to week 56



Clinical Trial Registration Number: NCT02963922

Poster

Poster presentation 576

Efficacy and safety of liraglutide 3.0 mg in individuals with overweight or obesity and type 2 diabetes treated with basal insulin: the SCALE insulin trial

G MINGRONE[1], T GARVEY[2], AL BIRKENFELD[3], D DICKER[4], SD PEDERSEN[5], A SATYLGANOVA[6], DC SKOVGAARD[6], D SUGIMOTO[7], N ZEUTHEN[6], O MOSENZON[8]
[1]UCSC, Rome, Italy; [2]University of Alabama, Birmingham, AL, USA; [3]Universitätsklinikum, Dresden, Germany; [4]D Hasharon Hospital, Petah Tikva, Israel; [5]C-ENDO Diabetes & Endocrinology Clinic, Calgary, AB, Canada; [6]Novo Nordisk, Søborg, Denmark; [7]Cedar Crosse Research Center, Chicago, IL, USA; [8]Hadassah Hebrew University Hospital, Jerusalem, Israel

Background and aims: Liraglutide 3.0 mg is approved for weight management in adults with and without type 2 diabetes (T2D). Liraglutide up to 1.8 mg has been used in combination with insulin for treatment of T2D, but combination of a 3.0 mg dose with insulin has not previously been investigated.

Materials and methods: The 56-week double-blind SCALE Insulin trial randomised individuals with insulin-treated T2D and overweight or obesity (BMI ≥27 kg/m^2) to liraglutide 3.0 mg or placebo, both as adjunct to intensive behaviour therapy. All individuals were on stable treatment with basal insulin and up to 2 oral antidiabetic drugs. Primary endpoints were mean change in body weight (%) and proportion with weight loss (WL) ≥5% at Week 56. Endpoints were analysed using all observed values regardless of Week 56 treatment status, and a jump-to-reference multiple imputation approach to missing data.

Results: Mean baseline characteristics at randomisation (n=198) for liraglutide 3.0 mg included: 55.9 years of age, 54.5% female, weight 101 kg, BMI 35.9 kg/m^2, diabetes duration 11.4 years, HbA_{1c} 7.9%. Corresponding placebo values (n=198) were 57.6 years, 50.0% female, weight 99 kg, BMI 35.3 kg/m^2, 12.8 years of age, HbA_{1c} 8.0%. Of those randomised, 195 were exposed to liraglutide 3.0 mg and 197 to placebo, with 166 (83.8%) and 168 (84.8%) on drug at Week 56. The primary analysis demonstrated WL at Week 56 of –5.85% and –1.53%, respectively, estimated treatment difference (ETD) –4.32 (95% CI –5.48; –3.16, p<0.0001). The proportion achieving WL ≥5% was 51.80% of individuals on liraglutide and 23.98% on placebo (OR 3.41, p<0.0001). Respective values for >10% WL were 22.77% and 6.55% (OR 4.21, p<0.0001) (other efficacy outcomes in **Table**). HbA_{1c} reduction was greater with liraglutide vs. placebo (–1.09 vs. –0.55%, p<0.0001), and there were respective changes in insulin dose of +2.8U and +17.8U from a baseline mean (both groups) of 38U (ETD –15U, p<0.0001). Documented hypoglycaemia (on-drug) occurred at respective rates of 7.42 and 9.38 events/patient-year with liraglutide 3.0 mg and placebo, with 3 and 2 severe events in each group respectively. Adverse event incidence was similar for liraglutide 3.0 mg and placebo, except in gastrointestinal events (liraglutide 3.0 mg, 62.1%; placebo, 46.7%).

Conclusion: In individuals with basal insulin-treated T2D, liraglutide 3.0 mg was superior to placebo with respect to mean and categorical WL, and improvements in glycaemic control. More hypoglycaemic episodes were reported in individuals with placebo vs. liraglutide 3.0 mg and no new safety or tolerability issues were observed.

Table. Endpoints at 56 weeks

Endpoint at 56 weeks	Liraglutide 3.0 mg	Placebo	Estimated treatment difference (ETD) or odds ratio (OR) [95% CI]
Change in weight (%)	–5.85	–1.53	ETD: –4.32 [–5.48; –3.16], p<0.0001
Individuals achieving ≥5% weight loss (%)	51.80	23.98	OR: 3.41 [2.19; 5.31], p<0.0001
Individuals achieving >10% weight loss (%)	22.77	6.55	OR: 4.21 [2.16; 8.18], p<0.0001
Change in waist circumference (cm)	–5.28	–2.56	ETD: –2.71 [–3.90; –1.53], p<0.0001
Change in HbA_{1c} (%)	–1.09	–0.55	ETD: –0.53 [–0.76; –0.31], p<0.0001
Change in heart rate (beats/min)	1.35	–0.16	ETD: 1.51 [–0.20; 3.21], p=NS
Change in systolic blood pressure (mmHg)	–5.60	–1.62	ETD: –3.98 [–6.41; –1.54], p=0.0014
Change in diastolic blood pressure (mmHg)	–2.34	–0.94	ETD: –1.40 [–3.01; 0.22], p=NS
Change in SF-36 Physical function score	2.68	2.28	ETD: 0.39 [–0.97; 1.76], p=NS
Change in IWQoL-Lite CT Physical function score	8.20	5.74	ETD: 2.46 [–1.48; 6.40], p=NS

NS, p≥0.05

Clinical Trial Registration Number: NCT02963922

Poster

Liraglutide + semaglutide – once weekly

Poster presentation 756

LA Leiter, SC Bain, DL Bhatt, JB Buse, CD Mazer, R Pratley, S Lindberg, S Rasmussen, H Vrazic, S Verma

Liraglutide and semaglutide improve cardiovascular and renal outcomes across baseline BP categories: analysis of LEADER and SUSTAIN 6

Poster presentation 998

V Perkovic, SC Bain, G Bakris, JB Buse, T Gondolf, T Idorn, N Lausvig, K Mahaffey, SP Marso, MA Nauck, R Pratley, P Rossing, B Zinman, J Mann

Estimated GFR (eGFR) loss with glucagon-like peptide-1 (GLP-1) analogue treatment: data from SUSTAIN 6 and LEADER

Poster presentation 758

B Zinman, S Verma, SC Bain, JB Honoré, J Mann, MA Nauck, R Pratley, S Rasmussen, M Sejersten Ripa, JB Buse

Impact of microvascular disease on cardiorenal outcomes in type 2 diabetes: an analysis from the LEADER and SUSTAIN 6 clinical trials

Poster presentation 1164

S Verma, SC Bain, DL Bhatt, LA Leiter, CD Mazer, DK McGuire, R Pratley, B Zinman, S Lindberg, S Rasmussen, H Vrazic, JB Buse

Liraglutide and semaglutide improve cardiovascular and renal outcomes across most BMI categories in type 2 diabetes: results of the LEADER and SUSTAIN 6 trials

Poster presentation 756

Liraglutide and semaglutide improve cardiovascular and renal outcomes across baseline BP categories: analysis of LEADER and SUSTAIN 6

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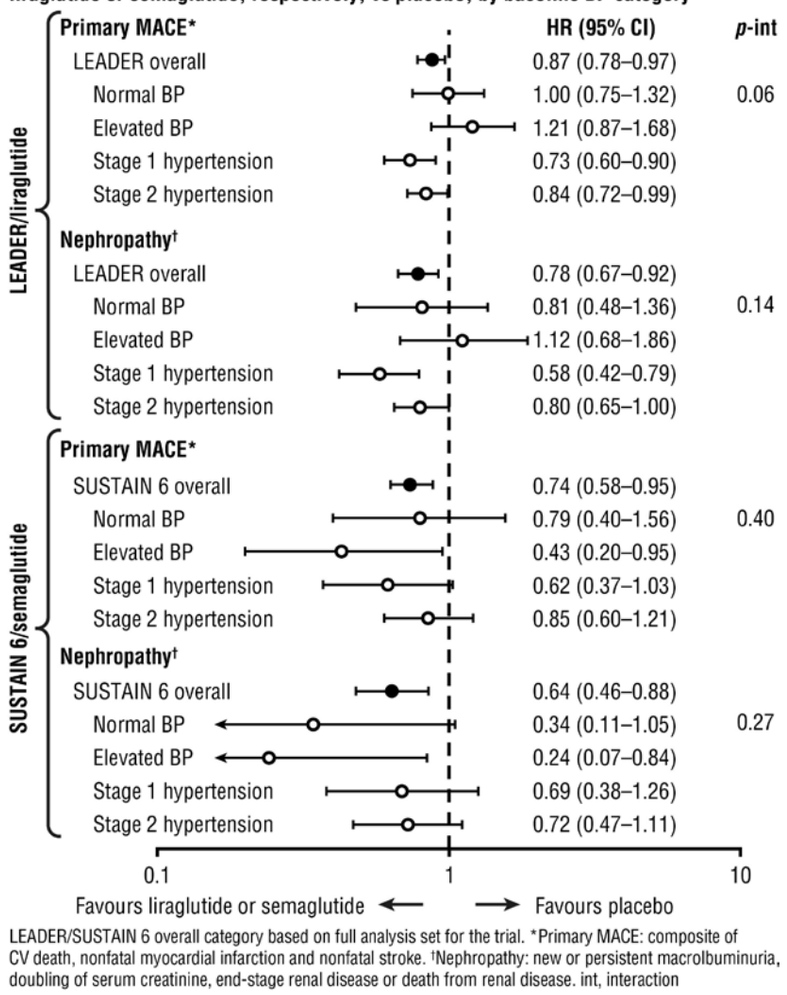
Background and aims: High blood pressure (BP) is prevalent in patients with type 2 diabetes (T2D). This *post hoc* analysis evaluated major adverse cardiovascular (CV) events (MACE) and renal events in patients from LEADER and SUSTAIN 6 (CV outcome trials) with T2D and high CV risk who received liraglutide or semaglutide (vs. placebo) according to BP categories: normal (<120/80 mmHg), elevated (systolic 120–129 and diastolic <80 mmHg), stage 1 hypertension (systolic 130–139 or diastolic 80–89 mmHg), and stage 2 hypertension (systolic ≥140 or diastolic ≥90 mmHg).

Materials and methods: LEADER and SUSTAIN 6 were global randomised CV outcome trials of liraglutide and semaglutide, vs. placebo, in 9340 and 3297 patients, respectively, with T2D and high CV risk. Primary outcome was MACE (CV death, nonfatal myocardial infarction or nonfatal stroke), with secondary outcomes including nephropathy. We evaluated the cardiorenal effect of liraglutide and semaglutide on the primary and secondary renal endpoints by baseline BP categories using Cox proportional hazards, with treatment and risk group as factors, adjusted for baseline characteristics related to cardiorenal risk.

Results: In LEADER, 15%, 14%, 30% and 41% of patients had normal BP, elevated BP, stage 1 or stage 2 hypertension, respectively; proportions for SUSTAIN 6 were 13%, 13%, 31% and 43%, respectively. Within each BP category, baseline demographics were generally well balanced across trial groups. The effects of liraglutide and semaglutide on MACE and secondary nephropathy endpoints across BP categories are shown in the **Figure**.

Conclusion: Liraglutide and semaglutide demonstrated consistent improvements in CV and renal outcomes across most baseline BP categories.

Hazard ratios (95% CIs) for cardiorenal outcomes within LEADER and SUSTAIN 6 for liraglutide or semaglutide, respectively, vs placebo, by baseline BP category



LEADER/SUSTAIN 6 overall category based on full analysis set for the trial. *Primary MACE: composite of CV death, nonfatal myocardial infarction and nonfatal stroke. †Nephropathy: new or persistent macrolbuminuria, doubling of serum creatinine, end-stage renal disease or death from renal disease. int, interaction

Clinical Trial Registration Numbers: NCT01179048; NCT01720446

Poster

Poster presentation 758

Impact of microvascular disease on cardiorenal outcomes in type 2 diabetes: an analysis from the LEADER and SUSTAIN 6 clinical trials

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Background and aims: History of microvascular disease in type 2 diabetes (T2D) may increase risk of cardiovascular (CV) events. We analysed LEADER and SUSTAIN 6 *post hoc* to evaluate this relationship, and the efficacy of glucagon-like peptide-1 (GLP-1) analogues in this context.

Materials and methods: LEADER and SUSTAIN 6 randomised patients with T2D and high CV risk to liraglutide or semaglutide vs. placebo. Primary endpoint was a composite of CV death, nonfatal myocardial infarction or stroke (major adverse cardiovascular event [MACE]). Other endpoints included expanded MACE and a nephropathy composite. We evaluated cardiorenal risk and effects of liraglutide and semaglutide in patients with a history of microvascular disease using an adjusted Cox proportional hazards model.

Results: In LEADER, 62% (5761/9340) of patients had a baseline history of ≥1 microvascular complication (SUSTAIN 6: 71% [2356/3297]). These individuals were older, with longer diabetes duration, greater insulin use and lower estimated GFR. Risk of MACE, irrespective of treatment, was higher in patients with microvascular and CV disease vs. CV disease alone. Placebo event rates for MACE, expanded MACE and nephropathy were higher in those with history of microvascular disease. Liraglutide and semaglutide reduced CV risk in those with and without microvascular disease and nephropathy in those with microvascular disease (**Table**). Few nephropathy events occurred in those without microvascular disease.

Conclusion: Liraglutide and semaglutide reduced the risk of cardiorenal events across patients with microvascular disease.

Table: Cardiorenal events in LEADER and SUSTAIN 6 by microvascular disease at baseline

Endpoint		Microvasc. disease at baseline	HR [95% CI] GLP-1 analogue vs placebo	GLP-1 analogue		Placebo		p-interaction
				N (%)	R	N (%)	R	
LEADER	MACE	Any microvasc.	0.86 [0.75; 0.99]	393 (13.6)	3.6	447 (15.6)	4.1	0.97
		None	0.87 [0.72; 1.04]	215 (12.1)	3.1	247 (13.7)	3.6	
	Nephropathy	Any microvasc.	0.72 [0.60; 0.86]	216 (7.5)	2.0	281 (9.8)	2.6	0.22
		None	0.94 [0.64; 1.37]	52 (2.9)	0.8	56 (3.1)	0.8	
SUSTAIN 6	MACE	Any microvasc.	0.83 [0.63; 1.10]	93 (8.0)	3.9	111 (9.3)	4.5	0.03
		None	0.41 [0.22; 0.74]	15 (3.1)	1.5	35 (7.6)	3.7	
	Nephropathy	Any microvasc.	0.57 [0.40; 0.80]	53 (4.5)	2.2	93 (7.8)	3.8	0.16
		None	1.19 [0.44; 3.21]	9 (1.9)	0.9	7 (1.5)	0.7	

GLP-1, glucagon like peptide-1; MACE, major adverse cardiovascular event; microvasc., microvascular; N, number of patients with event; R, events per 100 patient-years of observation.

Clinical Trial Registration Numbers: NCT01179048; NCT01720446

Poster

Poster presentation 998

Estimated GFR (eGFR) loss with glucagon-like peptide-1 (GLP-1) analogue treatment: data from SUSTAIN 6 and LEADER

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Background and aims: Previous SUSTAIN 6 and LEADER cardiovascular (CV) outcomes trials data indicate that the GLP-1 analogues semaglutide and liraglutide may have beneficial effects on kidney function. This *post hoc* analysis investigated the semaglutide and liraglutide effects on change in eGFR evaluated as total eGFR slope.

Materials and methods: SUSTAIN 6 and LEADER assessed CV, kidney and safety outcomes with semaglutide and liraglutide vs. placebo, in 3297 and 9340 patients with type 2 diabetes and at high CV risk, respectively. Median treatment duration was 2.1 and 3.8 years, respectively. In the current analysis, eGFR change over time was evaluated by overall population and baseline eGFR subgroup (<60 vs. ≥60 mL/min/1.73 m^2) for semaglutide (1.0 mg) and liraglutide vs. placebo using a linear regression model with random slope and intercept; treatment differences between annual slopes were estimated (estimated treatment differences [ETDs]).

Results: In the overall population, a slower rate of annual eGFR reduction was observed with semaglutide vs. placebo (mean annual ETD of 0.87 mL/min/1.73 m^2 favouring semaglutide); this effect appeared more pronounced for baseline eGFR <60 mL/min/1.73 m^2 (annual ETD: 1.62 mL/min/1.73 m^2 slower eGFR reduction, **Table**). In LEADER, the annual eGFR reduction was slower for liraglutide vs. placebo for the overall population; the effect was more marked in patients with baseline eGFR <60 mL/min/1.73 m^2 (annual ETD: 0.67 mL/min/1.73 m^2 slower eGFR reduction, **Table**).

Conclusion: Annual loss of kidney function was slower in patients treated with semaglutide or liraglutide vs. placebo. The benefit appears more pronounced in patients with pre-existing chronic kidney disease.

Table. Annual change in eGFR and estimated treatment difference in SUSTAIN 6 and LEADER

Population	Estimate [95% CI]; *p*-value			
	Semaglutide 1.0 mg	Placebo	Liraglutide 1.8 mg	Placebo
Overall population	N=821	N=1648	N=4512	N=4498
Annual eGFR change (mL/min/1.73 m^2)/year	−1.05 [−1.41; −0.69]	−1.92 [−2.18; −1.67]	−1.72 [−1.84; −1.61]	−1.98 [−2.10; −1.87]
ETD (mL/min/1.73 m^2)/year	0.87 [0.44; 1.31]; <0.0001		0.26 [0.11; 0.41]; 0.0009	
Baseline eGFR				
<60 mL/min/1.73 m^2	N=204	N=427	N=968	N=905
Annual eGFR change (mL/min/1.73 m^2)/year	−0.25 [−0.97; 0.48]	−1.87 [−2.37; −1.36]	−1.44 [−1.68; −1.19]	−2.11 [−2.37; −1.85]
ETD (mL/min/1.73 m^2)/year	1.62 [0.74; 2.50]; 0.0003		0.67 [0.33; 1.02]; 0.0001	
≥60 mL/min/1.73 m^2	N=617	N=1221	N=3544	N=3593
Annual eGFR change (mL/min/1.73 m^2)/year	−1.31 [−1.72; −0.90]	−1.94 [−2.24; −1.64]	−1.80 [−1.92; −1.67]	−1.95 [−2.08; −1.83]
ETD (mL/min/1.73 m^2)/year	0.63 [0.13; 1.14]; 0.0003		0.15 [−0.01; 0.32]; 0.0734	
p-value treatment by subgroup interaction	0.0567		0.0084	

A positive estimated treatment difference (ETD) value indicates lesser eGFR reduction with semaglutide or liraglutide vs placebo.

Clinical Trial Registration Numbers: NCT01179048; NCT01720446

Poster

Poster presentation 1164

Liraglutide and semaglutide improve cardiovascular and renal outcomes across most BMI categories in type 2 diabetes: results of the LEADER and SUSTAIN 6 trials

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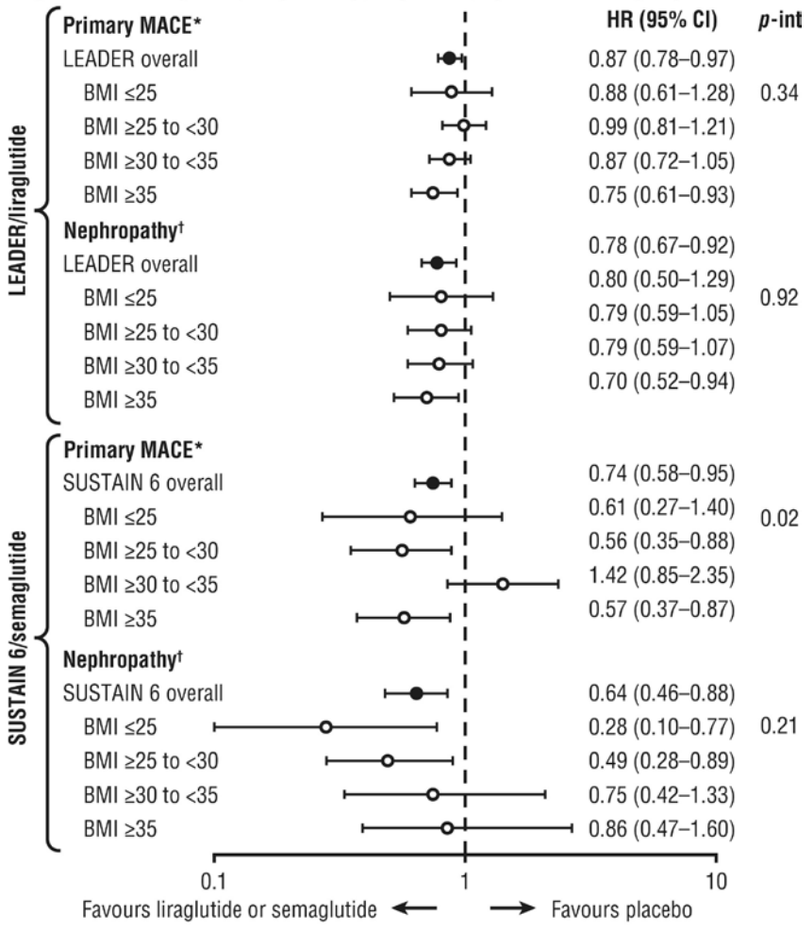
Background and aims: Whether cardiorenal benefits of liraglutide and semaglutide are consistent across BMI categories is unknown. We performed *post hoc* analyses on LEADER and SUSTAIN 6 data to evaluate cardiorenal efficacy by BMI groups in patients with type 2 diabetes (T2D) and high cardiovascular (CV) risk.

Materials and methods: LEADER and SUSTAIN 6 were randomised CV outcome trials of liraglutide and semaglutide vs. placebo in 9340 and 3297 patients, respectively, with T2D and high CV risk. The primary outcome was a composite of CV death, nonfatal myocardial infarction or nonfatal stroke (major adverse CV events, MACE), with secondary outcomes including nephropathy measures (new or persistent macroalbuminuria, serum creatinine doubling, end-stage kidney disease or death from kidney disease). We evaluated the effect of liraglutide and semaglutide on these cardiorenal outcomes, stratified by baseline BMI groups. HRs for treatment vs. placebo were calculated using a Cox proportional hazards model with treatment and eligibility risk group as factors, adjusted for baseline characteristics related to cardiorenal risk within BMI groups.

Results: In LEADER, 9%, 29%, 32% and 30% of patients had a baseline BMI of <25 kg/m^2, ≥25–<30 kg/m^2, ≥30–<35 kg/m^2 and ≥35 kg/m^2, respectively; for SUSTAIN 6, this was 8%, 28%, 33% and 31%. Baseline characteristics were mostly balanced within BMI groups. Both liraglutide and semaglutide improved MACE and nephropathy outcomes across most BMI groups vs. placebo (**Figure**). Additionally, more weight loss was observed with liraglutide (<25 kg/m^2: –0.85 kg; ≥25–<30 kg/m^2: –1.93 kg; ≥30-<35 kg/m^2: –2.06 kg; ≥35 kg/m^2: –3.25 kg; *p*-interaction: <0.001) and semaglutide (<25 kg/m^2: –3.34 kg; ≥25–<30 kg/m^2: –3.09 kg; ≥30–<35 kg/m^2: –3.65 kg; ≥35 kg/m^2: –3.99 kg; *p*-interaction: 0.09) vs. placebo.

Conclusion: In LEADER and SUSTAIN 6, liraglutide and semaglutide improved CV and renal outcomes with no apparent systematic differences across BMI groups.

Hazard ratios (95% CIs) for cardiorenal outcomes within LEADER and SUSTAIN 6 for liraglutide or semaglutide, respectively, vs placebo, by baseline BMI group



LEADER/SUSTAIN 6 overall category based on full analysis set for the trial. *Primary MACE: composite of CV death, nonfatal MI and nonfatal stroke. †Nephropathy: new or persistent macroalbuminuria, doubling of serum creatinine, end-stage kidney disease or death from kidney disease. BMI in kg/m^2; int, interaction.

Clinical Trial Registration Numbers: NCT01179048; NCT01720446

Poster

Semaglutide – once weekly

Oral presentation 52

I Lingvay, A Catarig, JP Frias, H Kumar, NL Lausvig, CW le Roux, D Thielke, A Viljoen, RJ McCrimmon

Once-weekly semaglutide vs. canagliflozin in type 2 diabetes: results of the SUSTAIN 8 trial

Oral presentation 53

MS Capehorn, A-M Catarig, JK Furberg, A Janez, HC Price, S Tadayon, B Vergès, M Marre

Efficacy and safety of semaglutide 1.0 mg once weekly vs. liraglutide 1.2 mg once daily as add-on to 1–3 oral glucose-lowering drugs in subjects with type 2 diabetes (SUSTAIN 10)

Oral presentation 54

RJ McCrimmon, A Catarig, JP Frias, NL Lausvig, CW le Roux, D Thielke, I Lingvay

Effects of once-weekly semaglutide vs. canagliflozin on body composition in type 2 diabetes: a substudy of the SUSTAIN 8 trial

Poster presentation 754

JPH Wilding, HW Rodbard, KT Uusinarkaus, L Van Gaal, T Hansen, AML Sandberg, S Tadayon, MJ Davies

Weight loss induced by semaglutide once weekly contributes to improved health-related quality of life and treatment satisfaction

Poster presentation 757

SC Bain, CV Desouza, T Gondolf, T Hansen, I Holst, RR Rea, J Seufert

The effect of once-weekly semaglutide on MACE, blood pressure and lipids by race and ethnicity: a SUSTAIN 6 post hoc analysis

Poster presentation 773

A Viljoen, JP Frias, T Gondolf, J Unger

Efficacy and safety of semaglutide by baseline BMI in SUSTAIN 1–5 and 7

Poster presentation 775

RE Pratley, VR Aroda, T Gondolf, T Hansen, I Lingvay, J Lüdemann, TV Skjøth, A Viljoen

Efficacy and safety of once-weekly semaglutide low dose 0.5 mg vs. once-weekly dulaglutide high dose 1.5 mg in type 2 diabetes: a post hoc analysis of SUSTAIN 7

Poster presentation 776

B Ludvik, V Bhosekar, RS Busch, I Holst, A Philis-Tsimikas, J Thrasher, VC Woo, E Yildirim, B Zinman

Efficacy and safety of semaglutide by background sodium-glucose cotransporter-2 inhibitor: a post hoc analysis of SUSTAIN 9

Poster presentation 821

M Löndahl, K Nihlberg, A Ericsson

Cost-effectiveness of once-weekly semaglutide versus empagliflozin in people with type 2 diabetes and inadequate glycaemic control in Sweden

Oral presentation 52

Once-weekly semaglutide vs. canagliflozin in type 2 diabetes: results of the SUSTAIN 8 trial

I LINGVAY[1], A CATARIG[2], JP FRIAS[3], H KUMAR[4], NL LAUSVIG[2], CW LE ROUX[5], D THIELKE[2], A VILJOEN[6], RJ MCCRIMMON[7]
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Background and aims: SUSTAIN 8 was a randomised, double-blind, double-dummy phase 3 trial assessing the efficacy and safety of semaglutide, a glucagon-like peptide-1 receptor agonist, vs. canagliflozin, a sodium-glucose cotransporter-2 inhibitor, in subjects with type 2 diabetes (T2D) uncontrolled on metformin.

Materials and methods: Adults with T2D (HbA_{1c} 7.0–10.5%) on stable metformin were randomised to once-weekly subcutaneous semaglutide 1.0 mg or daily oral canagliflozin 300 mg for 52 weeks (N=788). Primary endpoint was change in HbA_{1c}. Secondary endpoints included achievement of prespecified HbA_{1c} targets and change in body weight, and safety assessments. Primary hypothetical estimand was treatment difference (semaglutide vs. canagliflozin) at week 52 for all randomised subjects, if all subjects completed treatment without rescue medication. Primary analysis was an ANCOVA with treatment, stratification, region and baseline as fixed effects. Missing data were handled by multiple imputation using observed data from subjects in the same treatment group.

Results: Baseline characteristics were comparable across treatment groups (**Table**). Semaglutide led to superior reductions in HbA_{1c} from baseline vs. canagliflozin (mean, –1.5% vs. –1.0%; estimated treatment difference [ETD] –0.49; 95% confidence interval [CI]: –0.65;–0.33; $p<0.0001$). More semaglutide- vs. canagliflozin-treated subjects achieved HbA_{1c} targets of <7.0% (66.1% vs. 45.1%; odds ratio [OR] 2.77 [95% CI: 1.98;3.85]) and ≤6.5% (52.8% vs. 23.6%; OR 4.19 [95% CI: 2.97;5.92]) ($p<0.0001$ for both). Semaglutide demonstrated superior reductions in body weight vs. canagliflozin (–5.3 vs. –4.2 kg; ETD –1.06 [95% CI: –1.76;-0.36]; $p=0.0029$). Overall, 22.3% achieved ≥10% weight loss with semaglutide vs. 8.9% for canagliflozin (OR 2.99 [95% CI: 1.89;4.75]; $p<0.0001$); similar proportions in each group achieved ≥5% weight loss (**Table**). More subjects taking semaglutide vs. canagliflozin achieved composite outcome of HbA_{1c} <7.0%, no weight gain and no severe or blood glucose-confirmed hypoglycaemia (59.9% vs. 39.9%; OR 2.56 [95% CI: 1.84;3.54]), and HbA_{1c} reduction ≥1.0% point and ≥5% weight loss (39.2% vs. 24.3%; OR 1.99 [95% CI: 1.43;2.76]) ($p<0.001$ for both). Gastrointestinal adverse events (AEs) were the most common AEs with semaglutide (46.9%, n=184); infections and infestations were the most common with canagliflozin (34.5%, n=136). Overall, 9.7% and 5.1% discontinued study medication due to AEs in semaglutide vs. canagliflozin, respectively. There were no unexpected safety findings.

Conclusion: Semaglutide 1.0 mg once weekly led to superior reductions in HbA_{1c} and body weight vs. daily canagliflozin 300 mg.

Table. SUSTAIN 8: key baseline characteristics and efficacy results

	Semaglutide 1.0 mg OW (n=394)	Canagliflozin 300 mg OD (n=394)	Analysis [95% CI]
Baseline characteristics			
Age, years (SD)	55.7 (11.1)	57.5 (10.7)	
Diabetes duration, years (SD)	7.5 (5.9)	7.2 (5.4)	
HbA_{1c}			
Baseline % (SD)	8.3 (1.0)	8.2 (1.0)	
Change at week 52, %-point (SD)	–1.5 (1.3)	–1.0 (1.1)	ETD –0.49 [–0.65;–0.33]**
Subjects achieving ADA target HbA_{1c} <7.0%, %	66.1	45.1	OR 2.77 [1.98;3.85]**
Subjects achieving AACE target HbA_{1c} <6.5%, %	52.8	23.6	OR 4.19 [2.97;5.92]**
Body weight, kg			
Baseline (SD)	90.6 (22.6)	89.8 (22.6)	
Change at week 52 (SD)	–5.3 (5.5)	–4.2 (3.9)	ETD –1.06 [–1.76;–0.36]*
Subjects achieving weight loss ≥5%	51.1	46.6	OR 1.22 [0.90;1.66]
Subjects achieving weight loss ≥10%	22.3	8.9	OR 2.99 [1.89;4.75]**

*p=0.0029 vs canagliflozin. **p<0.0001 vs canagliflozin. Data are observed or imputed from the on-treatment-without-rescue-medication observation period. ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologists; CI, confidence interval; ETD, estimated treatment difference; OD, once daily; OR, odds ratio; OW, once weekly; SD, standard deviation.

Clinical Trial Registration Number: NCT03136484

Oral presentation 53

Efficacy and safety of semaglutide 1.0 mg once weekly vs. liraglutide 1.2 mg once daily as add-on to 1–3 oral glucose-lowering drugs in subjects with type 2 diabetes (SUSTAIN 10)

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Background and aims: Semaglutide and liraglutide are glucagon-like peptide-1 analogues for the treatment of type 2 diabetes (T2D). SUSTAIN 10 compared the efficacy and safety of the anticipated most frequent semaglutide dose (1.0 mg) vs. the most frequently prescribed liraglutide dose in Europe (1.2 mg).

Materials and methods: In this phase 3b, open-label trial, 577 adults with T2D (HbA_{1c} 7.0–11.0%) on 1–3 oral glucose-lowering drugs (metformin, sulphonylurea, sodium-glucose cotransporter-2 inhibitors) were randomised 1:1 to semaglutide 1.0 mg once weekly or liraglutide 1.2 mg once daily, both administered subcutaneously. Primary and confirmatory secondary endpoints were change in HbA_{1c} and body weight, respectively, from baseline to week 30. Supportive secondary efficacy endpoints included other glycaemic and weight parameters. Treatment satisfaction (change from baseline in Diabetes Treatment Satisfaction Questionnaire status version [DTSQs] scores) was also assessed.

Results: Mean HbA_{1c} (baseline 8.2%) decreased by 1.7%-point with semaglutide vs. 1.0%-point with liraglutide (estimated treatment difference [ETD] –0.69%-point; 95% CI –0.82 to –0.56; $p<0.0001$; **Table**); 80.4% vs. 45.9% of subjects achieved HbA_{1c} <7.0% (odds ratio [OR] 5.98; $p<0.0001$) and 58.5% vs. 24.8% achieved HbA_{1c} ≤6.5% (OR 4.84; $p<0.0001$). Mean body weight (baseline 96.9 kg) decreased by 5.8 kg with semaglutide vs. 1.9 kg with liraglutide (ETD –3.83 kg; 95% CI –4.57 to –3.09; $p<0.0001$); 55.9% vs. 17.7% of subjects achieved weight loss ≥5% (OR 5.89; $p<0.0001$) and 19.1% vs. 4.4% achieved weight loss ≥10% (OR 4.99; $p<0.0001$). HbA_{1c} <7.0% without severe or blood glucose-confirmed symptomatic hypoglycaemia and no weight gain was achieved by 75.6% of subjects on semaglutide and 36.8% on liraglutide (OR 6.07; $p<0.0001$). The DTSQs summary score improved in both treatment arms (ETD 0.63; $p=0.0814$). Overall, 70.6% and 66.2% of exposed subjects reported treatment-emergent adverse events (TEAEs) with semaglutide and liraglutide, respectively; 5.9% and 7.7% reported serious TEAEs. No fatal TEAEs were reported. The most frequently reported TEAEs with semaglutide (43.9%) and liraglutide (38.3%) were gastrointestinal (GI) disorders. The proportion of subjects with TEAEs leading to premature treatment discontinuation was 11.4% with semaglutide and 6.6% with liraglutide; 7.6% and 3.8% discontinued due to GI AEs.

Conclusion: Semaglutide 1.0 mg was superior to liraglutide 1.2 mg in reducing HbA_{1c} and body weight. Safety profiles were generally similar, except for a higher proportion of subjects with GI TEAEs with semaglutide.

Table. Key primary and secondary outcomes from the SUSTAIN 10 trial

	Overall baseline, mean	Change from baseline at week 30, mean		ETD [95% CI]
		Semaglutide 1.0 mg n=290	Liraglutide 1.2 mg n=287	
HbA_{1c}, %	8.2	–1.7	–1.0	–0.69* [–0.82; –0.56]
Body weight, kg	96.9	–5.8	–1.9	–3.83* [–4.57; –3.09]
FPG, mmol/L	9.9	–2.7	–1.4	–1.24* [–1.54; –0.93]
7-point SMBG: mean, mmol/L	10.3	–3.0	–2.1	–0.89* [–1.15; –0.64]
Postprandial increment of 7-point SMBG, mmol/L	2.3	–0.9	–0.4	–0.53* [–0.77; –0.28]
		Proportion of responders at week 30 (%)		
		Semaglutide 1.0 mg n=290	Liraglutide 1.2 mg n=287	OR [95% CI]
HbA_{1c} <7.0%		80.4	45.9	5.98* [3.83; 9.32]
HbA_{1c} ≤6.5%		58.5	24.8	4.84* [3.21; 7.30]
Weight loss ≥5%		55.9	17.7	5.89* [3.93; 8.81]
Weight loss ≥10%		19.1	4.4	4.99* [2.57; 9.68]
HbA_{1c} <7.0% without severe or BG-confirmed symptomatic hypoglycaemia and no weight gain		75.6	36.8	6.07* [4.02; 9.15]

*p<0.0001. BG, blood glucose; CI, confidence interval; ETD, estimated treatment difference; FPG, fasting plasma glucose; OR, odds ratio; SMBG, self-measured blood glucose.

Clinical Trial Registration Number: NCT03191396

Oral presentation 54

Effects of once-weekly semaglutide vs. canagliflozin on body composition in type 2 diabetes: a substudy of the SUSTAIN 8 trial

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Background and aims: SUSTAIN 8 was a randomised, double-blind, double-dummy, phase 3 trial of semaglutide 1.0 mg once weekly vs. canagliflozin 300 mg once daily over 52 weeks in adults with type 2 diabetes (T2D) on stable treatment with metformin. In SUSTAIN 8, treatment with semaglutide led to superior reductions in HbA_{1c} and body weight vs. daily canagliflozin. Because these two agents have different mechanisms for weight loss, whole-body dual-energy X-ray absorptiometry (DXA) was performed in a subset of subjects to investigate the effects of semaglutide vs. canagliflozin on body composition.

Materials and methods: A total of 178 subjects underwent DXA to assess change in total fat mass. Prespecified supportive secondary measures of body composition included changes in total lean mass, ratio of total fat mass to total lean mass and visceral fat mass. Additional parameters such as waist circumference were also assessed *post hoc*. Data from the on-treatment without rescue medication period were analysed using ANCOVA with treatment, region and baseline values as fixed effects using multiple imputation for missing data where missing values were imputed using observed data from subjects in the same treatment group.

Results: In this subset of the SUSTAIN 8 population (n=178/788), the overall reduction in total fat plus lean mass was 5.7 kg with once-weekly semaglutide vs. 4.1 with canagliflozin once daily (**Table**). Total fat mass decreased by 3.4 and 2.6 kg in the semaglutide and canagliflozin groups, respectively (estimated treatment difference [ETD] –0.79 kg [95% confidence interval (CI): –2.10;0.51]). Similarly, total lean mass decreased by 2.3 and 1.5 kg (ETD –0.78 kg [95% CI: –1.61;0.04]). These changes resulted in slight decreases in the ratio of total fat mass to total lean mass in both groups; similar reductions were observed for visceral fat mass in both treatment arms (**Table**).

Conclusion: Both once-weekly semaglutide 1.0 mg and canagliflozin 300 mg once daily showed beneficial effects on body composition, including reduction in total and visceral fat mass, after 52 weeks treatment in subjects with T2D. There was no statistically significant difference between the arms for any of the body composition endpoints.

Table. SUSTAIN 8 substudy: key baseline characteristics and changes in body composition from baseline at week 52.

	Semaglutide 1.0 mg OW (n=88)	Canagliflozin 300 mg OD (n=90)	Analysis ETD [95% CI]
Baseline characteristics			
Age, years	57.8 (9.9)	58.6 (10.1)	
Diabetes duration, years	8.8 (5.8)	8.5 (5.2)	
Body weight, kg	89.0 (18.2)	87.6 (18.2)	
Changes in body composition at 52 weeks			
Total fat mass			
Baseline, kg / %	33.9 (11.9) / 38.0 (8.4)	32.5 (10.0) / 37.3 (7.3)	
Change at week 52, kg / %-point	–3.4 (0.51) / –1.43 (0.39)	–2.62 (0.45) / –1.21 (0.35)	–0.79 [–2.10;0.51] / –0.21 [–1.26;0.84]
Total lean mass			
Baseline, kg / %	51.3 (10.1) / 59.1 (8.0)	51.3 (10.7) / 59.7 (6.9)	
Change at week 52, kg / %-point	–2.26 (0.31) / –1.24 (0.39)	–1.48 (0.28) / –1.10 (0.34)	–0.78 [–1.61;0.04] / 0.14 [–0.89;1.18]
Total fat plus lean mass, kg			
Baseline	85.2	83.9	
Change at week 52	–5.7	–4.1	
Total fat mass / total lean mass ratio, kg			
Baseline	0.7 (0.23)	0.7 (0.20)	
Change at week 52	–0.04 (0.01)	–0.03 (0.01)	–0.01 [–0.04;0.02]
Visceral fat mass			
Baseline, kg / %	1.5 (0.8) / 43.7 (16.2)	1.5 (0.8) / 44.0 (15.3)	
Change at week 52, kg / %-point	–0.18 (0.05) / –0.94 (0.94)	–0.11 (0.04) / 0.44 (0.69)	–0.07 [–0.20;0.06] / –1.38 [–3.65;–0.88]
Waist circumference, cm			
Baseline	104.0 (13.5)	105.9 (13.1)	
Change at week 52*	–3.9 (5.6)	–2.5 (5.5)	

*Not prespecified for the substudy. Data for changes at week 52 are mean (standard error). All other data are mean (standard deviation) unless otherwise specified. CI, confidence interval; ETD, estimated treatment difference; OD, once daily; OW, once weekly.

Clinical Trial Registration Number: NCT03136484

Poster presentation 754

Weight loss induced by semaglutide once weekly contributes to improved health-related quality of life and treatment satisfaction

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Background and aims: Semaglutide, a glucagon-like peptide-1 analogue for the once-weekly subcutaneous treatment of type 2 diabetes (T2D), provided superior glycaemic control and weight loss vs. comparators in the SUSTAIN clinical trial programme. Weight loss is recognised as an important outcome in the management of T2D. This *post hoc* analysis assessed if weight loss was associated with improvements in patient-reported health-related quality of life (HRQoL) and treatment satisfaction in SUSTAIN 2–5 and 7.

Materials and methods: The proportions of subjects who achieved weight loss responses of ≥5% and ≥10% in the semaglutide arms were pooled across the trials (N=2,808; comparator data not evaluated), and presented both overall and by dose (semaglutide 0.5 mg or 1.0 mg). Changes in HRQoL (measured by the Physical Component Summary [PCS] and Mental Component Summary scores of the Short Form-36 Health Survey version 2® [SF 36v2®]) and treatment satisfaction scores (measured by the Diabetes Treatment Satisfaction Questionnaire, status version [DTSQs]) were evaluated in subjects who achieved ≥5% and ≥10% weight loss vs. those who did not at end of treatment (30, 40 or 56 weeks). Norm-based scoring is used for the SF-36v2®, setting the general population mean to 50 for each domain; higher and increasing scores indicate better health. The standard DTSQs scales range from 0 to 6 on a 7-point Likert scale, where 6 indicates the highest treatment satisfaction and 0 the lowest, with the exception of questions on the perception of hyper- and hypoglycaemia, where 6 indicates the lowest treatment satisfaction and 0 the highest.

Results: Overall, 51.0% and 17.4% of subjects achieved ≥5% and ≥10% weight loss with semaglutide (pooled groups). Significantly greater improvements in most of the PCS components and the overall PCS and DTSQs scores were reported by subjects achieving ≥5% and ≥10% weight loss vs. those not achieving these responses in the semaglutide 1.0 mg and pooled semaglutide groups (**Table**). The DTSQs perception of hyperglycaemia improved in each weight loss and semaglutide group, while there was no change in the perception of hypoglycaemia in any group.

Conclusion: Weight loss induced by semaglutide 1.0 mg was associated with improvements in PCS domains of the SF-36v2®, overall treatment satisfaction and perception of hyperglycaemia across the SUSTAIN 2–5 and 7 trials. These data suggest that weight loss may be an important factor determining HRQoL improvements during T2D treatment with semaglutide.

Table. Comparison of health-related quality of life and treatment satisfaction scores in subjects achieving weight loss responses (≥5% and ≥10%) vs subjects not achieving weight loss responses in the SUSTAIN 2–5 and 7 trials

		Semaglutide 0.5 mg ERD [95% CI]		Semaglutide 1.0 mg ERD [95% CI]		Semaglutide pooled (0.5 mg and 1.0 mg) ERD [95% CI]	
		Weight loss ≥5% vs <5%†	Weight loss ≥10% vs <10%†	Weight loss ≥5% vs <5%‡	Weight loss ≥10% vs <10%‡	Weight loss ≥5% vs <5%§	Weight loss ≥10% vs <10%§
HRQoL (SF-36v2® scores)	PCS	0.27 [−0.40;0.94]	0.25 [−0.80;1.30]	0.77 [0.20;1.35]**	1.62 [0.92;2.31]***	0.60 [0.16;1.03]**	1.26 [0.69;1.84]***
	Bodily pain	−0.13 [−1.06;0.80]	−0.39 [−1.84;1.06]	0.35 [−0.46;1.16]	1.55 [0.58;2.51]**	0.14 [−0.47;0.74]	0.98 [0.19;1.78]**
	General health	0.30 [−0.44;1.04]	0.41 [−0.75;1.58]	1.18 [0.55;1.81]***	1.53 [0.77;2.29]***	0.83 [0.36;1.31]**	1.20 [0.57;1.83]***
	Physical functioning	0.47 [−0.26;1.21]	0.82 [−0.31;1.96]	0.9 [0.29;1.55]**	1.38 [0.63;2.14]**	0.73 [0.25;1.21]**	1.26 [0.63;1.88]***
	Role-physical	0.06 [−0.76;0.88]	0.39 [−0.89;1.66]	0.01 [−0.69;0.72]	0.57 [−0.28;1.42]	0.17 [−0.36;0.70]	0.70 [−0.00;1.40]*
	MCS	−0.35 [−1.18;0.48]	0.32 [−0.97;1.60]	0.02 [−0.69;0.74]	−0.03 [−0.89;0.84]	−0.09 [−0.63;0.45]	0.08 [−0.63;0.78]
Treatment satisfaction (DTSQs scores)	Overall treatment satisfaction	0.39 [−0.08;0.86]	0.28 [−0.44;1.01]	0.50 [0.12;0.87]**	0.75 [0.30;1.20]**	0.51 [0.21;0.80]**	0.67 [0.28;1.05]**
	Perception of hyperglycaemia	−0.34 [−0.52;−0.16]***	−0.36 [−0.64;−0.09]**	−0.39 [−0.53;−0.24]***	−0.56 [−0.73;−0.39]***	−0.41 [−0.52;−0.29]***	0.55 [−0.70;−0.41]***
	Perception of hypoglycaemia	−0.04 [−0.19;0.12]	−0.04 [−0.29;0.20]	−0.05 [−0.18;0.08]	−0.02 [−0.18;0.13]	−0.05 [−0.15;0.05]	−0.04 [−0.17;0.09]

*p<0.05; **p<0.01; ***p<0.0001, vs subjects without weight loss response. †FAS: n=1,204. ‡FAS: n=1,604. §FAS: N=2,808. SF-36v2® and DTSQs responses were analysed using an analysis of covariance controlled for treatment, strata and baseline values of body weight and patient-reported outcomes. The principal components of the MCS score (Vitality, Social Functioning, Role Emotional and Mental Health) are not shown, as the overall MCS score was not significant. CI, confidence interval; DTSQs; Diabetes Treatment Satisfaction Questionnaire status version; ERD, estimated responder group difference of body weight loss (≥5% vs <5% and ≥10% vs <10%); FAS, full analysis set; HRQoL, health-related quality of life; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-36v2®; Short Form-36 Health Survey version 2®.

Clinical Trial Registration Numbers: NCT01930188, NCT01885208, NCT02128932, NCT02305381, NCT02648204

Poster

Poster presentation 757

The effect of once-weekly semaglutide on MACE, blood pressure and lipids by race and ethnicity: a SUSTAIN 6 post hoc analysis

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Background and aims: In the SUSTAIN 6 cardiovascular (CV) outcomes trial, once-weekly subcutaneous semaglutide added to standard of care significantly reduced major adverse cardiovascular events (MACE: non-fatal myocardial infarction, non-fatal stroke or cardiovascular death) versus placebo over 2 years in subjects with type 2 diabetes. The aim of this *post hoc* analysis was to assess the effect of semaglutide versus placebo on MACE, blood pressure (BP) and lipids by race and ethnicity in SUSTAIN 6.

Materials and methods: Two subgroup analyses were carried out, where data were analysed and stratified by race (Asian, Black/African American, Caucasian, Other) or ethnicity (Hispanic or non-Hispanic). In SUSTAIN 6, subjects were randomised to semaglutide 0.5 mg, 1.0 mg or volume-matched placebo. Data for the two semaglutide-dose groups were pooled and compared with the pooled placebo groups. Time-to-event results were analysed with a Cox proportional hazards model. Changes from baseline to week 104 of MACE and individual outcomes, BP and lipids were analysed using an analysis of covariance (ANCOVA), adjusted for country, treatment, baseline value and subgroup. The interaction between treatment and subgroup was added to the models.

Results: Of the total 3,297 subjects randomised to treatment, 2,736 were defined by investigators as Caucasian, 273 Asian, 221 Black/African American and 67 subjects reported as other races; 2,787 subjects were of non-Hispanic and 510 of Hispanic ethnicity. Mean baseline characteristics were similar across subgroups (age 64.7 years, males 61.5%, HbA_{1c} 8.7%, diabetes duration 14.2 years). Time to composite MACE and individual components were improved with semaglutide across all subgroups. Treatment with semaglutide affected BP similarly across race and ethnicity, except for systolic BP in Black/African American subjects where an estimated treatment difference for semaglutide vs. placebo of 4.47 [0.15;8.79] mmHg was reported from baseline to week 104. The effect of semaglutide on lipids was similar, irrespective of race or ethnicity (**Table**).

Conclusion: Overall, there was no evidence of a differential effect of semaglutide on risk reduction in MACE and its components nor lipids across race and ethnicity subgroups in this *post hoc* analysis of the SUSTAIN 6 CV outcomes trial. An increase from baseline in systolic BP in Black/African American subjects was reported with semaglutide. No effect was observed in other subgroups for systolic BP, nor on diastolic BP.

Table. Effect of semaglutide on MACE and individual outcomes, blood pressure and lipids by race and ethnicity subgroups in SUSTAIN 6

		Race					Ethnicity		
		Caucasian	Asian	Black/African American	Other	Interaction p-value	Hispanic	Non-Hispanic	Interaction p-value
Semaglutide (n)		1,384	121	108	35		256	1,392	
Placebo (n)		1,352	152	113	32		254	1,395	
MACE and individual outcomes HR [95% CI]	MACE	0.76 [0.58;1.00]	0.58 [0.25;1.34]	0.72 [0.23;2.28]	0.46 [0.08;2.50]	0.8793	0.67 [0.33;1.36]	0.74 [0.57;0.96]	0.7978
	CV death	0.98 [0.63;1.50]	0.32 [0.04;2.85]	1.01 [0.06;16.20]	N/A*	0.8089	0.79 [0.31;2.00]	1.00 [0.63;1.59]	0.6521
	Non-fatal MI	0.69 [0.45;1.07]	0.97 [0.36;2.60]	1.37 [0.31;6.12]	0.31 [0.03;3.00]	0.6637	0.65 [0.18;2.31]	0.74 [0.50;1.10]	0.8562
	Non-fatal stroke	0.70 [0.42;1.16]	0.31 [0.04;2.77]	N/A†	N/A†	0.9176	0.73 [0.16;3.27]	0.60 [0.36;0.99]	0.7995
Blood pressure at week 104 ETD (mmHg) [95% CI]	Systolic BP‡	–1.92 [–3.09;–0.74]	–4.98 [–8.61;1.35]	4.47 [0.15;8.79]	–11.02 [–18.45;–3.60]	0.0008	–3.22 [–5.93;–0.51]	–1.81 [–2.98;–0.64]	0.3489
	Diastolic BP‡	0.36 [–0.32;1.04]	–1.31 [–3.43;0.80]	–0.07 [–2.56;2.43]	–3.41 [–7.73;0.92]	0.1871	–0.18 [–1.75;1.39]	0.16 [–0.52;0.83]	0.6981
Lipids ETR (mmol/L) [95% CI]	Total cholesterol§	0.98 [0.96;0.99]	1.01 [0.96;1.06]	1.02 [0.96;1.08]	0.94 [0.85;1.05]	0.2913	0.98 [0.94;1.02]	0.98 [0.97;1.00]	0.9404
	LDL cholesterol§	0.97 [0.94;1.00]	0.98 [0.90;1.07]	1.08 [0.98;1.20]	0.89 [0.74;1.05]	0.1280	0.97 [0.91;1.03]	0.98 [0.95;1.00]	0.7455
	HDL cholesterol§	1.02 [1.00;1.03]	1.03 [0.99;1.07]	1.08 [1.02;1.13]	0.98 [0.90;1.07]	0.1214	1.01 [0.98;1.04]	1.02 [1.01;1.04]	0.5242
	Triglycerides§	0.95 [0.92;0.98]	1.01 [0.92;1.12]	0.86 [0.76;0.97]	0.95 [0.77;1.16]	0.2170	1.00 [0.93;1.07]	0.94 [0.91;0.97]	0.1946
	FFAs§	0.96 [0.92;0.99]	1.02 [0.92;1.14]	0.90 [0.79;1.02]	0.89 [0.71;1.11]	0.4132	0.95 [0.87;1.03]	0.96 [0.93;0.99]	0.7568

*No events in the placebo group. †No events in the semaglutide or placebo group. ‡Treatment difference between semaglutide and placebo (pooled 0.5 and 1.0 mg values for each treatment group) at week 104. §Treatment difference between semaglutide and placebo (pooled 0.5 and 1.0 mg values for each treatment group) at week 104. Lipids were analysed by log-transformation, therefore reported as ETR between semaglutide and placebo (pooled 0.5 and 1.0 mg values for each treatment group) at week 104. BP, blood pressure; CI, confidence interval; CV, cardiovascular; ETD, estimated treatment difference; ETR, estimated treatment ratio; FFA, free fatty acid; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events; MI, myocardial infarction; N/A, not applicable.

Clinical Trial Registration Number: NCT01720446

Poster

Poster presentation 773

Efficacy and safety of semaglutide by baseline BMI in SUSTAIN 1–5 and 7

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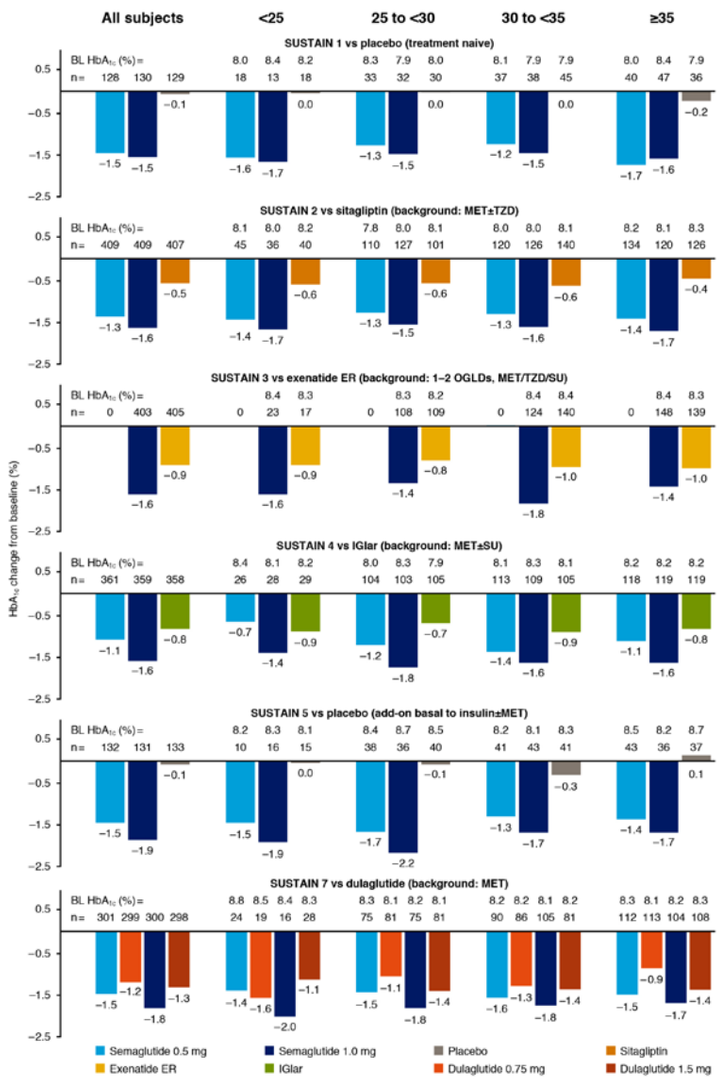
Background and aims: The SUSTAIN clinical trial programme evaluated the efficacy and safety of semaglutide, a once-weekly subcutaneous glucagon-like peptide-1 analogue, across the continuum of care in subjects with type 2 diabetes, including drug-naive subjects and those on background medication with oral glucose-lowering drugs ± insulin. Across the SUSTAIN trials, semaglutide showed superior reductions in HbA_{1c} and body weight vs. placebo and all active comparators (sitagliptin, exenatide extended release, insulin glargine, dulaglutide), and enabled a greater proportion of subjects to achieve clinically meaningful (≥5%) weight-loss responses. Higher body mass index (BMI) at baseline was generally associated with greater weight loss during semaglutide therapy. As exposure to a drug may be affected by body weight, this *post hoc* analysis was conducted to evaluate if reductions in HbA_{1c} were affected by baseline BMI in the SUSTAIN trials.

Materials and methods: Change in HbA_{1c} was evaluated by baseline BMI (<25, 25–<30, 30–<35 and ≥35 kg/m^2) for semaglutide vs. comparators (volume-matched placebo [SUSTAIN 1 and 5], sitagliptin 100 mg [SUSTAIN 2], exenatide extended release 2.0 mg [SUSTAIN 3], insulin glargine [SUSTAIN 4] and dulaglutide 0.75 and 1.5 mg [SUSTAIN 7]) by trial for SUSTAIN 1–5 and 7 in a mixed model for repeated measurement, with treatment, BMI subgroup and HbA_{1c} at baseline as covariates, and interaction between treatment and BMI subgroups at baseline. Safety data were pooled and analysed by a Cochran-Mantel-Haenszel analysis stratified by trial.

Results: There were no significant interactions between treatment and BMI, with the exception of semaglutide 0.5 mg in SUSTAIN 7, indicating a consistent effect of semaglutide vs. comparator on change in HbA_{1c} across BMI subgroups. Reductions in mean HbA_{1c} (%) from baseline were greater in all BMI subgroups with semaglutide vs. all comparators. The only exception was the <25 kg/m^2 BMI subgroup for semaglutide 0.5 mg vs. insulin glargine (–0.7% vs. –0.9%, respectively) and semaglutide 0.5 mg vs. dulaglutide 0.75 mg (–1.4% vs. –1.6%, respectively) (**Figure**). In all treatment arms, adverse events (AEs) occurred in a similar proportion of subjects across BMI subgroups. Gastrointestinal AEs were higher with semaglutide, but decreased with increasing baseline BMI, vs. comparators (semaglutide: <25 kg/m^2=48.8%, 25–<30 kg/m^2=43.0%, 30–<35 kg/m^2=39.4% and ≥35 kg/m^2=39.3% vs. comparators range: 21.2–28.9%). Premature treatment discontinuation due to AEs was higher in all BMI subgroups with semaglutide vs. comparators (5.6–15.3% vs. 2.3–8.3%).

Conclusion: The estimated treatment differences in mean HbA_{1c} (%) for semaglutide vs. placebo or active comparators do not appear to be influenced by baseline BMI. Semaglutide had an acceptable safety profile in all BMI subgroups.

Table. Change in HbA_{1c} (%) by baseline BMI (kg/m^2) in SUSTAIN 1–5 and 7



Values shown are estimated mean changes from baseline for subjects on treatment without rescue medication. BL, baseline; BMI, body mass index; exenatide ER, exenatide extended release; IGlar, insulin glargine; MET, metformin; OGLD, oral glucose-lowering drug; SU, sulphonylurea; TZD, thiazolidinedione.

Clinical Trial Registration Numbers: NCT02054897, NCT01930188, NCT01885208, NCT02128932, NCT02305381, NCT02648204

Poster

Poster presentation 775

Efficacy and safety of once-weekly semaglutide low dose 0.5 mg vs. once-weekly dulaglutide high dose 1.5 mg in type 2 diabetes: a *post hoc* analysis of SUSTAIN 7

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Background and aims: Semaglutide and dulaglutide are glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes (T2D). In SUSTAIN 7, an international, open-label, parallel group trial, adults with inadequately controlled T2D were randomised (1:1:1:1) to once-weekly subcutaneous semaglutide or once-weekly dulaglutide at low (0.5 vs. 0.75 mg) or high (1.0 vs. 1.5 mg) doses. Semaglutide provided superior glycaemic control and reductions in body weight at both low and high doses.

Materials and methods: This *post hoc* analysis was conducted to compare the effects of semaglutide low (0.5 mg) vs. dulaglutide high (1.5 mg) dose at Week 40, a comparison not prespecified and therefore not performed in the primary analyses of the SUSTAIN 7 trial. The analyses were performed using the prespecified statistical methods previously reported for the SUSTAIN 7 primary analyses, using data for all patients (full analysis set) randomised and exposed to treatment and before onset of any rescue medication. The mean age of study subjects was 56 years, baseline HbA_{1c} 8.2%, diabetes duration was 7.4 years, and 77% were Caucasian.

Results: Efficacy data (**Table**) showed similar glycaemic control as well as similar systolic and diastolic blood pressure, and greater weight loss, for semaglutide 0.5 mg vs. dulaglutide 1.5 mg. The frequency and severity of adverse events (AEs) were similar for semaglutide and dulaglutide, including gastrointestinal AEs (nausea: 23% vs. 20%, respectively; diarrhoea: 14% vs. 18%, respectively; vomiting: 10%, each treatment). Overall treatment discontinuation was 16% with semaglutide 0.5 mg and 12% with dulaglutide 1.5 mg, whereas premature discontinuation due to AEs was similar with semaglutide 0.5 mg and dulaglutide 1.5 mg (8% vs. 7%, respectively), of which discontinuation due to gastrointestinal AEs was the most frequent (5% each).

Conclusion: Semaglutide 0.5 mg showed similar improvements in glycaemic control, although with greater weight loss, vs. dulaglutide 1.5 mg at Week 40, with similar tolerability in subjects with T2D.

Table. Efficacy data for semaglutide low (0.5 mg) vs dulaglutide high (1.5 mg) once-weekly doses

		Semaglutide 0.5 mg n=301	Dulaglutide 1.5 mg n=299	p-values
HbA_{1c}, %	Baseline	8.3 (1.0)	8.2 (0.9)	
	Change from baseline at week 40	−1.5 (0.1)	−1.4 (0.1)	
	ETD [95% CI]	−0.14 [−0.30;0.01]		p=0.0756
Glycaemic responses, %	Proportion of subjects achieving HbA_{1c} <7.0% at week 40	68	67	p=0.4509
	Proportion of subjects achieving HbA_{1c} ≤6.5% at week 40	49	47	p=0.4226
Body weight, kg	Baseline	96.4 (24.4)	93.4 (21.8)	
	Change from baseline at week 40	−4.6 (0.3)	−3.0 (0.3)	
	ETD [95% CI]	−1.58 [−2.35;−0.82]		p<0.0001
Weight loss responses, %	Proportion of subjects achieving weight loss ≥5%	44	30	p=0.0093
	Proportion of subjects achieving weight loss ≥10%	14	8	p=0.0138
SBP, mmHg	Baseline	134 (14.8)	132 (13.6)	
	Change from baseline at week 40	−2.4 (0.8)	−2.9 (0.8)	
	ETD [95% CI]	0.42 [−1.68;2.52]		p=0.697
DBP, mmHg	Baseline	81 (9.0)	80 (8.7)	
	Change from baseline at week 40	−0.6 (0.5)	−0 (0.5)	
	ETD [95% CI]	0.54 [−1.86;0.79]		p=0.426
Adverse events, n(%)	Adverse events	204 (68)	221 (74)	
	Serious adverse events	17 (6)	22 (7)	
	Adverse events leading to premature discontinuation	24 (8)	20 (7)	
GI adverse events, n(%)	Nausea	68 (23)	60 (20)	
	Diarrhoea	43 (14)	53 (18)	
	Vomiting	31 (10)	29 (10)	

Values are mean (standard error) change from overall baseline mean (standard deviation) or ETD [95% CI], unless otherwise indicated, from a mixed model for repeated measurements analysis using on-treatment without rescue medication data. CI, confidence interval; DBP, diastolic blood pressure; ETD, estimated treatment difference; GI, gastrointestinal; SBP, systolic blood pressure.

Clinical Trial Registration Number: NCT02648204

Poster

Poster presentation 776

Efficacy and safety of semaglutide by background sodium-glucose cotransporter-2 inhibitor: a post hoc analysis of SUSTAIN 9

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Background and aims: The SUSTAIN trials demonstrated the efficacy and safety of once-weekly subcutaneous semaglutide, a glucagon-like peptide 1 analogue for the treatment of type 2 diabetes (T2D). SUSTAIN 9 investigated semaglutide 1.0 mg vs. placebo as add-on to sodium-glucose cotransporter-2 inhibitor (SGLT-2i) therapy, with or without metformin or a sulphonylurea. In SUSTAIN 9, change from baseline to Week 30 in HbA_{1c} (primary endpoint) and body weight (confirmatory secondary endpoint) were greater with semaglutide vs. placebo. No safety concerns were identified when adding semaglutide to SGLT-2i therapy. The aim of this *post hoc* analysis was to determine whether the effect of semaglutide vs. placebo on HbA_{1c}, body weight and adverse events (AEs) was consistent in subjects on different background SGLT 2is.

Materials and methods: Changes in HbA_{1c} and body weight from baseline to Week 30 were analysed by background SGLT-2i (empagliflozin [empa], canagliflozin [cana], dapagliflozin and dapagliflozin propanediol monohydrate [dapa] or other [ipragliflozin L-proline, luseogliflozin and tofogliflozin; drugs available only in Japan]) using an analysis of covariance. Proportions of subjects achieving HbA_{1c} targets, weight-loss responses and the triple composite endpoint of HbA_{1c} <7.0%, no weight gain and no severe or blood glucose-confirmed hypoglycaemia were analysed by background SGLT-2i using a logistic regression model. A test for interaction was used to evaluate any impact of background SGLT-2i on treatment effect.

Results: There was no significant interaction between background SGLT-2i and treatment effect (interaction p>0.05 for all endpoints). Across background SGLT-2i groups, reductions in HbA_{1c} and body weight were greater with semaglutide vs. placebo (**Table**). Similarly, the proportions of subjects achieving HbA_{1c} targets, weight loss responses and the triple composite endpoint were greater with semaglutide vs. placebo. There was no imbalance in AEs in the different subgroups.

Conclusion: In SUSTAIN 9, the effect of semaglutide vs. placebo on HbA_{1c} and body weight was consistent across SGLT-2i subgroups, and treatment was well tolerated.

Table. Efficacy endpoints in SUSTAIN 9 by background SGLT-2i therapy†

Background SGLT-2i	Empagliflozin (N=102)		Canagliflozin (N=68)		Dapagliflozin (N=106)		Other (N=25)		p-value for interaction
	Sema 1.0 mg (n=52)	Placebo (n=50)	Sema 1.0 mg (n=39)	Placebo (n=29)	Sema 1.0 mg (n=44)	Placebo (n=62)	Sema 1.0 mg (n=15)	Placebo (n=10)	
Baseline (SD) HbA_{1c}, %	8.0 (0.7)	7.9 (0.8)	7.8 (0.8)	7.8 (0.8)	8.1 (0.9)	8.2 (0.9)	8.5 (0.6)	8.3 (0.5)	
Estimated change from baseline (SE) at week 30 in HbA_{1c}, %	−1.4 (0.1)	−0.2 (0.1)	−1.4 (0.1)	+0.1 (0.2)	−1.5 (0.1)	−0.2 (0.1)	−2.2 (0.2)	−0.2 (0.2)	
ETD [95% CI]	−1.3 [−1.58;−0.97]**		−1.5 [−1.89;−1.13]**		−1.3 [−1.65;−1.03]**		−2.0 [−2.62;−1.43]**		0.169
Baseline (SD) body weight, kg	90.6 (17.2)	95.8 (23.4)	96.4 (20.9)	98.1 (20.0)	90.7 (16.9)	93.7 (21.9)	65.3 (13.2)	72.5 (12.9)	
Estimated change from baseline (SE) at week 30 in body weight, kg	−5.2 (0.5)	−1.3 (0.5)	−5.5 (0.6)	−0.2 (0.7)	−4.6 (0.6)	−1.1 (0.5)	−1.2 (0.9)	−0.2 (1.1)	
ETD [95% CI]	−3.9 [−5.37;−2.40]**		−5.3 [−7.10;−3.47]**		−3.4 [−4.91;−1.97]**		−1.0 [−3.90;1.85]		0.098
Subjects achieving HbA_{1c} <7.0% at week 30, %	76.3	28.3	82.4	16.6	73.3	13.4	92.4	10.0	
OR [95% CI]	14.44 [4.95;42.10]**		37.63 [8.40;168.49]**		31.41 [9.05;108.93]**		154.06 [10.45;2,270.38]*		0.3421
Subjects achieving HbA_{1c} ≤6.5% at week 30, %	53.8	2.1	63.6	4.3	46.8	5.9	69.9	0	
OR [95% CI]	70.05 [11.05;444.18]**		36.91 [5.78;235.70]*		16.21 [4.39;59.89]**		NE		0.5300
Subjects achieving weight loss ≥5% at week 30, %	51.8	7.4	51.7	4.4	55.4	10.3	22.8	10.0	
OR [95% CI]	10.96 [3.19;37.70]*		17.17 [2.78;105.85]*		12.87 [3.95;41.91]**		1.80 [0.20;16.36]		0.4421
Subjects achieving weight loss ≥10% at week 30, %	17.6	<0.1	21.8	3.5	9.4	1.7	7.1	0	
OR [95% CI]	NE		5.08 [0.81;31.75]		5.05 [0.78;32.53]		NE		0.7465
Subjects achieving HbA_{1c} <7.0% without weight gain and without severe or BG-confirmed hypoglycaemia, %	70.5	22.2	73.1	15.0	65.3	12.8	64.8	0	
OR [95% CI]	10.91 [3.96;30.01]**		16.72 [4.40;63.53]**		16.55 [5.40;50.70]**		NE		0.7562

*p<0.01 vs placebo. **p<0.0001 vs placebo. †302 subjects were randomised and 301 received trial medication; one subject was randomised but not included in this analysis due to not receiving an SGLT-2i at screening. For changes in HbA_{1c} and body weight, 'On-treatment without rescue medication' data were analysed using an analysis of covariance with treatment, subgroup and treatment by subgroup interaction, stratification factor and region as fixed factors, and baseline value as covariate. For all other endpoints, 'on-treatment without rescue medication' data were analysed using a logistic regression model with treatment, stratification factor and region as fixed factors, and baseline values as covariates. BG, blood glucose; CI, confidence interval; ETD, estimated treatment difference; NE, not estimable; OR, odds ratio; SD, standard deviation; SE, standard error; Sema, semaglutide; SGLT-2i, sodium–glucose cotransporter-2 inhibitor.

Clinical Trial Registration Number: NCT03086330

Poster

Poster presentation 821

Cost-effectiveness of once-weekly semaglutide versus empagliflozin in people with type 2 diabetes and inadequate glycaemic control in Sweden

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Background and aims: Once-weekly semaglutide is a glucagon-like peptide-1 (GLP-1) analogue for the treatment of type 2 diabetes (T2D). This abstract describes a cost-effectiveness analysis (CEA) of semaglutide 1.0 mg versus empagliflozin 25 mg in patients with T2D inadequately controlled with metformin monotherapy in Sweden.

Materials and methods: The CEA was made using the Institutet för Hälso- och Sjukvårdsekonomi (IHE) Diabetes Cohort Model. The model is based on metabolic risk equations from the Swedish National Diabetes Register and UKPDS, and does not regard any plausible cardiovascular benefits in addition to the traditional risk factors (including HbA_{1c}, BMI, lipids, blood pressure, age) in these equations. Analyses were conducted from a Swedish societal perspective reaching over a time horizon of 40 years. Data on the difference in HbA_{1c} decline (–8.5 mmol/mol (95% C.I –11.2, –6.0)/-0.8% (95% C.I. –1.04, –0.58)) and weight reduction (–2.05 kg (95% C.I –2.94, –1.15)) between the treatments was obtained from a published network meta-analysis investigating the differences in glycemic control between semaglutide and different SGLT-2 treatments. Baseline values of HbA_{1c}, BMI and age were varied over analyses to identify the patient groups in which semaglutide may be most cost-effective.

Results: Our results indicate that semaglutide is a cost-effective treatment option compared with empagliflozin in patients with inadequate control on oral anti-diabetic treatment. Semaglutide imposed a higher societal cost and more quality-adjusted life-years (QALYs) in all analyses vs. empagliflozin (cost difference: SEK 3,300–55,700 over a 40-year perspective and QALY gain 0.137–0.242). Cost per QALY varied from SEK 16,000–407,000, where the lowest cost per QALY was found in patients with higher baseline HbA_{1c} and lower age (**Table 1**), while baseline BMI did not have any significant impact on the results. A treatment is valued cost-effective in Sweden if cost per QALY is below SEK 500,000. The results are largely driven by the reduction in complications due to the larger HbA_{1c} decline with semaglutide compared to empagliflozin.

Conclusion: This CEA suggests that semaglutide could be a cost-effective treatment option versus empagliflozin in patients with T2D inadequately controlled with OADs from a Swedish societal perspective. The lowest cost per QALY was found in patients with higher baseline HbA_{1c} and lower age, while baseline BMI did not have any significant impact on the results.

Table 1: Cost per QALY (SEK) depending on baseline HbA1c, age and BMI

		HbA1c			
Age	BMI	55 mmol/mol (7.2%)	60 mmol/mol (7.65%)	65 mmol/mol (8.1%)	70 mmol/mol (8.55%)
56 years	28	224 000	142 000	50 000	16 000
	30	226 000	143 000	52 000	18 000
	34	232 000	148 000	56 000	23 000
66 years	28	389 000	290 000	186 000	156 000
	30	394 000	293 000	188 000	158 000
	34	407 000	302 000	193 000	162 000

(€ 1 = SEK 10.47 2019-03-19)

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M Haluzík, R Bauer, JW Eriksson, ST Hoff, K Kallenbach, RE Pratley, JB Buse

Efficacy of oral semaglutide according to diabetes duration: an exploratory subgroup analysis of the PIONEER trial programme

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K Dahl, J Blundell, C Gibbons, A Brooks, F Almazedi, ST Hoff, S Lövdahl, TA Bækdal

Oral semaglutide improves postprandial glucose and lipid metabolism and delays first-hour gastric emptying in subjects with type 2 diabetes

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Oral semaglutide reduces appetite and energy intake and improves control of eating in subjects with type 2 diabetes

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Similar efficacy and gastrointestinal tolerability versus exposure for oral and subcutaneous semaglutide

Oral presentation 49

Efficacy of oral semaglutide according to diabetes duration: an exploratory subgroup analysis of the PIONEER trial programme

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Background and aims: Oral semaglutide is the first oral glucagon-like peptide-1 receptor agonist for the treatment of type 2 diabetes. An exploratory analysis of data from the global Phase 3a PIONEER clinical development programme (PIONEER 1–5 and 7–8 trials) was conducted to assess the efficacy of once daily oral semaglutide 3, 7, 14 mg versus comparators by duration of diabetes at baseline.

Materials and methods: Data were included from all patients who participated in PIONEER 1–5, 7 and 8 (n=5657). Patients were grouped according to diabetes duration (<5, 5–<10 and ≥10 years) and by trial. In the PIONEER trials, patients were randomised to treatment with oral semaglutide (3, 7 or 14 mg) or comparator (placebo, empagliflozin, sitagliptin or liraglutide). Endpoints were change from baseline in HbA_{1c} (%) and body weight (kg) at Week 26 (Week 52 in PIONEER 7) and data were analysed for all randomised patients using the trial product estimand.

Results: Mean duration of diabetes at baseline ranged from 3.5 (PIONEER 1) to 15.0 years (PIONEER 8) across the trials. At baseline the mean HbA_{1c} (%) was similar across the diabetes duration subgroups within each trial, whereas the mean body weight was higher and age was lower in the subgroup with diabetes duration <5 years. Reductions in HbA_{1c} were generally greater with increasing oral semaglutide dose but were not affected by diabetes duration (**Table**). Estimated treatment differences in HbA_{1c} (%) at Week 26 (Week 52 in PIONEER 7) were consistent across the range of diabetes durations. In general, there were no statistically significant interactions between treatment and diabetes duration (**Table**). The estimated odds of achieving HbA_{1c} target <7.0% were greater with oral semaglutide 7 mg and 14 mg versus comparators in all groups, irrespective of diabetes duration subgroup.

Conclusion: Across the PIONEER trials, oral semaglutide improved glycaemic control versus comparators, with an effect that was consistent across subgroups of diabetes duration. These findings support the use of oral semaglutide across a broad population of patients with type 2 diabetes.

Table. Change from baseline in HbA_{1c} by diabetes duration in 7 global Phase 3a PIONEER trials

Trial	Diabetes duration (years)	Number of patients	Baseline HbA_{1c} (%)	Estimated mean change from baseline in HbA_{1c} (%-points)					
				Oral semaglutide				Comparator(s)	
				3 mg	7 mg	14 mg	Flex	Pbo	Active
PIONEER 1 (diet and exercise)	<5	529	7.9	–0.9	–1.4	–1.6	-	–0.3	-
	5–<10	108	7.9	–0.6	–1.1	–1.4	-	0.6	-
	≥10	66	8.0	–0.3	–1.0	–1.3	-	0.3	-
PIONEER 2 (vs empagliflozin 25 mg)	<5	347	8.1	-	-	–1.5	-	-	–0.9
	5–<10	274	8.1	-	-	–1.5	-	-	–0.9
	≥10	200	8.2	-	-	–1.1	-	-	–0.7
PIONEER 3 (vs sitagliptin 100 mg)	<5	577	8.2	–0.5	–1.3*	–1.4	-	-	–0.8
	5–<10	687	8.3	–0.5	–1.0	–1.4	-	-	–0.7
	≥10	599	8.3	–0.6	–0.9	–1.4	-	-	–0.9
PIONEER 4 (vs liraglutide 1.8 mg and pbo)	<5	278	7.9	-	-	–1.3	-	–0.1	–1.2
	5–<10	238	8.1	-	-	–1.3	-	–0.1	–1.2
	≥10	195	7.9	-	-	–1.3	-	–0.1	–1.0
PIONEER 5 (renal impairment)	<5	30	7.9	-	-	–1.5	-	0.0	-
	5–<10	82	7.9	-	-	–1.3	-	–0.5	-
	≥10	212	8.0	-	-	–1.0	-	0.0	-
PIONEER 7 (flex vs sitagliptin 100 mg)	<5	168	8.3	-	-	-	–1.4	-	–0.8
	5–<10	153	8.3	-	-	-	–1.4	-	–0.5
	≥10	183	8.3	-	-	-	–1.3	-	–0.7
PIONEER 8 (added-on to insulin)	<5	69	8.2	–0.5*	–0.7	–1.3	-	–0.1	-
	5–<10	145	8.2	–0.2	–0.9	–1.6	-	–0.3	-
	≥10	517	8.2	–0.7	–1.1	–1.4	-	0.0	-

Mixed model for repeated measures analysis with treatment, region, stratification factors and interaction between them, as well as diabetes duration group and interaction between treatment and diabetes duration groups as factors, and baseline value of dependent variable as covariate. *p<0.05 unadjusted two-sided test of no treatment by subgroup interaction (no * indicates that the p-value did not reach statistical significance). -, dose/treatment was not investigated in trial; BL, baseline; flex, flexible dose adjustment; pbo, placebo.

Clinical Trial Registration Numbers: NCT02906930; NCT02863328; NCT02607865; NCT02863419; NCT02827708; NCT02849080; NCT03021187

Oral presentation 50

Oral semaglutide improves postprandial glucose and lipid metabolism and delays first-hour gastric emptying in subjects with type 2 diabetes

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Background and aims: Subcutaneous (s.c.) administration of semaglutide, a glucagon-like peptide-1 analogue, improves postprandial glucose (PPG) and postprandial lipid (PPL) metabolism and delays first-hour gastric emptying (GE) in subjects with obesity and without type 2 diabetes (T2D). In this trial, the effects of a novel once-daily oral formulation of semaglutide on postprandial metabolism and GE was investigated in subjects with T2D.

Materials and methods: In this double-blind, cross-over trial, male and female subjects with T2D were randomised to a treatment sequence of two 12-week periods with oral semaglutide/placebo or placebo/oral semaglutide, separated by a washout period of 5–9 weeks. Oral semaglutide was dose-escalated to steady-state at 14 mg via two 4-week dosing steps of 3 mg and 7 mg. At the end of each treatment period, PPG metabolism was assessed following a standardised breakfast, PPG and PPL metabolism were assessed following a standardised fat-rich breakfast, and GE was assessed (by a paracetamol absorption test) following a standardised lunch. Primary endpoint was serum glucose AUC from 0 to 5 hours ($AUC_{0–5h}$) after start of standardised breakfast.

Results: A total of 15 subjects were randomised (13 male/2 female, mean age 58.2 years, mean HbA_{1c} 6.9%, mean BMI 30.8 kg/m^2), two of whom withdrew before completing the trial. After 12 weeks of treatment, fasting levels of glucose were significantly lower and C-peptide levels significantly higher with oral semaglutide vs. placebo. After a standardised breakfast, postprandial glucose ($AUC_{0–5h}$) and mean postprandial increments in glucose (mean incremental area under the 0–5-hour curve [$iAUC_{0–5h}$]) were significantly lower with oral semaglutide vs. placebo (**Table**). Postprandial glucagon was also significantly reduced with oral semaglutide. No significant differences were shown in fasting or postprandial serum insulin levels. Similar results for glucose metabolism were observed after a standardised fat-rich breakfast. Fasting levels of total, LDL, and VLDL-cholesterol, triglycerides (TG) and apolipoprotein B48 were significantly lower with oral semaglutide vs. placebo after 12 weeks of treatment. In addition, postprandial TG ($AUC_{0–8h}$) and mean postprandial increments in TG ($iAUC_{0–8h}$) were significantly lower for oral semaglutide vs. placebo. Postprandial VLDL-cholesterol and apolipoprotein B48 were also significantly reduced with oral semaglutide. During the first hour after a meal, GE was delayed (31% decrease in paracetamol $AUC_{0–1h}$) with oral semaglutide vs. placebo, which could explain at least part of the effect on PPG and PPL.

Conclusion: Oral semaglutide significantly improved fasting and postprandial glucose and lipid metabolism, and delayed GE during the first postprandial hour, results consistent with those seen with s.c. semaglutide.

Table. Fasting and postprandial glucose and lipid metabolism endpoints after 12 weeks of treatment

Oral semaglutide/placebo:	**ETR (95% CI)**		**ETD (95% CI)**	**Relative difference**
Standardised breakfast	**Fasting**	**Postprandial ($AUC_{0–5h}$)**	**Mean postprandial increment ($iAUC_{0–5h}$)**	
Glucose (mmol/L)	0.78 (0.70, 0.87)*	0.71 (0.63, 0.81)*	−1.25 (−2.04, −0.45)*	−86.8%
Insulin (pmol/L)	1.24 (0.86, 1.79)	0.91 (0.75, 1.12)	−44.02 (−96.86, 8.82)	−30.9%
Glucagon (pg/mL)	0.76 (0.55, 1.06)	0.71 (0.59, 0.85)*	−2.22 (−11.23, 6.79)	−76.3%
C-peptide (nmol/L)	1.20 (1.01, 1.42)*	0.99 (0.86, 1.13)	−0.18 (−0.44, 0.08)	−25.0%
Standardised fat-rich breakfast	**Fasting**	**Postprandial ($AUC_{0–8h}$)**	**Mean postprandial increment ($iAUC_{0–8h/8h}$)**	
Glucose (mmol/L)	0.77 (0.73, 0.82)*	0.77 (0.68, 0.87)*	−0.32 (−1.11, 0.47)	400.0%
Insulin (pmol/L)	1.47 (1.11, 1.96)*	1.00 (0.83, 1.22)	−33.96 (−76.95, 9.03)	−48.9%
Glucagon (pg/mL)	0.81 (0.64, 1.03)	0.77 (0.67, 0.89)*	−5.06 (−15.90, 5.77)	−36.3%
C-peptide (nmol/L)	1.25 (1.05, 1.48)*	1.01 (0.89, 1.15)	−0.18 (−0.32, −0.04)*	−48.6%
Triglycerides (mmol/L)	0.81 (0.72, 0.92)*	0.76 (0.64, 0.91)*	−0.36 (−0.68, −0.04)*	−32.1%
Free fatty acids (mmol/L)	0.95 (0.77, 1.17)	1.01 (0.82, 1.25)	0.03 (−0.02, 0.09)	−60.0%
VLDL (mmol/L)	0.80 (0.67, 0.95)*	0.79 (0.68, 0.93)*	−0.08 (−0.21, 0.06)	−32.0%
Apolipoprotein B48 (g/L)	0.75 (0.58, 0.98)*	0.70 (0.57, 0.85)*	−0.004 (−0.008, 0.000)	−44.4%

Relative difference: estimated treatment difference/estimated mean for placebo x 100%. *p<0.05. ETD, estimated treatment difference; ETR, estimated treatment ratio; iAUC, mean postprandial increment in AUC after start of meal; VLDL, very-low-density lipoprotein.

Clinical Trial Registration Number: NCT02773381

Oral presentation 51

Efficacy of oral semaglutide according to baseline HbA_{1c}: an exploratory subgroup analysis of the PIONEER trial programme

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Background and aims: The efficacy and safety of oral semaglutide, a glucagon-like peptide-1 receptor agonist, has been investigated in patients with type 2 diabetes in the global PIONEER Phase 3a trial programme. This exploratory subgroup analysis of the PIONEER programme evaluated the effect of baseline HbA_{1c} values on the overall HbA_{1c} and body weight reductions achieved during each trial.

Materials and methods: Data were included from all patients who participated in PIONEER 1–5, 7 and 8 (n=5657). Patients were grouped by trial and according to baseline HbA_{1c} (≤8.0%, >8.0–≤9.0% and >9.0%). In the PIONEER trials, patients were either randomised to once daily treatment with oral semaglutide (3, 7 or 14 mg, or flexibly dosed) or at least one comparator (placebo, empagliflozin 25 mg, sitagliptin 100 mg or liraglutide 1.8 mg). Endpoints were change from baseline in HbA_{1c} and body weight at week 26 (week 52 in PIONEER 7), and data were analysed for all randomised patients using the trial product estimand.

Results: Reductions from baseline in HbA_{1c} and body weight were greater with increasing oral semaglutide dose. HbA_{1c} reductions were also greater with higher baseline HbA_{1c}, but there was no consistent relationship between change in body weight and baseline HbA_{1c}. Reductions in HbA_{1c} were greater with oral semaglutide 7 mg and 14 mg versus placebo and versus active comparator in all subgroups (**Table**). Significant interactions by baseline HbA_{1c} were observed for oral semaglutide vs. the comparator in PIONEER 3 (14 mg), PIONEER 4 (14 mg vs. placebo), and PIONEER 8 (7 and 14 mg). The proportion of patients achieving an HbA_{1c} target of <7% was greater with oral semaglutide 7 mg and 14 mg versus comparators in all trials and all subgroups. Across the trials, an HbA_{1c} target of <7% was achieved with oral semaglutide 14 mg by 71–90% in the lowest HbA_{1c} subgroup (≤8%), by 49–71% in the middle HbA_{1c} subgroup (>8.0–≤9.0%) and by 29–62% in the highest HbA_{1c} subgroup (>9%).

Conclusion: Oral semaglutide consistently showed improved glycaemic control across baseline HbA_{1c} subgroups in the PIONEER trials with greater reductions in HbA_{1c} with oral semaglutide 7 and 14 mg versus all comparators in all subgroups. Reductions in HbA_{1c} were greater with higher oral semaglutide dose and higher baseline HbA_{1c}.

Table. Change from baseline in HbA_{1c} by baseline HbA_{1c} subgroup in 7 of the global Phase 3a PIONEER trials

Trial	HbA_{1c} (%) at baseline	Estimated mean change from baseline in HbA_{1c} (%-points)					
		Oral semaglutide				Comparator(s)	
		3 mg	7 mg	14 mg	Flex	Pbo	Active
PIONEER 1 (diet and exercise)	≤8 (n=409)	–0.5	–1.1	–1.2	-	0.0	-
	>8–≤9 (n=244)	–1.1	–1.6	–1.8	-	–0.1	-
	>9 (n=50)	–1.5	–1.8	–2.6	-	–0.6	-
PIONEER 2 (vs empagliflozin 25 mg)	≤8 (n=457)	-	-	–1.0	-	-	–0.5
	>8–≤9 (n=211)	-	-	–1.8	-	-	–1.1
	>9 (n=153)	-	-	–2.0	-	-	–1.7
PIONEER 3 (vs sitagliptin 100 mg)	≤8 (n=850)	–0.3	–0.6	–0.9	-	-	–0.5
	>8–≤9 (n=593)	–0.5	–1.1	–1.5	-	-	–0.8
	>9 (n=420)	–1.0	–1.9	–2.2	-	-	–1.4
PIONEER 4 (vs liraglutide 1.8 mg and pbo)	≤8 (n=403)	-	-	–1.0	-	–0.0	–0.8
	>8–≤9 (n=248)	-	-	–1.6	-	–0.1	–1.4
	>9 (n=60)	-	-	–2.2	-	–0.1	–2.0
PIONEER 5 (renal impairment)	≤8 (n=188)	-	-	–0.8	-	0.1	-
	>8–≤9 (n=108)	-	-	–1.5	-	–0.3	-
	>9 (n=28)	-	-	–2.1	-	–0.4	-
PIONEER 7 (flex vs sitagliptin 100 mg)	≤8 (n=201)	-	-	-	–1.0	-	–0.5
	>8–≤9 (n=246)	-	-	-	–1.5	-	–0.7
	>9 (n=57)	-	-	-	–2.0	-	–1.5
PIONEER 8 (added-on to insulin)	≤8 (n=329)	–0.3	–0.6	–1.0	-	0.2	-
	>8–≤9 (n=296)	–0.7	–1.2	–1.6	-	–0.2	-
	>9 (n=106)	–1.2	–1.8	–2.3	-	–0.1	-

Mixed model for repeated measures analysis with treatment, region, stratification factors and interaction between them, as well as baseline HbA_{1c} group and interaction between treatment and baseline HbA_{1c} groups as factors, and baseline value of dependent variable as covariate. -, not investigated in trial; flex, flexible dose adjustment; pbo, placebo

Clinical Trial Registration Numbers: NCT02906930; NCT02863328; NCT02607865; NCT02863419; NCT02827708; NCT02849080; NCT03021187

Poster presentation 753

Oral semaglutide reduces appetite and energy intake and improves control of eating in subjects with type 2 diabetes

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Background and aims: Subcutaneous semaglutide, a glucagon-like peptide-1 analogue, has been shown to reduce appetite and energy intake in obese subjects. Semaglutide is in development for oral once-daily treatment of type 2 diabetes (T2D). This trial compared the effect of once-daily oral semaglutide on appetite and energy intake with placebo in subjects with T2D.

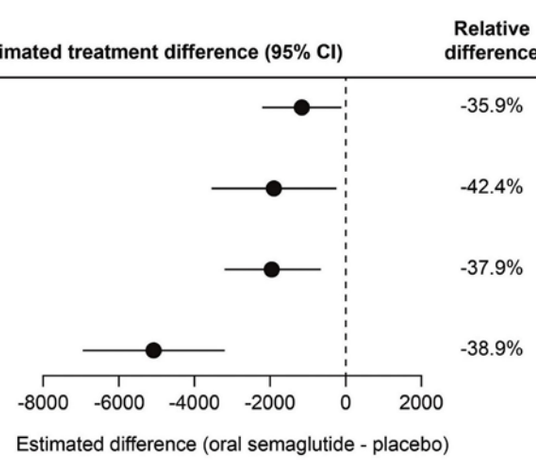
Materials and methods: Subjects were randomised to a double-blind, two-period, crossover trial with a 12-week period of oral semaglutide (dose-escalated to steady-state at 14 mg) followed by placebo for 12 weeks or *vice versa*, separated by a washout period of 5–9 weeks. At the end of each 12-week period, there was a 4-day in-house period in which energy intake was measured during an *ad libitum* lunch, evening meal and evening snack box. Appetite ratings were measured using a visual analogue scale (VAS) after an overnight fast and during 5-hour standardised breakfast and 8-hour standardised fat-rich breakfast meal tests. Control of eating and craving control were evaluated using the Control of Eating Questionnaire (CoEQ). Changes in body weight and composition after treatment were assessed by air displacement plethysmography; these are reported for the first treatment period only due to a possible rebound effect in subjects receiving oral semaglutide in the first period.

Results: Fifteen subjects were randomised (13 males, mean age 58.2 years, mean HbA_{1c} 6.9%, mean BMI 30.8 kg/m^2), two of whom withdrew before completing the trial. *Ad libitum* energy intake was reduced with oral semaglutide vs. placebo during the lunch meal, evening meal and evening snack box, leading to a reduction in total daily energy intake of 5096 kJ (**Figure**). Mean palatability VAS ratings after the meal indicated no food aversion with either oral semaglutide or placebo. There were no significant differences between oral semaglutide and placebo in overall appetite ratings pre-meal (in a fasting state) or during a standardised breakfast meal. After the standardised fat-rich breakfast meal, there was a significantly greater mean postprandial fullness rating in subjects treated with oral semaglutide compared with placebo. No other significant differences in appetite ratings were observed after a standardised fat-rich breakfast meal. The CoEQ indicated fewer food cravings and better control of eating with oral semaglutide vs. placebo. During the first treatment period, mean ± SD body weight loss with oral semaglutide was 2.9 ± 4.3 kg vs. 1.2 ± 3.2 kg with placebo. Body weight loss with oral semaglutide was attributable to loss of body fat mass.

Conclusion: Twelve weeks of treatment with once-daily oral semaglutide resulted in reduced energy intake in subjects with T2D. Appetite was unchanged, control of eating improved and body weight was reduced.

Estimated mean energy intake

	Oral semaglutide	Placebo	Estimated treatment difference (95% CI)	Relative difference
Lunch meal (kJ)	2133.5	3330.5	-1197.1	-35.9%
Evening meal (kJ)	2620.3	4546.1	-1925.8	-42.4%
Snack box (kJ)	3237.3	5210.5	-1973.2	-37.9%
Total daily intake (kJ)	7991.0	13087.1	-5096.0	-38.9%



Relative difference: estimated treatment difference/estimated mean for placebo x 100%.

Clinical Trial Registration Number: NCT02773381

Poster

Poster presentation 777

Similar efficacy and gastrointestinal tolerability versus exposure for oral and subcutaneous semaglutide

RV OVERGAARD, A NAVARRIA, CL HERTZ, SH INGWERSEN
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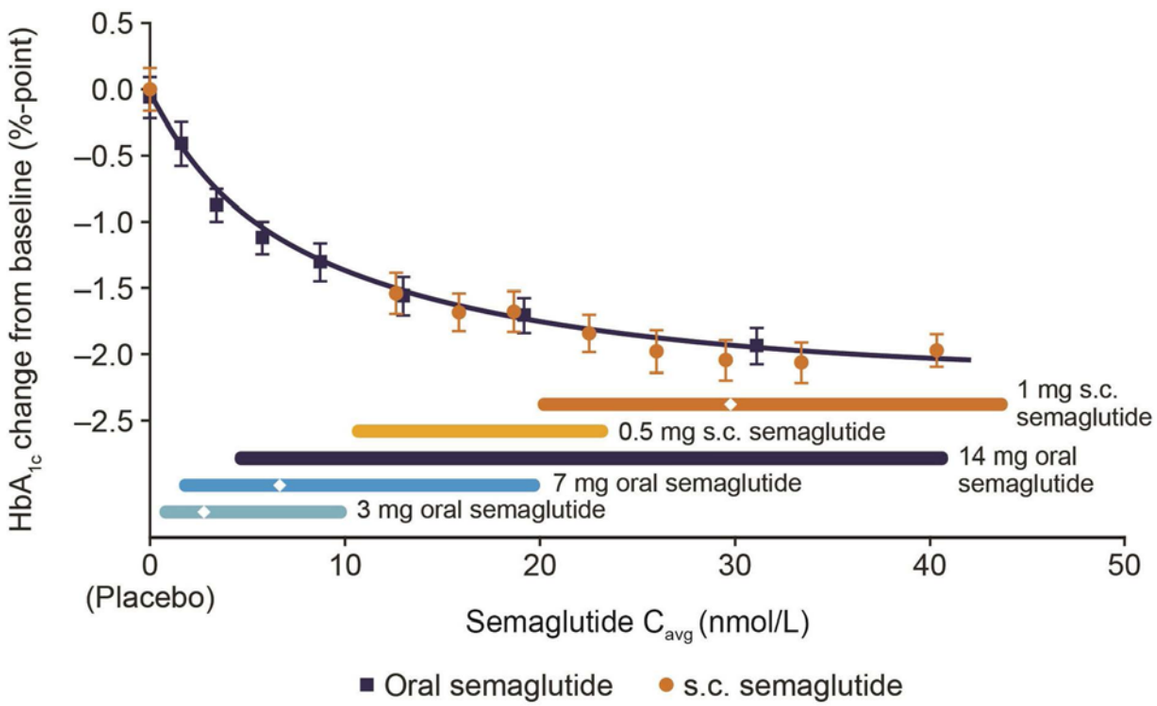
Background and aims: Semaglutide is a glucagon-like peptide-1 analogue formulated as both an approved once-weekly subcutaneous (s.c.) injection and a once-daily oral tablet in development for the treatment of type 2 diabetes. The s.c. and oral formulations have been evaluated across several trials in the SUSTAIN and PIONEER programmes, respectively. Lower bioavailability associated with oral administration results in more variable plasma concentrations of semaglutide compared to those obtained following s.c. administration. Using populations from SUSTAIN and PIONEER trials, the present analyses aim to investigate if the oral route of administration changes the efficacy and tolerability of semaglutide compared to s.c. administration.

Materials and methods: Population pharmacokinetic (PK) and exposure–response analyses were based on average semaglutide concentrations at steady-state. Response data from four trials (SUSTAIN 1, 2, 3 and SUSTAIN-Japan) of once-weekly s.c. semaglutide 0.5 and 1.0 mg over 30 weeks (n=1552) were compared with data from six trials (PIONEER 1, 2, 3, 5, 8 and 9) of once-daily oral semaglutide 3, 7 or 14 mg over 26 weeks (n=3003). Using graphical and model-based techniques, exposure–response relationships were investigated for changes from baseline in HbA_{1c} and body weight, and the proportion of subjects reporting gastrointestinal adverse events of nausea or vomiting at any time during treatment.

Results: The SUSTAIN and PIONEER populations were fairly similar, with 55% and 58% male subjects, 65% and 78% aged 18–64 years, mean baseline HbA_{1c} of 8.1% and 8.1% and mean body weight of 88.2 kg and 86.3 kg, respectively. Population PK analysis indicated dose proportional PK, where body weight was the main covariate for exposure for both s.c. and oral semaglutide. Exposure–response analyses showed greater HbA_{1c} and weight reductions with increasing semaglutide exposure (**Figure**). The main covariate for glycaemic effect was baseline HbA_{1c} (larger HbA_{1c} change from baseline at higher baseline HbA_{1c}). The proportion of subjects reporting nausea or vomiting during s.c and oral semaglutide treatment increased with increasing semaglutide exposure. The exposure range following oral semaglutide was wider than for s.c. dosing but with a considerable overlap between oral semaglutide 7 and 14 mg and s.c. semaglutide 0.5 and 1.0 mg, indicating similar exposure levels across formulations. Across the efficacy and safety parameters studied, exposure–response relationships were similar for the SUSTAIN and PIONEER datasets.

Conclusion: Similar exposure–response relationships were observed for efficacy and tolerability of semaglutide, regardless of the route of administration, indicating that greater variability in plasma concentration levels for oral semaglutide do not impact response.



Data are mean response values with 95% confidence intervals obtained after 30 weeks of treatment with s.c. semaglutide, and 26 weeks with oral semaglutide vs exposure expressed as quantiles of the average steady-state concentration in a dosing interval (C_{avg}) (plus placebo at C_{avg} of 0 nmol/L). The fitted solid line represents covariate-adjusted, model-derived relations for each programme; note that the lines for oral and s.c. semaglutide are fully superimposed for HbA_{1c} response. Horizontal lines with diamonds along the x-axis represent medians and 90% exposure ranges.

Clinical Trial Registration Numbers: NCT02054897; NCT01930188; NCT01885208; NCT02207374; NCT02906930; NCT02863328; NCT02607865; NCT02827708; NCT03021187; NCT03018028

Poster

Oral presentation 17

W Lane, K Bozkurt, E Favaro, HC Jang, MIS Kjærsgaard, A Oviedo, L Rose, P Senior, G Sesti, A Soto Gonzalez, E Franek

Efficacy and safety of fast-acting insulin aspart compared with insulin aspart, both with insulin degludec with or without metformin, in adults with type 2 diabetes

Oral presentation 17

Efficacy and safety of fast-acting insulin aspart compared with insulin aspart, both with insulin degludec with or without metformin, in adults with type 2 diabetes

W LANE[1], K BOZKURT[2], E FAVARO[2], HC JANG[3], MIS KJÆRSGAARD[4], A OVIEDO[5], L ROSE[6], P SENIOR[7], G SESTI[8], A SOTO GONZALEZ[9], E FRANEK[10]
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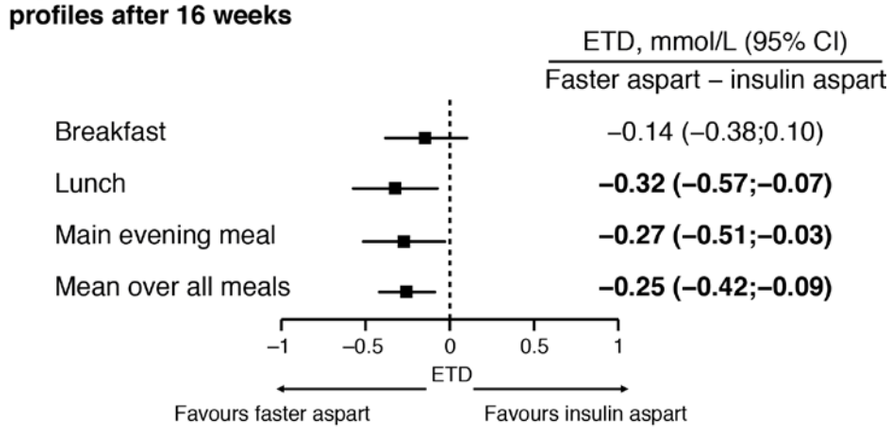
Background and aims: Fast-acting insulin aspart (faster aspart) is a mealtime insulin with more rapid absorption and greater early glucose-lowering effect than insulin aspart (IAsp). The aim of this trial (onset 9) was to evaluate the efficacy and safety of faster aspart compared with IAsp, both with insulin degludec with or without metformin, in adults with advanced type 2 diabetes (T2D) not optimally controlled with a basal-bolus regimen.

Materials and methods: This was a 16-week, multicentre, double-blind, treat-to-target trial. Following a 12-week run-in period to optimise basal insulin, participants were randomised (1:1) to mealtime faster aspart (n=546) or IAsp (n=545), both with insulin degludec. All available information regardless of treatment discontinuation or use of ancillary treatment was used for evaluation of effect.

Results: Non-inferiority (0.4% margin) with regard to change from baseline in HbA_{1c} 16 weeks after randomisation (primary endpoint) was confirmed for faster aspart vs. IAsp (estimated treatment difference [ETD] [95% CI] –0.04% [–0.11;0.03]; –0.39 mmol/mol [–1.15;0.37]). Faster aspart was superior to IAsp for change from baseline in 1-h postprandial glucose (PPG) increment using a meal test (ETD [95% CI] –0.40 mmol/L [–0.66;–0.14]; –7.23 mg/dL [–11.92;–2.55]). Change from baseline in 1-h PPG increment based on self-measured blood glucose profiles was statistically in favour of faster aspart after lunch, the main evening meal and over all meals (**Figure**). Change from baseline in 1,5-anhydroglucitol also favoured faster aspart over IAsp (ETD [95% CI] 0.50 ug/mL [0.11;0.89]). The overall rate of treatment-emergent severe or blood glucose (BG)-confirmed (plasma glucose equivalent <3.1 mmol/L [56 mg/dL]) hypoglycaemia was statistically significantly lower for faster aspart vs. IAsp (estimated treatment ratio [ETR] [95% CI] 0.81 [0.68;0.97]), as was the rate within 4 h after a meal (ETR [95% CI] 0.78 [0.63;0.98]). Adverse event profiles were similar between treatments.

Conclusion: In combination with insulin degludec, faster aspart provided effective overall glycaemic control, superior PPG control and a lower rate of severe or BG-confirmed hypoglycaemia vs. IAsp in adults with advanced T2D not optimally controlled with a basal-bolus regimen.

Figure. Change from baseline in 1-h PPG increment from SMBG profiles after 16 weeks



Change from baseline in PPG increment analysed using an analysis of variance model after multiple imputation. ETD, estimated treatment difference; faster aspart, fast-acting insulin aspart; PPG, postprandial glucose; SMBG, self-measured blood glucose assessed with glucose meter as plasma equivalent values of capillary whole blood glucose

Clinical Trial Registration Number: NCT03268005

Poster presentation 795

NV Hartvig, J Hellman, A Kaas, N Nygård Knudsen, A-C Mårdby, JB Møller, P Adolfsson

Improved insulin adherence after introduction of a smart connected insulin pen

Poster presentation 796

A Kaas, NV Hartvig, J Hellman, N Nygård Knudsen, A-C Mårdby, P Adolfsson

Increased time in range observed after introduction of a connected insulin pen

Poster presentation 795

Improved insulin adherence after introduction of a smart connected insulin pen

NV HARTVIG[1], J HELLMAN[2], A KAAS[3], N NYGÅRD KNUDSEN[4], A-C MÅRDBY[5], JB MØLLER[6], P ADOLFSSON[7]
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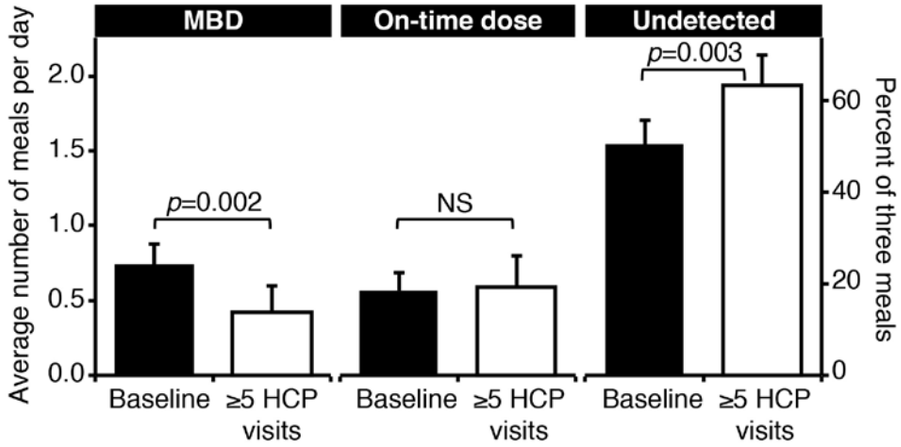
Background and aims: An association between missed insulin injections and its impact on HbA_{1c} levels has been established. The smart connected NovoPen® 6 captures and allows visualisation of insulin injections (date and time of injection and number of units). This has the potential to improve the dialogue between patients and healthcare professionals (HCPs) and eliminate any guessing about doses taken, missed doses and optimal injection time in relation to meals. This non-interventional study investigated whether the use of NovoPen® 6 influenced the behaviour of patients with type 1 diabetes (T1D) in terms of missed bolus dose (MBD) meals.

Materials and methods: Patients were recruited from 12 Swedish diabetes clinics. At baseline they received a NovoPen® 6 for bolus insulin injections. At each HCP visit, pen data were downloaded at the clinic. Follow-up was after ≥5 HCP visits. Adults with T1D (n=81) using continuous glucose monitoring (CGM) and NovoPen® 6 for bolus injections were included in the analyses. The frequency of MBD was analysed using the GRID algorithm to detect meals from the CGM signal combined with the injection data. MBD was defined as meals with no bolus injection within –15 to +60 minutes from the start of the meal, as detected by the algorithm. The change in number of MBD meals from baseline to ≥5 HCP visits was analysed using a mixed Poisson model.

Results: A significant decrease of 43% in the average daily number of MBD meals was observed from baseline to after ≥5 HCP visits (median time in study: 6 months) from 0.74 (95% CI [0.62;0.88]) to 0.42 (95% CI [0.30;0.60]) (p=0.002; **Figure**). This corresponded to a decrease from 25% to 14% in MBD meals assuming that patients have three main meals per day (0.74/3 = 25%; 0.42/3 = 14%). The number of meals detected with a bolus injection was stable, while the number of undetected meals increased from baseline to follow-up.

Conclusion: These real-world findings confirm that MBD injections is the reality for patients with T1D and that a smart connected pen can support good injection behaviour, leading to less MBD meals. This could potentially lead to better glycaemic outcomes.

Figure. Average number of daily meals from baseline to after ≥5 HCP visits



Estimated mean number of daily meals with 95% confidence intervals. MBD are meals with missed bolus doses. On-time dose are meals where a bolus dose is taken. Undetected are meals that are not detected by the CGM, assuming an average of three meals per day.
CGM, continuous glucose monitoring; HCP, healthcare professionals; MBD, missed bolus dose; NS, not significant.

Poster

Poster presentation 796

Increased time in range observed after introduction of a connected insulin pen

A KAAS[1], NV HARTVIG[2], J HELLMAN[3], N NYGÅRD KNUDSEN[4], A-C MÅRDBY[5], P ADOLFSSON[6]

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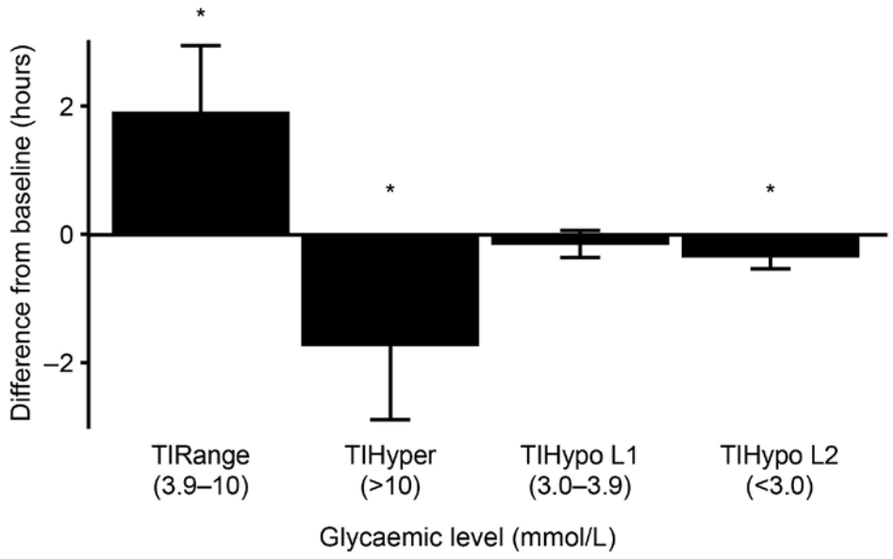
Background and aims: The capture and visualisation of insulin injection patterns together with blood glucose data has potential to improve dialogue between patients and HCPs about dose, injection time and missed injections. This may improve glycaemic control. The objective of this non-interventional study was to investigate how a smart connected insulin pen (NovoPen® 6) influences glycaemic control in patients with type 1 diabetes (T1D) in a real world setting.

Materials and methods: Patients were recruited from 12 Swedish diabetes clinics. At baseline patients received a NovoPen® 6, which logs time and date of injection and number of insulin units. Healthcare professional (HCP) visits were conducted according to ordinary clinical practice. At each visit, pen data were downloaded at the clinic to support patient-HCP dialogue. Adults with T1D (n=94) using NovoPen® 6 for basal and/or bolus injections and continuous glucose monitoring (CGM) were included in the analyses. The effect on time in range (TIR) was analysed based on a 14-day interval after each visit using a linear mixed-effects model.

Results: A significant increase in TIR (3.9–10.0 mmol/L) from baseline to after ≥5 HCP visits (median time in study: 6 months) of 1.9 hours/day (9.2 to 11.1 hours/day) was found (p=0.0009; **Figure**). Accordingly, significant reduction in time spent in hyperglycaemia (>10 mmol/L) and L2 hypoglycaemia (<3.0 mmol/L; –1.8 hours/day, p=0.003; –0.3 hours/day, p=0.005) was observed. There was no change in time in L1 hypoglycaemia (3.0–3.9 mmol/L; p=0.181). A significant increase in bolus insulin dose (n=81) from baseline to after ≥5 HCP visits of 27.9%/day was observed. There was no significant change in mean basal insulin dose (n=22).

Conclusion: These real-world findings in patients with T1D highlight the potential benefit on glycaemic control when accurate connected pen data contribute to patient-HCP dialogue.

Figure: Time spent in normal glycaemic range increased significantly with a corresponding decrease primarily in time in hyperglycaemia



*p<0.05 Estimated mean difference in time spent in glycaemic ranges with 95% confidence intervals. The difference is observed between baseline and HCP visits ≥5. Baseline is the period after treatment initiation but before the first visit. Analysis is based on CGM data from a 14-day interval after each visit (≥70% coverage). TIRange = Time in range (3.9–10 mmol/L), TIHyper = Time in hyper (>10 mmol/L), TIHypo L1 = Time in L1 hypo (3.0–3.9 mmol/L), T1Hypo L2 = Time in L2 hypo (<3.0 mmol/L). Patients above 18 (n=94) are included.

Poster

Poster presentation 860

SR Heller, E Hachmann-Nielsen, K Kvist

Non-severe hypoglycaemia predicts increased risk of subsequent severe events in patients with type 2 diabetes

Poster presentation 860

Non-severe hypoglycaemia predicts increased risk of subsequent severe events in patients with type 2 diabetes

SR HELLER[1], E HACHMANN-NIELSEN[2], K KVIST[2]
[1]The University of Sheffield, Sheffield, UK; [2]Novo Nordisk A/S, Søborg, Denmark

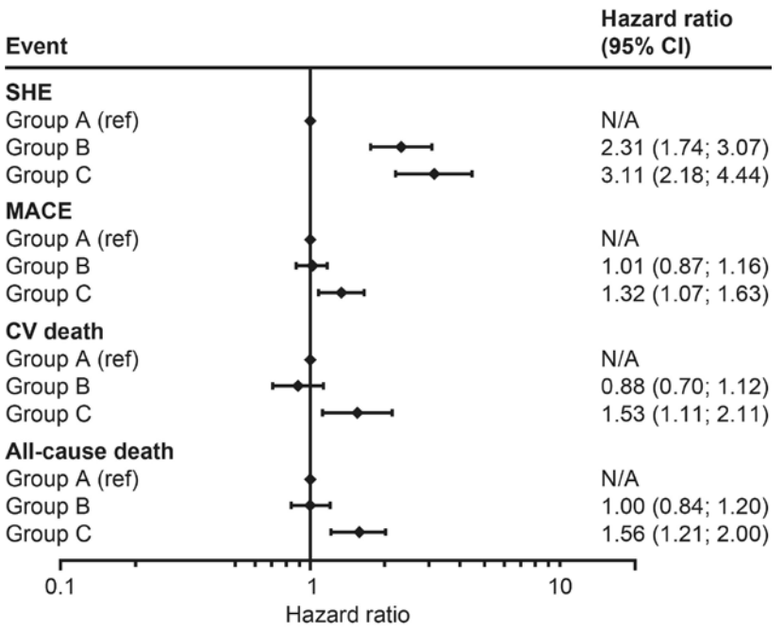
Background and aims: It is well-known that higher rates of non-severe hypoglycaemic episodes (NSHEs) associate with a greater risk of severe hypoglycaemic episodes (SHEs) in patients with type 1 diabetes.

Materials and methods: We investigated whether a similar association existed in patients with type 2 diabetes (T2D). We explored if annual rate of NSHEs was associated with time to first SHE, cardiovascular (CV) death, time to first major adverse CV event (MACE), and all-cause death in patients with T2D using data from LEADER, a CV outcomes trial with 9340 patients with T2D. We used a Cox proportional hazards model adjusted for randomised treatment arm, and annual rate of NSHE as a time-dependent covariate with three levels; A: <2 NSHEs per year (reference), B: 2–11 NSHEs or C: ≥12 NSHEs. Hazard ratios were used to estimate the association between NSHE and each of the outcomes.

Results: Higher rates of NSHE were associated with a higher rate of severe hypoglycaemia, MACE, CV death and all-cause death in patients with T2D (**Figure**).

Conclusion: Our results suggest that in this T2D population, a high rate of NSHEs may be associated with more harmful outcomes.

Figure: Hazard ratios (95% CI) for severe hypoglycaemia, MACE, CV death and all-cause death by NSHE rate groups



Group A: <2 NSHEs per year (ref), group B: 2–11 NSHEs per year, group C: ≥12 NSHEs per year. p-values for the associations were: SHE, p<0.001; MACE, p=0.03; CV death, p=0.013; all-cause death, p=0.002. N/A, not applicable; ref, reference.

Clinical Trial Registration Number: NCT01179048

Poster

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Outcomes of Type 2 Diabetes (T2D) Clustering Replicated in the DEVOTE and LEADER Trials

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qrs.ly/5labn81

Aim

- Type 2 diabetes (T2D) is a heterogeneous disease. Multiple studies have therefore attempted to characterize more precise T2D patient populations.[1,2]
- Individuals in the Swedish All New Diabetics in Scania (ANDIS) cohort with newly diagnosed diabetes were grouped by 6 demographic and clinical variables (autoantibodies, sex, age at diagnosis, body mass index (BMI), hemoglobin A_{1c} (HbA_{1c}), and HOMA estimates of beta cell function and insulin resistance) to show 4 distinct T2D subtypes with differential risk for nephropathy and retinopathy.[2] (Cluster 1 was essentially identical to type 1 diabetes).
  - Cluster 2 (SIDD- severe insulin-deficit diabetes)
  - Cluster 3 (SIRD- severe insulin-resistant diabetes)
  - Cluster 4 (MOD- mild obesity-related diabetes)
  - Cluster 5 (MARD- mild age-related diabetes).
- The objective of this study was to test the predictive validity of the same clustering system for advanced T2D in the DEVOTE trial and the LEADER trial for predicting time to first episode of severe hypoglycemia (SH), time to first major adverse cardiovascular event (MACE), time to cardiovascular (CV) death, and time to all-cause mortality.

Methods

- Data came from the DEVOTE and LEADER trials. DEVOTE was a large, geographically diverse cardiovascular outcomes trial in advanced T2D patients at high risk of CV events.[3] For confirmation, all analyses were replicated in the LEADER trial, likewise a cardiovascular outcomes trial in advanced T2D patients.[4]
- Individuals enrolled in the DEVOTE and LEADER trials were included in the analysis if they had data on three key variables for clustering (BMI, HbA_{1c}, and age at diagnosis, calculated as baseline age in years minus years since diagnosis). C-peptide and auto-antibodies were not measured in the DEVOTE and LEADER trials.
- Participants were assigned to one of the four clusters described in the ANDIS cohort based on baseline HbA_{1c}, BMI, and calculated age at diagnosis. The Euclidean distance to exact cluster centers were calculated and participants were assigned to the cluster for which the distance was the smallest.
- Time-to-event analysis was used to compare differences in outcomes between the four clusters. Specifically Kaplan-Meyer curves were depicted and p-values for the log-rank test were determined.

Results

- The analysis included:
  - 7,673 participants in the DEVOTE trial with a mean age of 65.0 years, mean T2D duration of 16.4 years, and mean HbA_{1c} of 8.4%.
  - 9,340 participants in the LEADER trial with mean age of 64 years, mean T2D duration of 12.8 years, and mean HbA_{1c} of 8.7%.
- The four T2D clusters from the ANDIS cohort were represented in the DEVOTE trial as (a similar distribution was seen in the LEADER trial):
  - SIDD-like: 16.7% (N = 1,261)
  - SIRD-like: 24.5% (N = 1,847)
  - MOD-like: 26.8% (N = 2,632)
  - MARD-like: 34.9% (N = 2,632).
- The four replicated clusters showed differences in baseline characteristics consistent with the original ANDIS clusters despite clustering on a subset of the variables (**Figure 1**). For example, patients in the SIDD-like cluster had higher HbA_{1c}, and lower BMI. No other cluster had this profile.
- Differences in HbA_{1c} and BMI were retained over time [**Figure 2**].

Figure 1 Comparison of baseline characteristics of T2D Clusters in the DEVOTE trial (top row), the LEADER trial (bottom row).

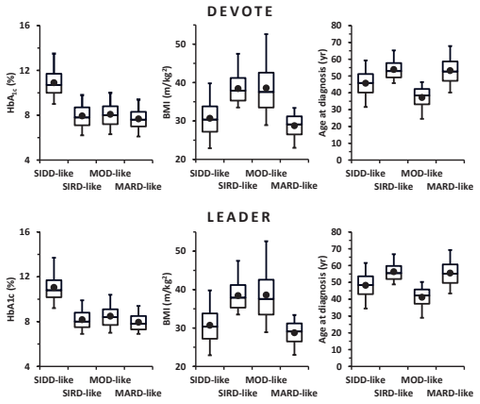
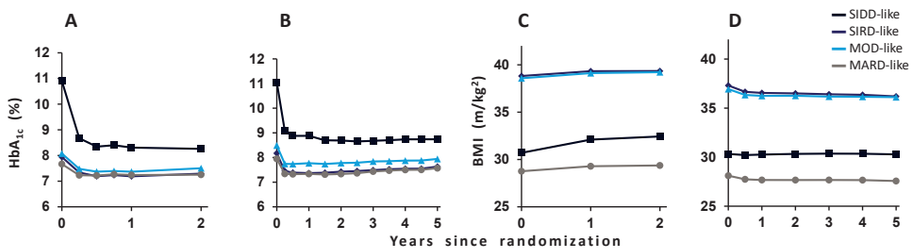
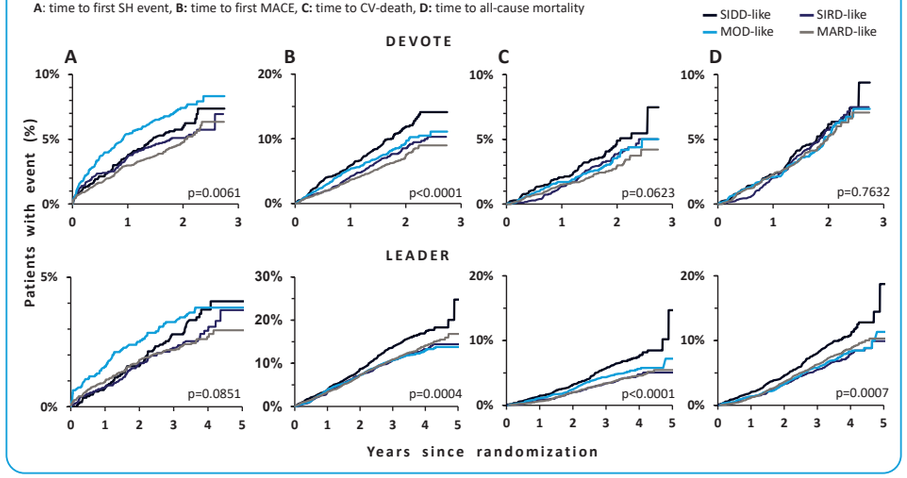


Figure 2 Mean HbA_{1c} and BMI over time in DEVOTE (A & C) and LEADER (B & D) according to T2D cluster



Key Result

Figure 3 Time to first event for the four T2D clusters: Upper panel DEVOTE data, lower panel LEADER data.
A: time to first SH event, **B:** time to first MACE, **C:** time to CV-death, **D:** time to all-cause mortality



- There was significant difference ($p<0.05$) across the T2D clusters in time to first SH and time to first MACE in the DEVOTE trial, and time to first MACE, time to first CV death and time to all-cause mortality in the LEADER trial [**Figure 3**].
- In the DEVOTE trial, the proportion of MACE incidence and CV death was highest among Cluster 2 SIDD (12.0% and 4.8% respectively) and lowest among the Cluster 4 MARD (7.7% and 3.2%, respectively). The LEADER trial showed similar trends.
- The results were not modified by sex or insulin use at baseline.

Discussion

- The data replicate patterns of previous T2D clusters derived in a predominantly northern European cohort early in T2D,[2] and further replicated in Chinese and US populations.[5]
- T2D clusters in DEVOTE and LEADER represent a geographically-diverse population with higher HbA_{1c}, greater CVD risk, and longer disease duration (mean diabetes duration: 16.4 years).
- Overall, the SIDD-like cluster appeared to have to highest risk of MACE, CV and all-cause mortality and may benefit from early intervention.
- The SIDD-cluster has previously shown significantly higher rates of retinopathy compared the other clusters in the ANDIS cohort.[2]
- To reduce disparity in survival outcomes, more work is needed to understand if and how optimal treatment regimens may differ according to subgroups.
- T2D clusters that are optimized by incorporation of treatment response variables over longitudinal follow-up could inform future treatment algorithms for clinical practice.

Conclusion

- Clusters derived from early T2D can be replicated in long-standing T2D and may confer information about time to first SH, MACE, CV mortality, and all-cause mortality.
- Patients with T2D, a high HbA_{1c} and low BMI (i.e. the SIDD-like phenotype) show significantly shorter time to first MACE and CV-death compared to other subgroups of T2D.
- The consistency of clusters across different populations adds to the evidence that T2D is not a homogeneous disease, but instead may have different prognoses and require different treatment according to specific disease subtypes.

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Presenter John B. Buse's contracted consulting fees are paid to the University of North Carolina by Adocia, AstraZeneca, Dance Biopharm, Eli Lilly, MannKind, NovaTarg, Novo Nordisk, Senseonics, vTv Therapeutics, and Zafgen; grant support from Novo Nordisk, Sanofi, and vTv Therapeutics. He is a consultant to Cirius Therapeutics Inc, CSL Behring, Neurimmune AG. He holds stock options in Mellitus Health, PhaseBio and Stability Health. He is supported by a grant from the National Institutes of Health (UL1TR002489).
Presented at the American Diabetes Association, 79th Scientific Sessions, June 7–11, 2019, San Francisco, CA, USA.

References: (**1**) Li L, Cheng W-Y et al. Sci Transl Med 2015; 7 (311): 311ra174-311ra174. (**2**) Ahlqvist E et al. Lancet Diabetes Endocrinol 2018; 6 (5): 361-9. (**3**) Marso SP et al. Am Heart J 2016; 179: 175-183. (4) Marso SP et al. New Eng J Med. 2016; 375 (4): 311-22. (5) Zou Xet al. Lancet Diabetes Endocrinol 2019; 7 (1): 9-11.

Abstract

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Hypoglycaemia, irrespective of the definition used, is reduced when switching to insulin degludec from other basal insulins in routine clinical care: the ReFLeCT study

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qrs.ly/5labn81

Background

- Hypoglycaemia is a frequent event in patients with diabetes treated with insulin and has been linked to impaired glycaemic control.[1,2]
- Randomised controlled trials have demonstrated that degludec is associated with less hypoglycaemia than with other basal insulins at equivalent glycaemic control, across a broad spectrum of patients with diabetes.[3–7]
- ReFLeCT (Results From Real-World Clinical Treatment with Tresiba®) was a multicentre, prospective, observational study that evaluated the safety and effectiveness of switching from other basal insulins to degludec, as part of routine clinical care, in patients with type 1 (T1D) or type 2 diabetes (T2D).[8,9]
- As different hypoglycaemia definitions can impact study outcomes, the present analysis of the ReFLeCT study analysed previous (pre-specified) and updated (*post hoc*) American Diabetes Association (ADA) hypoglycaemia definitions.

Aim

- The objective of this secondary analysis of the ReFLeCT study was to investigate the change in the rate of hypoglycaemia after switching to degludec from other basal insulins, according to different hypoglycaemia definitions, in patients with T1D or T2D.

Methods

ReFLeCT study

- ReFLeCT was a prospective, observational study conducted across seven European countries.[8,9]
- Patients aged ≥18 years with T1D or T2D who were already on insulin, and whose physician advised that they should switch to degludec treatment, were eligible for inclusion.[8,9]
- The study comprised a baseline period (4 weeks prior to switching to degludec) and a follow-up period (up to 12 months after switching to degludec).[8,9]
- Patients attended visits according to routine clinical practice, and could attend up to four visits during the 12-month follow-up period.
- Patients were instructed to complete 4-week study diaries prior to each visit, collecting day-by-day information on hypoglycaemic events.
- The primary endpoint was the change from the baseline period in the number of overall hypoglycaemic events during the 12-month follow-up period.[8,9]
- In ReFLeCT, switching to degludec from other basal insulins was associated with significantly reduced rates of overall hypoglycaemia in combination with improved glycaemic control in insulin-treated adults with T1D or T2D.[8,9]

Hypoglycaemia definitions

- The hypoglycaemia definitions included in this analysis consisted of:
  - » Previous (pre-specified) ADA definitions
    - – **Asymptomatic hypoglycaemia:** an event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ≤3.9 mmol/L (70 mg/dL).[10]
    - – **Documented symptomatic hypoglycaemia:** an event during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤3.9 mmol/L (70 mg/dL).[10]
    - – **Pseudo-hypoglycaemia:** an event during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration >3.9 mmol/L (70 mg/dL) but approaching that level.[10]
    - – **Probable symptomatic hypoglycaemia:** an event during which symptoms typical of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤3.9 mmol/L (70 mg/dL).[10]
    - – **Severe hypoglycaemia (Level 3 hypoglycaemia):** severe hypoglycaemia, denoted by severe cognitive impairment that requires external assistance for recovery.[10–12]
  - » Updated (*post hoc*) ADA definitions
    - – **Level 2 hypoglycaemia:** an event with a measured plasma glucose concentration <3.0 mmol/L (54 mg/dL) indicating serious, clinically important hypoglycaemia.[11,12]
    - – **Level 1 hypoglycaemia:** an event with a measured plasma glucose concentration ≥3.0–<3.9 mmol/L (54–70 mg/dL).[11,12]

Statistical analysis

- The numbers of hypoglycaemic events were converted to rates per patient-year of exposure for analysis purposes.
- Rate ratios for hypoglycaemia between the 4-week baseline and 12-month follow-up periods, according to different definitions, were analysed using negative binomial regression specifying a log-transformed follow-up time offset term adjusted for baseline covariates. Baseline covariates included period (pre/post-switch to degludec), baseline HbA_{1c}, gender, body mass index, duration of diabetes, age and country, in addition to bolus insulin (Yes/No) and sulfonylureas or glinides (Yes/No) for T2D.
- All statistical tests were two-sided with a significance level of $p<0.05$.

Results

- Baseline characteristics from the overall ReFLeCT study are presented in Table 1.
- Seventy (12.6%) patients in the T1D group and 67 (11.0%) in the T2D group withdrew from the study during the follow-up period.
- In total, 481 patients with T1D and 516 patients with T2D contributed to the present analysis with diary data and complete covariate information.

T1D

- Estimated rate ratios (ERRs) demonstrated significantly lower rates of hypoglycaemia across the previous ADA hypoglycaemia definitions during the 12-month follow-up versus the 4-week baseline period, except for asymptomatic hypoglycaemia in patients with T1D (Figure 1a).
- ERRs also demonstrated significantly lower rates of hypoglycaemia for the updated ADA definitions during the 12-month follow-up versus the baseline period (Figure 1a).

T2D

- ERRs demonstrated significantly lower rates of hypoglycaemia across all previous ADA hypoglycaemia definitions during the 12-month follow-up versus the 4-week baseline period in patients with T2D (Figure 1b). The number of Level 3 hypoglycaemic events in patients with T2D was insufficient to allow for statistical comparison.
- ERRs also demonstrated significantly lower rates of hypoglycaemia for the updated ADA definitions for hypoglycaemia during the 12-month follow-up versus the baseline period (Figure 1b).

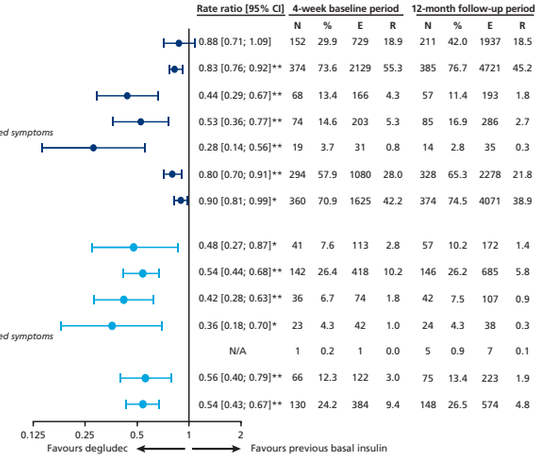
Table 1: Baseline characteristics of patients

	T1D	T2D
Full analysis set, n	556	611
Age, years	47.4 (15.7)	65.2 (9.6)
Female/male, %	44.2/55.8	40.4/59.6
Duration of diabetes, years	21.4 (13.5)	18.0 (9.5)
BMI, kg/m²	26.1 (4.7)	31.1 (6.3)
Body weight, kg	76.4 (15.6)	87.6 (19.6)
HbA_{1c}, %	8.1 (1.3)	8.2 (1.4)
FPG, mmol/L mg/dL	8.8 (3.9) 159 (70)	9.0 (3.1) 162 (56)
Antidiabetic therapies at baseline, n (%)		
Proportion on basal insulin	556 (100.0)	611 (100.0)
Proportion on bolus insulin	508 (91.4)	384 (62.8)
Proportion on ≥1 non-insulin antidiabetic therapy	54 (9.7)	379 (62.0)

Data are mean (SD), unless otherwise specified.
BMI, body mass index; FPG, fasting plasma glucose; SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes.

Figure 1: Rate ratios of hypoglycaemia according to different hypoglycaemia definitions in patients with (a) T1D and (b) T2D

Key result



*p<0.05; **p<0.001. †Severe hypoglycaemia, an episode requiring the assistance of another person to actively administer carbohydrate, glucagon or take other corrective actions.
Fig 1a: Models were adjusted for period (pre/post-switch to degludec), baseline HbA_{1c}, gender, BMI, duration of diabetes, age and country. Total follow-up time (patient years) was 38.5 for the 4-week baseline period and 104.5 for the 12-month follow-up period.
Fig 1b: Models were adjusted for period (pre/post-switch to degludec), baseline HbA_{1c}, gender, BMI, duration of diabetes, bolus insulin (Yes/No), sulfonylureas or glinides (Yes/No), age and country. Total follow-up time (patient years) was 40.8 for the 4-week baseline period and 118.8 for the 12-month follow-up period.
%, percentage of patients with an event; ADA, American Diabetes Association; BMI, body mass index; CI, confidence interval; E, number of events; R, rate of events per patient-year of exposure; N, number of patients with an event; T1D, type 1 diabetes; T2D, type 2 diabetes.

Conclusions

- Switching to degludec from other basal insulins in routine clinical practice was generally associated with lower rates of hypoglycaemia when using different hypoglycaemia definitions in patients with diabetes.
- Definitions for Level 1, 2 and 3 hypoglycaemia were well represented in the rate of events and for the change between the baseline and follow-up periods (except for Level 3 hypoglycaemia for T2D), strengthening the generalisability of the results from this study.
- This analysis of ReFLeCT corroborates the findings of the primary study that switching to degludec from other basal insulins is associated with reduced rates of overall hypoglycaemia in patients with T1D and T2D in routine clinical care.

The study was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT02392117).
Presenter Michael Feher has taken part in advisory panels and speakers bureaux with AstraZeneca, Novo Nordisk, Sanofi and Eli Lilly, and received research support from Amgen and Novo Nordisk.
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Presented at the European Association for the Study of Diabetes, 55th Annual Meeting.
September 16–20, 2019, Barcelona, Spain.

References: (**1**) Zekarias & Seaquist. *Hypoglycemia in Diabetes: Epidemiology, Impact, Prevention and Treatment*. 2017. www.smgebooks.com/hypoglycemia-causes-occurrences/chapters/HG-17-04.pdf (Accessed Mar 2019); (**2**) UK Hypoglycemia Study Group. *Diabetologia* 2007;50:1140–7; (**3**) Ratner *et al. Diabetes Obes Metab* 2013;15:175–84; (**4**) Davies *et al. Diabetes Obes Metab* 2016;18:96–9; (**5**) Marso *et al. N Engl J Med* 2017;377:723–32; (**6**) Lane *et al. JAMA* 2017;318:33–44; (**7**) Wysham *et al. JAMA* 2017;318:45–56; (**8**) Fadini *et al. Diabetic Medicine* 2019:36 (Suppl. 1);60 (Poster 81); (**9**) Fadini *et al. Diabetic Medicine* 2019:36 (Suppl. 1);60 (Poster 82); (**10**) Seaquist *et al. Diabetes Care* 2013;36:1384–95; (**11**) American Diabetes Association. *Diabetes Care* 2019;42(Suppl. 1):S61–S70; (**12**) Agiostratidou *et al. Diabetes Care* 2017;40:1622–30.

Abstract

Real-World Cost-Effectiveness of Insulin Degludec in Type 1 and Type 2 Diabetes Mellitus – from a Swedish Societal One Year Perspective

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Background and aims

- Randomised controlled trials have shown a lower risk of hypoglycemia in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D) on treatment with insulin degludec compared with insulin glargine 100 units/mL (IGlar U100).[1,2,4] Observational studies have also shown lower risk of hypoglycemia when T1D[3,5] and T2D[3] patients switched to insulin degludec from other basal insulins.[1–5] Several of these studies have also shown an insulin dose reduction for patients treated with insulin degludec compared with IGlar U100.[1,3,4,5]
- The aim of this study was to assess the cost-effectiveness (C/E) of insulin degludec vs other basal insulin treatment before switch to insulin degludec in a Swedish societal one year perspective in people with T1D and T2D.

Materials and methods

This study used a Swedish societal one year perspective to assess C/E of insulin degludec compared with basal insulin treatment prior to switching to insulin degludec. The C/E analyses used global data from the ReFLeCT study.[5] ReFLeCT was a prospective, observational study including patients with T1D (n=566) and T2D (n=611) from seven European countries (Figure 1).[5] It comprised a four-week baseline period and a 12-month follow-up period (insulin degludec).

ReFleCT endpoints of relevance for this study, comparing baseline vs 12-month follow-up.[5]

- Change in rate of any hypoglycemia.
- Change in daily total, basal and bolus insulin dose.

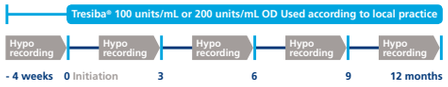
Insulin information

- Baseline basal units used to represent costs (weighted) before switch:[5]
  - T1D: IGlar U100 63.8%, insulin detemir (IDet) 22.7%, other/missing 13.5%.
  - T2D: IGlar U100 59.1%, IDet 20.8%, other/missing 20.1%.
  - If data was missing the lowest basal insulin price (insulin NPH) was used as a conservative approach.
- IGlar U100 price:
  - Base case: the Swedish original IGlar U100 price.
  - Sensitivity analyses: IGlar U100 biosimilar price.

Cost-effectiveness analyses

- C/E was analysed over a 1-year time horizon from a Swedish societal perspective.
- Only results from the ReFLeCT analyses[5] with statistical significant differences (p<0.05) were included in the analysis.
- Pharmacy selling prices in Sweden, March 2019, were used in the analyses (www.tlv.se).
- The cost per non-severe hypoglycemic event was based on data from published sources[6,7] and calculated to be SEK 27 (T1D) and SEK 159 (T2D) per event.
- Costs are expressed in 2019 Swedish krona (SEK). (€ 1 = SEK 10.47, 19MAR2019).

Figure 1: ReFLeCT study overview[5]



OD: once daily; T1D: type 1 diabetes; T2D: type 2 diabetes.
Participating countries: Denmark, The Netherlands, Spain, Sweden, Switzerland, Italy, United Kingdom

Study information

- T1D (n=566)
- T2D (n=611)
- Planned to initiate insulin degludec
- Multicentre, prospective, non-interventional

Key inclusion/exclusion criteria

- Male or female ≥ 18 years, T1D and/or T2D, insulin using, planned initiation with insulin degludec
- No previous use of insulin degludec

Results

Insulin doses

Table 1 shows the basal and bolus doses at baseline and at the 12 month follow-up. At 12 months estimated basal and bolus insulin dose ratios were 0.91 (95 % C.I. 0.83–0.91) and 0.87 (0.83–0.91) for T1D and 0.98 (0.95–1.01) and 0.96 (0.94–1.01) for T2D.

Incidence Rate Ratio (IRR) hypoglycemia

When patients with T1D switched to insulin degludec a reduced IRR for daytime, nocturnal and severe hypoglycemia was observed at 12 months follow-up (Table 2). For patients with T2D the IRR was reduced for daytime and nocturnal hypoglycemia.

Cost-effectiveness of insulin degludec

Switching to insulin degludec was cost-saving for patients with T1D compared to previous basal therapy. In T2D, insulin degludec was highly cost-effective, with a cost per quality-adjusted life-year (QALY) of SEK 15 000–24 000 (Tables 3–5). In Sweden a treatment is considered cost-effective if cost/QALY is <500 000 SEK.

Sensitivity analyses showed that the results were robust to changes in efficacy and cost parameters in both T1D and T2D.

Table 1: Insulin doses at baseline and at one year follow-up

Dose	Before	After	Difference	%	
T1D					
Basal insulin	25.0	22.8	-2.2	-9%	
Bolus insulin	27.3	23.8	-3.5	-13%	
Total dose	52.3	46.6	-5.7	-11%	
T2D					
Basal insulin	37.5	35.9	-1.6	-2%	(NS)
Bolus insulin	38.9	38.3	-0.6	-4%	(NS)
Total dose	76.4	74.2	-2.2	-3%	(NS)

NS: Non-significant in T2D, and therefore NOT included in analysis

Table 2: Incidence Rate Ratio (IRR) hypoglycemia

	T1D RR (95% CI)	T2D RR (95% CI)
Non-severe daytime hypoglycemic event	0.85 (0.78, 0.93)*	0.56 (0.46, 0.69)*
Non-severe nocturnal hypoglycemic event	0.63 (0.52, 0.76)*	0.38 (0.22, 0.64)*
Severe hypoglycemic event	0.28 (0.14, 0.56)*	N/A

* p<0.001

Table 3: Cost-effectiveness of insulin degludec vs treatment before switch of basal insulin (SEK)

Diabetes type	Scenario	Cost Difference (SEK)	QALY Difference	Cost (SEK)/ QALY
T1D	IGlar U100 price: original	-1 249	0.079	Dominant
T1D	IGlar U100 price: biosimilar	-995	0.079	Dominant
T2D	IGlar U100 price: original	560	0.038	14 911
T2D	IGlar U100 price: biosimilar	912	0.038	24 259

SEK: Swedish kronor; QALY: Quality-Adjusted Life Years; T1D: Type 1 Diabetes; T2D: Type 2 Diabetes; IGlar U100: Insulin Glargine U100. (€ 1 = SEK 10.47, 19MAR2019).

Table 4: Cost distribution in T1D (SEK)

Costs	Insulin Degludec	IGlar U100 (Original)	Δ Costs	IGlar U100 (Biosimilar)	Δ Costs
TOTAL	**12 582**	**13 830**	**-1 249**	**13 577**	**-995**
Basal insulin	3 680	3 065	614	2 812	868
Bolus insulin	1 466	1 685	-219	1 685	-219
Hypoglycemia	1 853	3 044	-1 191	3 044	-1 191
Production loss	804	1 257	-453	1 257	-453
Needle & SMBG*	4 779	4 779	0	4 779	0

*SMBG:Self Monitoring Blood Glucose (lancet and strip). (€ 1 = SEK 10.47, 19MAR2019).

Table 5: Cost distribution in T2D (SEK)

Costs	Insulin Degludec	IGlar U100 (Original)	Δ Costs	IGlar U100 (Biosimilar)	Δ Costs
TOTAL	**13 633**	**13 073**	**560**	**12 722**	**912**
Basal insulin	6 039	4 418	1 621	4 066	1 973
Bolus insulin	1 506	1 506	0	1 506	0
Hypoglycemia	556	996	-440	996	-440
Production loss	753	1 374	-621	1 374	-621
Needle & SMBG*	4 779	4 779	0	4 779	0

*SMBG:Self Monitoring Blood Glucose (lancet and strip). (€ 1 = SEK 10.47, 19MAR2019).

Discussion

- The switch to insulin degludec was cost-saving for patients with T1D relative to previous basal therapy with IGlar U100 priced as original or biosimilar independent of changes in efficacy and cost parameters.
- Switching to insulin degludec was highly cost-effective for patients with T2D compared with previous basal therapy with IGlar U100 priced as original or biosimilar independent of changes in efficacy and cost parameters.
- The C/E of insulin degludec was driven by lower insulin doses in T1D and reduced risk of hypoglycemia in T1D and T2D.
- Patients with T1D had more hypoglycemic events than patients with T2D. However, the cost per event is higher in T2D, mainly due to a larger proportion of health care visits after the event.

Conclusion

Compared to previous basal insulin therapy, with IGlar U100 priced as original or biosimilar, the switch to insulin degludec is cost-saving in patients with T1D and highly cost-effective in patients with T2D after one year from a Swedish societal perspective when using real-world data from ReFLeCT.

The study was sponsored by Novo Nordisk. Presenter Johan Jendle has received grants from Dexcom, Medtronic, NovoNordisk, and has received consulting fees and/or honoraria for advisory board and speaking for Abbott, AstraZeneca, Boehringer Ingelheim, Dexcom, Eli Lilly, MSD, NovoNordisk, Medtronic, Sanofi. Presented at EASD, 18th of September 2019, Barcelona, Spain.

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Abstract

Cost-Effectiveness of Insulin Degludec vs. Insulin Glargine U100 in Type 1 Diabetes Mellitus in a Swedish Setting after One Year

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Background and aims

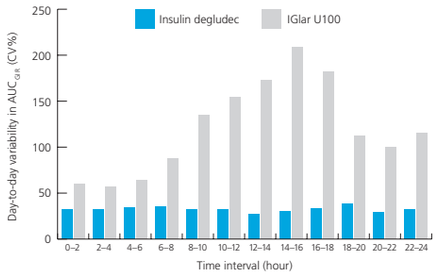
Background

- Insulin degludec is a basal insulin with a long duration of action and a flat glucose-lowering profile under steady-state conditions in type 1 diabetes (T1D).[1–3] Under these conditions insulin degludec has a four-fold lower day-to-day variability than insulin glargine 100 units/mL (IGlar U100, Figure 1).[3]
- According to randomised controlled trials, insulin degludec has a beneficial hypoglycaemia profile compared with IGlar U100.[4,5]
- Cost-effectiveness, as well as safety and efficacy, is an important factor in the decision to implement a new medication, and required for reimbursement in various countries, like Sweden.

Aim

This analysis was made to assess the cost-effectiveness of insulin degludec compared with original and biosimilar IGlar U100 in T1D in a Swedish health care setting, using evidence from SWITCH 1.

Figure 1: Lower day-to-day variability in glucose-lowering effect for degludec versus IGlar U100[3]



AUC, area under the curve; CV, coefficient of variation; GIR, glucose infusion rate; IGlar U100, insulin glargine U100

Methods

- Evidence from the total data set of SWITCH 1[4] was used in this cost-effectiveness study.

SWITCH 1

- SWITCH 1 was a treat-to-target, multinational, double-blinded, two-armed, randomised, cross-over clinical trial (RCT) with two full treatment periods of 32 weeks respectively, with 16 weeks titration period and 16 weeks maintenance period.[4]
- Patients were randomised 1:1 to insulin degludec or IGlar U100 once daily, with insulin aspart 2–4 times daily as bolus insulin.
- At randomisation and at crossover, the starting dose of basal insulin was reduced by 20% in both treatment arms. The basal insulin dose was then titrated once weekly according to the trial algorithm.[4]
- Patients included in the study were at least 18 years old and had at least one risk factor of hypoglycaemia.
- Endpoints were difference blood glucose-confirmed symptomatic hypoglycaemic episodes (< 3.1 mmol/L; total, nocturnal and severe), reported after 16 weeks of maintenance period and after full treatment period.[4]
- A post hoc analyses of SWITCH 1 data showed a difference in rates of non-severe diurnal hypoglycaemia (Rate Ratio (RR) 0.98 (95% Confidence Interval [CI]: 0.94; 1.03)), but a significant reduction in both non-severe nocturnal (RR 0.76 (95% CI: 0.69; 0.84)) and severe (RR 0.74 (95% CI: 0.61; 0.91)) hypoglycaemic events in favour of insulin degludec. (Table 1)
- Insulin doses at the end of trial: IGlar U100 basal dose was 40.58 units/day. Insulin degludec/IGlar U100 basal dose ratio was 0.97 [95% CI: 0.94–0.99]. The bolus dose used in the IGlar U100 arm was 31.93 U/day and the bolus dose ratio for the two arms (insulin degludec/IGlar U100) was 0.97 [0.94–1.01]. (Table 1)

Table 1: Hypoglycaemic event rates, full treatment period, and end-of-trial insulin doses from SWITCH 1

	IGlar U100	Insulin Degludec*	Rate Ratio
Non-severe daytime hypoglycaemia	1 718.08	1 683.72	0.98 (NS)
Non-severe nocturnal hypoglycaemia	345.07	261.54	0.76
Severe hypoglycaemia	104.82	77.89	0.74
Basal insulin dose (IUs per day)	40.58	39.36	0.97
Bolus insulin dose (IUs per day)	31.93	30.97	0.97 (NS)

*Calculated insulin degludec hypoglycaemic event ratio and dose ratio.

Cost-effectiveness analysis

- Cost-effectiveness was analysed over a 1-year time horizon with a Swedish health care perspective.
- The health economics model (DOSE) has been described elsewhere[6], and was used in the reimbursement application for insulin degludec in Sweden.
- Only differences with p<0.05 were included in the analysis.
- Costs were estimated based on the different rates of hypoglycaemic events and actual doses of insulin from SWITCH 1. (Table 1)
- Analyses were made for two different scenarios:
  - Insulin degludec vs IGlar U100 with a price = original IGlar U100. (Table 2)
  - Insulin degludec vs IGlar U100 with a price = biosimilar IGlar U100. (Table 3)
- The cost of pharmaceuticals was based on the Pharmacy Selling Price, PSP (Apotekens utpris, AUP) in April 2019.
- The cost of hypoglycaemic events was derived from studies measuring the cost of severe[7] and non-severe[8] events in Sweden (adjusted to the current price level by the consumer price index for health).
  - Costs are expressed in 2019 Swedish krona (SEK). (€ 1 = SEK 10.47, 19MAR2019)
- Difference in Quality-Adjusted Life-Years (QALYs) was calculated by applying a disutility value (which measures the impact of a health state on quality of life) to each type of hypoglycaemic event.[9]

Results

- Costs, QALYs and Incremental Cost-Effectiveness Ratios (ICERs) for insulin degludec compared with original and biosimilar IGlar U100 are shown in Table 2 and 3, respectively. Pharmacy costs were higher for insulin degludec, but were partly offset by the costs of non-severe nocturnal and severe hypoglycaemia.
- Total cost difference was SEK 575–1 219.
- Insulin degludec was highly cost-effective compared with IGlar U100, with an incremental cost-effectiveness ratio (ICER) of SEK 25 000–52 000.

Table 2: Cost-effectiveness of insulin degludec compared with IGlar U100 (price=original)

	Insulin Degludec	IGlar U100 (Original)	Incremental Cost (Insulin Degludec-IGlar)
Pharmacy costs	**13 095**	**12 097**	**998**
Insulin	8 316	7 318	998
Needles	1 010	1 010	0
SMBG tests	3 769	3 769	0
Hypoglycaemic events	**1 626**	**2 049**	**-423**
Non-severe diurnal events	398	398	0
Non-severe nocturnal events	61	80	-19
Severe events	1 167	1 571	-404
Total costs	**14 721**	**14 146**	**575**
Effects			
QALYs	0.782	0.759	0.023
ICER (cost per QALY)			**24 752**

(€ 1 = SEK 10.47, 19MAR2019)

Table 3: Cost-effectiveness of insulin degludec compared with IGlar U100 (price=biosimilar)

	Insulin Degludec	IGlar U100 (Biosimilar)	Incremental Cost (Insulin Degludec-IGlar)
Pharmacy costs	**13 095**	**11 453**	**1 642**
Insulin	8 316	6 674	1 642
Needles	1 010	1 010	0
SMBG tests	3 769	3 769	0
Hypoglycaemic events	**1 626**	**2 049**	**-423**
Non-severe diurnal events	398	398	0
Non-severe nocturnal events	61	80	-19
Severe events	1 167	1 571	-404
Total costs	**14 721**	**13 502**	**1 219**
Effects			
QALYs	0.782	0.759	0.023
ICER (cost per QALY)			**52 480**

(€ 1 = SEK 10.47, 19MAR2019)

Discussion

- Insulin degludec was highly cost-effective compared with IGlar U100 since a diabetes treatment is considered cost-effective in Sweden if cost/QALY is below SEK 500 000.
- The rigorous design of the SWITCH 1 trial1, including a hypoglycaemic sensitive T1D patient population and a relevant definition of hypoglycaemia, makes the results of this trial generalisable.
- The result was driven by reduced risk of hypoglycaemia and lower insulin doses.

Conclusion

In this cost-effectiveness analysis, insulin degludec was highly cost-effective as compared to original and biosimilar IGlar U100 in patients with T1D in a Swedish health care setting after one year.

The study was sponsored by Novo Nordisk. Presented at EASD, 18th of September 2019, Barcelona, Spain.

References: (**1**) Heise et al. Diabetes Obes Metab 2012;14:944–50. (**2**) Heise et al. J Diabetes 2016;8:132–138. (**3**) Heise et al. Diabetes Obes Metab 2012;14:859–64. (**4**) Lane W et al. JAMA 2017;318(1):33—44. (**5**) Marso et al. The New England Journal of Medicine 2017;377(8):723–32. (**6**) Evans M et al. Diabetes Ther 2018;9:1919–30. (**7**) Jonsson L et al. Value Health 2006;9(3):193–8. (**8**) Geelhoed-Duijvestijn PHLM et al. Value Health 2012;15(7):A502. (**9**) Evans M et al. Health and Quality of Life Outcomes 2013;11:90–9.

Abstract

Liraglutide as add-on to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes: a 26-week, randomised, double-blind, placebo-controlled trial

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qrs.ly/uwabn8i

Background

- Type 2 diabetes (T2D) is a progressive disease typically requiring treatment intensification to achieve and/or maintain good glycaemic control;[1] this can be achieved through combining therapies that have complementary mechanisms of action.
- Both glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 inhibitors (SGLT2is) are associated with improved glycaemic control, low rates of hypoglycaemia, reductions in body weight, cardiovascular benefits and a favourable safety profile in patients with T2D.[1–3]
- Despite limited evidence for the concomitant use of GLP-1 receptor agonists with SGLT2is,[4–5] the combination of these drug classes has been increasingly used by clinicians, and is now recommended by guidelines.[1]
- The LIRA-ADD2SGLT2i trial assessed the effect on glycaemic control of the GLP-1 analogue liraglutide, versus placebo, when administered in combination with an SGLT2i (± metformin) in patients with inadequate glycaemic control.
- This trial addresses limitations in the available data for combined use of these drugs, aiming to strengthen the scientific rationale behind clinical decisions for the management of T2D.

Methods

Study design

- LIRA-ADD2SGLT2i (NCT02964247) was a 26-week, double-blind, randomised, placebo-controlled, parallel-arm, multicentre, multinational phase 3b trial.
- Enrolled patients had T2D, glycated haemoglobin (HbA_{1c}) levels of 7.0–9.5%, body mass index (BMI) ≥20 kg/m², received a stable dose of SGLT2i (canagliflozin, dapagliflozin or empagliflozin) for at least 90 days as monotherapy or in combination with a stable dose of metformin (≥1500 mg or maximum tolerated dose), no history of diabetic ketoacidosis (DKA) while on SGLT2i, and had an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m².
- Patients were randomised 2:1 to receive either liraglutide 1.8 mg or placebo, added to a continuous stable treatment with an SGLT2i ± metformin for 26 weeks with a subsequent 1-week follow-up.
- The primary endpoint was change in HbA_{1c} from baseline to 26 weeks.
- Secondary assessments included: change in body weight from baseline, proportion of patients achieving HbA_{1c} <7% and ≤6.5% and safety.

Statistical analysis

- Two distinct statistical approaches were used to address different aspects of the treatment effect.
- The treatment policy estimand (primary estimand) was analysed with a pattern mixture model; it evaluated the average treatment effect of adding liraglutide versus placebo to a stable regimen of SGLT2i with or without metformin in all randomised patients, regardless of adherence to treatment or use of rescue glucose-lowering medication (i.e. effectiveness).
- The trial product estimand (secondary estimand) was estimated using a mixed model for repeated measurements; it evaluated the average treatment effect of adding liraglutide to stable SGLT2i with or without metformin treatment for all randomised patients, under the assumption that all patients remained on trial product for the entire planned duration of the trial and did not use rescue glucose-lowering treatment (i.e. efficacy).

Results

- Of the 412 patients screened, 303 were randomised to either liraglutide (203) or placebo (100); 280 patients (92.4%) completed treatment (92.1% vs 93.0% for liraglutide and placebo, respectively).
- Baseline characteristics were balanced across both arms (Table 1).
- At week 26, the mean change in HbA_{1c} from baseline was –0.98% for the liraglutide group vs –0.30% for the placebo group, with an estimated treatment difference (ETD) of –0.68% (95% confidence interval [CI] –0.89, –0.48; p<0.001 [Figure 1]).
- The mean change in body weight was –2.81 kg vs –1.99 kg for the liraglutide and placebo groups, respectively (ETD –0.82 kg; 95% CI –1.73, 0.09; p=0.077 [Figure 2]).
- A higher proportion of patients in the liraglutide group versus placebo (Figure 3) achieved:
  - » HbA_{1c} <7.0%;
  - » HbA_{1c} ≤6.5%.

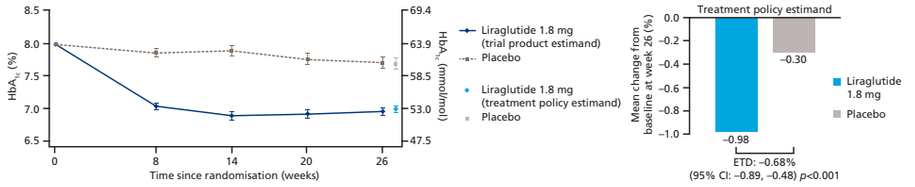
Table 1: Baseline demographics and clinical characteristics

Mean (SD)	Liraglutide 1.8 mg N=203	Placebo N=100	Total N=303
Sex (% males)	62	58	60
Age, years	54.7 (10.1)	56.0 (9.9)	55.2 (10.0)
Diabetes duration, years	10.1 (7.2)	9.6 (6.7)	9.9 (7.0)
HbA_{1c}, mmol/mol	63.9 (8.0)	63.4 (6.9)	63.8 (7.6)
HbA_{1c}, %	8.0 (0.7)	8.0 (0.6)	8.0 (0.7)
FPG, mg/dL	160.7 (41.7)	159.1 (46.3)	160.2 (43.2)
FPG, mmol/L	8.9 (2.3)	8.8 (2.6)	8.9 (2.4)
Body weight, kg	91.0 (21.0)	91.4 (21.4)	91.1 (21.1)
BMI, kg/m²	32.0 (6.0)	32.6 (6.5)	32.2 (6.1)
SBP, mmHg	127.5 (12.7)	128.5 (14.4)	127.8 (13.3)
DBP, mmHg	79.2 (9.0)	79.3 (8.9)	79.3 (8.9)
SGLT2i and metformin use, N (%)			
SGLT2i			
Dapagliflozin	96 (47.3)	54 (54.0)	150 (49.5)
Empagliflozin	55 (27.1)	23 (23.0)	78 (25.7)
Canagliflozin	52 (25.6)	23 (23.0)	75 (24.8)
Metformin	191 (94.1)	95 (95.0)	286 (94.4)

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; SBP, systolic blood pressure; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor

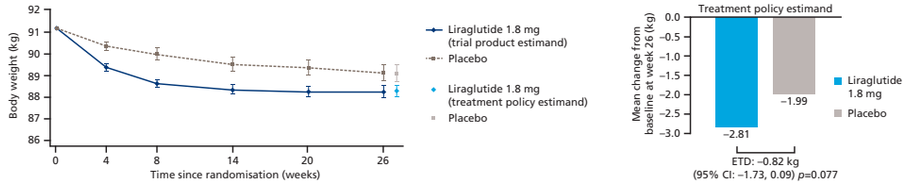
Figure 1: Change in HbA_{1c} from baseline

Key result



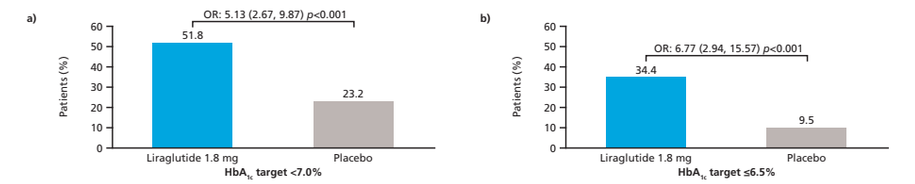
Estimated treatment effect was calculated using treatment policy estimands with a PMM, which were based on the in-trial observation period, including the effect of any rescue medication, regardless of whether patients prematurely discontinued trial product. Trial product estimands calculated using MMRM were based on the on-treatment without rescue medication observation period. CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin; MMRM, mixed model of repeated measurements; PMM, pattern mixture model

Figure 2: Change in body weight from baseline



Estimated treatment effect was calculated using treatment policy estimands with a PMM, which were based on the in-trial observation period, including the effect of any rescue medication, regardless of whether patients prematurely discontinued trial product. Trial product estimands calculated using MMRM were based on the on-treatment without rescue medication observation period. CI, confidence interval; ETD, estimated treatment difference; MMRM, mixed model of repeated measurements; PMM, pattern mixture model

Figure 3: Proportion of patients reaching HbA_{1c} targets (at week 26): a) HbA_{1c} target <7.0%, b) HbA_{1c} target ≤6.5%



HbA_{1c}, glycated haemoglobin; OR, odds ratio

- A higher proportion of patients reported ≥1 treatment-emergent adverse event (AE) in the liraglutide group than the placebo group (66.3 vs 47.0%, respectively [Table 2]).
  - » Nausea was the most commonly reported AE (26.2% and 6.0% for liraglutide versus placebo, respectively) and was predominately early-onset and transient.
  - » Serious AEs were reported by a low proportion of patients in both liraglutide (2.5%) and placebo (1.0%) groups and there were no fatalities, reports of acute renal failure, DKA, diabetic foot ulcers or amputations with liraglutide in combination with an SGLT2i.
  - » The proportion of patients reporting hypoglycaemia was similar across liraglutide (8.9%) and placebo (8.0%) groups, and none of these episodes were severe (defined as requiring assistance from another person according to the American Diabetes Association criterion).[6]

Table 2: Summary of adverse events

	Liraglutide 1.8 mg N=202 n (%)	Placebo N=100 n (%)
Deaths	0 (0.0)	0 (0.0)
Serious adverse events*	5 (2.5)	1 (1.0)
Treatment-emergent adverse events†	134 (66.3)	47 (47.0)
Severe	6 (3.0)	2 (2.0)
Possibly or probably related	102 (50.5)	18 (18.0)
Trial treatment discontinuation due to adverse events	8 (4.0)	2 (2.0)
All hypoglycaemic episodes	18 (8.9)	8 (8.0)
Severe or BG-confirmed symptomatic†	0 (0.0)	3 (3.0)‡
Severe (ADA)	0 (0.0)	0 (0.0)

Data presented are from the safety analysis set. *One serious adverse event (cholecystitis in the liraglutide group) was judged by the investigator as possibly or probably related to trial product, which led to premature trial product discontinuation for the remainder of the trial. The event had resolved by the end of the trial. No cases of acute pancreatitis or medullary thyroid cancer were reported. Hypoglycaemia plasma glucose cut-off: †Novo Nordisk definition is <3.1 mmol/L (56 mg/dL); ADA level 1 definition is 3.0–3.9 mmol/L (≥54–<70 mg/dL). ‡One patient was on rescue medication with sulphonylureas. %, proportion of patients; ADA, American Diabetes Association; BG, blood glucose; N, number of patient.

Conclusions

- In patients with T2D, the addition of liraglutide to SGLT2i therapy (± metformin) provided superior glycaemic control versus placebo, with safety profiles consistent with that of both drug classes.
- The LIRA-ADD2SGLT2i trial provides clinical evidence to support use of GLP-1 analogues with SGLT2is to help improve glycaemic control.

The LIRA-ADD2SGLT2i trial was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT02964247).
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September 16–20, 2019, Barcelona, Spain.

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Abstract

575

Effect of liraglutide 3.0 mg on glycaemic parameters in adults with overweight/obesity and T2D treated with basal insulin: SCALE Insulin trial

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qrs.ly/h7abn8q

Background

- Liraglutide 3.0 mg is approved for weight management in individuals with overweight or obesity and has been investigated in individuals with type 2 diabetes (T2D) as part of the Satiety and Clinical Adiposity—Liraglutide Evidence (SCALE) phase 3a programme.[1]
- Liraglutide up to 1.8 mg has been used in combination with insulin for treatment of T2D, but combination of a 3.0 mg dose with insulin has not previously been investigated.
- In SCALE Diabetes, a 56-week trial in individuals with overweight or obesity and T2D, liraglutide 1.8 mg and 3.0 mg showed significant weight- and glucose-lowering effects, with an acceptable safety profile.[2] However, individuals treated with insulin were excluded from the trial.
- To our knowledge, no pharmacotherapeutic agents approved for the treatment of obesity have been specifically investigated in individuals with obesity and insulin-treated T2D.
- The aim of the SCALE Insulin phase 3b trial was to evaluate the efficacy and safety of liraglutide 3.0 mg for weight management in individuals with overweight or obesity and T2D treated with basal insulin and up to two oral antidiabetic drugs (OADs). This poster reports the effect on glycaemic parameters and hypoglycaemic safety data from the trial.

Methods

Study design

- SCALE Insulin (NCT02963922) was a 56-week, randomised, double-blind, placebo-controlled, multicentre trial in individuals with obesity.
- A total of 396 adults with T2D (glycated haemoglobin [HbA_{1c}] 6.0–10.0%) and overweight or obesity (body mass index [BMI] ≥27 kg/m^2) were randomised 1:1 to liraglutide 3.0 mg or placebo, both as adjunct to intensive behaviour therapy (IBT).
- An IBT programme was provided in both arms which included reduced caloric intake, increased physical activity goals (increasing up to 250 min/week) and 23 behavioural counselling sessions.
- The diabetes treatment regimens for all individuals included basal insulin and up to two OADs. It was recommended that doses of sulphonylureas were reduced by 50% at randomisation to avoid the risk of hypoglycaemia.
  - » Individuals on sulphonylureas were stratified between the two arms.
- Similarly, doses of basal insulin were recommended to be reduced by 15–20% for individuals who had HbA_{1c} ≤8%. The trial was designed such that glycaemic control was similar between the two arms (e.g. insulin doses adjusted weekly).
- Weekly dose escalation of the trial drug was implemented during the first 4 weeks at randomisation in accordance with the label.[2]

Statistical analysis

- Outcomes were assessed based on data for all randomised individuals regardless of premature discontinuation of trial product (treatment policy estimand or intention-to-treat [ITT] principle); missing values were handled using a jump-to-reference multiple imputation model.
- Continuous and categorical variables were calculated using analysis of covariance (ANCOVA) and logistic regression, respectively, with treatment arm, gender and BMI as factors and baseline endpoint as a covariate.

Results

- In total, 396 individuals were randomised (1:1) to liraglutide 3.0 mg or placebo, of which 195 and 197 were exposed, respectively.
- To increase retention, the trial allowed individuals to return to study drug after discontinuation. At 56 weeks, 166 (83.8%) and 168 (84.8%) individuals remained on liraglutide 3.0 mg and placebo, respectively.
- Baseline demographics were similar between treatment arms (Table 1).
- Estimated mean change in weight at 56 weeks was –5.8% with liraglutide 3.0 mg and –1.5% with placebo (estimated treatment difference [ETD]: –4.3%, 95% CI: –5.5; –3.2, p<0.0001). Additional weight loss data available from the trial (see poster 576[3]).
- Mean estimated change in HbA_{1c} at 56 weeks was –1.09% and –0.55% with liraglutide 3.0 mg and placebo, respectively (ETD: –0.53, 95% CI: –0.76; –0.31, p<0.0001) (Figure 1).
- Mean estimated change in fasting plasma glucose at 56 weeks was –1.02 and –0.64 mmol/L (ETD: –0.39, 95% CI: –0.91; 0.14, p=not significant).
- Change in estimated mean daytime glucose value (based on 7-point self-measured blood glucose profile) at 56 weeks was –2.2 and –1.5 mmol/L for liraglutide 3.0 mg and placebo, respectively (ETD: –0.69, 95% CI: –1.14; –0.23, p=0.0032).
- Treatment with liraglutide 3.0 mg resulted in a smaller increase in mean insulin dose requirement at 56 weeks versus placebo; +2.8U and +17.8U, respectively, from a baseline mean in both groups of 38U. This represented a relative difference of 15U (95% CI: 22; 8, p<0.0001).
- At 56 weeks, more liraglutide 3.0 mg- than placebo-treated individuals achieved the composite endpoint of reaching HbA_{1c} target[4] <7.0% + ≥5% weight loss (39.0% vs 13.9%; odds ratio 3.94, p<0.0001). Similarly, more liraglutide 3.0 mg- than placebo-treated individuals met the composite endpoint of HbA_{1c} <7.0% + ≥5% weight loss + no documented symptomatic hypoglycaemia[5] (17.8% vs 6.2%; odds ratio 3.28, p=0.0006).
- Adverse event incidence was similar for liraglutide 3.0 mg and placebo, except for gastrointestinal events (liraglutide 3.0 mg, 62.1%; placebo, 46.7%).
- Total number of hypoglycaemic events (on-drug) occurred at the respective rates of 742 and 938 events per 100 patient-years of exposure with liraglutide and placebo, with three and two severe events, respectively (Table 2).
- Documented symptomatic hypoglycaemia (on-drug) occurred at rates of 425 and 299 events per 100 patient-years of exposures, with liraglutide versus placebo respectively, in patients taking sulphonylureas at baseline; and 290 vs 475 events per 100 patient-years of exposure in patients not taking sulphonylureas at baseline with liraglutide versus placebo, respectively.

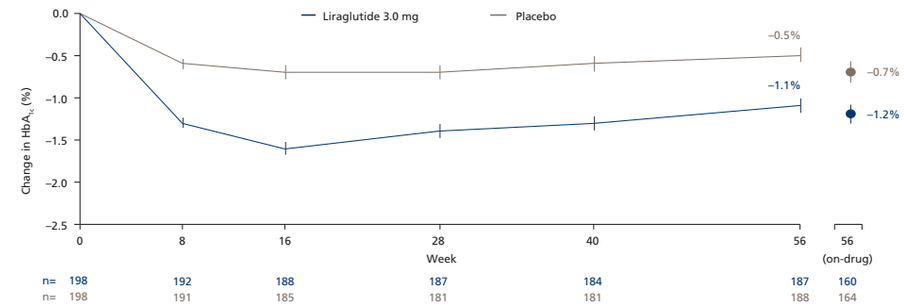
Table 1: Baseline demographics and anthropometry

	Liraglutide 3.0 mg (n=198)	Placebo (n=198)
Sex, male, n (%)	90 (45.5)	99 (50.0)
Mean age, years (SD)	55.9 (11.3)	57.6 (10.4)
Race, White, n (%)	174 (87.9)	180 (90.9)
Mean body weight, kg	100.6 (20.8)	98.9 (19.9)
Mean BMI, kg/m^2 (SD)	35.9 (6.5)	35.3 (5.8)
Mean HbA_{1c}, % (SD)	7.9 (1.1)	8.0 (1.0)
Mean FPG, mmol/L (SD)	7.8 (2.2)	8.1 (2.5)
Mean diabetes duration, years	11.4 (6.8)	12.8 (6.9)
Anti diabetic medications at screening		
SGLT-2is, n (%)	44 (22.2)	44 (22.2)
Sulphonylureas, n (%)	68 (34.3)	71 (35.9)
Long-acting basal insulins/analogues, n (%)	180 (90.9)	184 (92.9)
Intermediate-acting basal insulins/analogues, n (%)	18 (9.1)	14 (7.1)

Values are observed mean (SD) for full analysis set, unless otherwise stated. BMI, body mass index; FPG, fasting plasma glucose; SD, standard deviation; SGLT2-i; sodium-glucose co-transporter-2 inhibitor

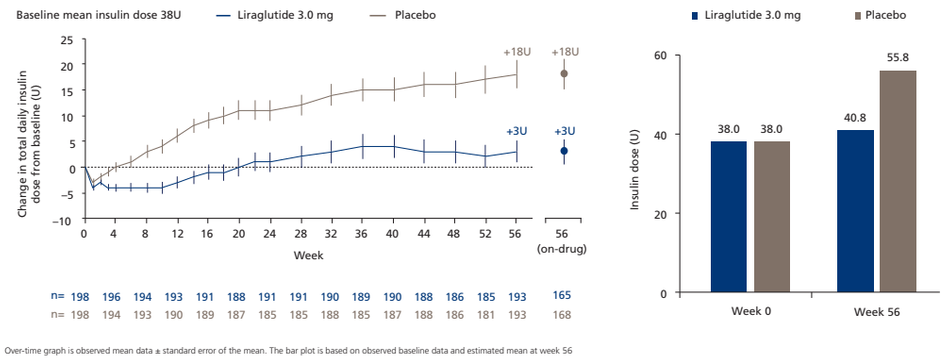
Figure 1: Change in HbA_{1c} over time (%)

Key result



Graph is observed mean data ± standard error of the mean

Figure 2: Change in total daily insulin dose (U)



Over-time graph is observed mean data ± standard error of the mean. The bar plot is based on observed baseline data and estimated mean at week 56

Table 2: Hypoglycaemic episodes* from randomisation to week 56

	Liraglutide 3.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of individuals exposed	195				197			
Hypoglycaemic episodes	140	(71.8)	1462	742.3	140	(71.1)	1859	937.9
Severe episodes	3	(1.5)	3	1.5	2	(1.0)	2	1.0
BG ≤3.9 mmol/L								
Asymptomatic	116	(59.5)	742	376.7	116	(58.9)	988	498.4
Documented symptomatic	92	(47.2)	662	336.1	102	(51.8)	816	411.7

Data are from patients on-drug. Episodes recorded in patient diaries. BG, blood glucose; E, number of events; R, event rate per 100 patient-years of exposure. *Based on American Diabetes Association 2013 criteria[4]

Conclusions

- In insulin-treated individuals with overweight/obesity and longstanding T2D, treatment with liraglutide 3.0 mg resulted in better glycaemic control versus placebo, in addition to clinically relevant weight loss, with need for less basal insulin.
- Total number of hypoglycaemic episodes was higher in individuals treated with placebo versus liraglutide 3.0 mg.

The study was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT02963922).
Presenter Dror Dicker reports consulting and lecture fees from Novo Nordisk, Boehringer Ingelheim, Sanofi, AstraZeneca and Teva Pharmaceutical Industries.
The authors are grateful to Sasha Walton, Watermeadow Medical, an Ashfield Company (supported by Novo Nordisk), for writing assistance.
Presented at the European Association for the Study of Diabetes, 55th Annual Meeting.
September 16–20, 2019, Barcelona, Spain.

References: (**1**) Davies *et al. JAMA* 2015;314:687–99; (**2**) Novo Nordisk. Saxenda® EU SmPC. https://www.ema.europa.eu/; (**3**) Migrone *et al.* Poster 576. Presented at EASD 2019; (**4**) American Diabetes Association. *Diabetes Care* 2019;42(Suppl 1):S61–70; (**5**) Seaquist *et al. Diabetes Care* 2013;36:1384–95.

Abstract

576

Efficacy and safety of liraglutide 3.0 mg in individuals with overweight or obesity and type 2 diabetes treated with basal insulin: the SCALE Insulin trial

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Introduction

- Individuals with type 2 diabetes (T2D) typically find it more difficult to lose weight than matched counterparts without T2D, owing, in part, to the weight-promoting effects of glucose-lowering treatments with sulphonylureas and/or insulin.[1,2]
- Liraglutide 3.0 mg is approved for weight management in individuals with overweight or obesity and has been investigated in individuals with T2D as part of the Satiety and Clinical Adiposity – Liraglutide Evidence (SCALE) phase 3a programme.[3]
- In the SCALE Diabetes trial, liraglutide 1.8 mg and 3.0 mg resulted in clinically significant weight loss (WL) and glycaemic benefits, with an acceptable safety profile.[4] Individuals treated with insulin, however, were excluded from this trial.
- To our knowledge, no pharmacotherapeutic agents approved for weight management have been specifically investigated in individuals with overweight or obesity and insulin-treated T2D.
- The aim of the SCALE Insulin trial was to evaluate the efficacy and safety of liraglutide 3.0 mg for weight management in individuals with overweight or obesity and T2D treated with basal insulin and up to two oral antidiabetic drugs (OADs). This poster reports the measures of body weight and safety data from the trial.

Methods

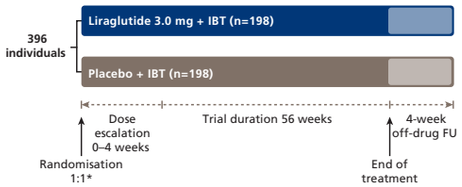
Study design

- SCALE Insulin (NCT02963922) was a 56-week, randomised, double-blind, placebo-controlled, multicentre trial in 396 individuals with T2D (glycated haemoglobin [HbA_{1c}] 6.0–10.0%) and overweight or obesity (body mass index [BMI] ≥27 kg/m^2).
- Individuals were randomised 1:1 to liraglutide 3.0 mg or placebo, both as adjunct to intensive behaviour therapy (IBT) (Figure 1).
- An IBT programme was provided in both arms, which included a hypocaloric diet, increased physical activity goals (increasing up to 250 min/week) and 23 behavioural counselling sessions.
- Primary endpoints were mean change in body weight (%) and proportion with WL ≥5% at week 56; a number of relevant secondary endpoints are reported here.
- All individuals were on stable treatment with basal insulin and up to 2 OADs. It was recommended that doses of sulphonylureas were reduced by 50% at randomisation to avoid the risk of hypoglycaemia.
  - » Individuals on sulphonylureas were stratified between the two treatment arms.
- Similarly, it was recommended that doses of basal insulin be reduced by 15–20% for individuals who had HbA_{1c} ≤8%. The trial was designed to target similar glycaemic control in the two arms by weekly adjustments of insulin dose.
- Weekly dose escalation of the trial drug was implemented during the first 4 weeks following randomisation in accordance with the label.[3]

Statistical analysis

- Outcomes were assessed based on data for all randomised individuals regardless of premature discontinuation of trial product (treatment policy estimand); missing values were handled using a jump-to-reference multiple imputation model.
- Continuous and categorical variables were calculated using analysis of covariance (ANCOVA) and logistic regression, respectively, with treatment arm, gender and BMI as factors and baseline endpoint as a covariate.

Figure 1: Study design



*Insulin dose decreased by 15–20% after randomisation for individuals with HbA_{1c} ≤8% at randomisation; dose adjusted once weekly according to pre-breakfast. SMBG target 4.0–5.0 mmol/L (basal insulin dose was not to exceed the entry dose in the first 5 weeks). BMI, body mass index; BW, body weight; FU, follow-up; IBT, intensive behaviour therapy; OAD, oral antidiabetic drug; SMBG, self-measured blood glucose; T2D, type 2 diabetes

Results

- In total, 396 individuals were randomised (1:1) to liraglutide 3.0 mg or placebo, of which 195 and 197 were exposed, respectively. Subject disposition was similar between treatment arms (Table 1).
- To increase retention, the trial allowed individuals to return to study drug after discontinuation. At 56 weeks, 166 (83.8%) and 168 (84.8%) individuals remained on liraglutide 3.0 mg and placebo, respectively.
- Baseline demographics were similar between both treatment groups (Table 1).

Table 1: Subject disposition and baseline characteristics

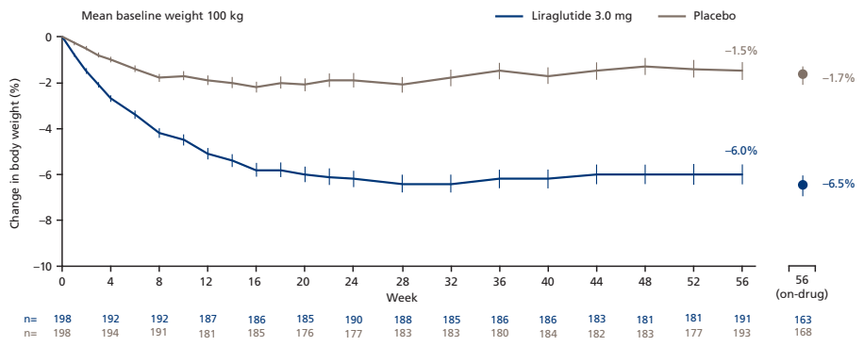
	Liraglutide 3.0 mg (n=198)	Placebo (n=198)
Randomised, n	198	198
Exposed, n	195	197
On drug at week 56 visit, n [%]	166 [83.8]	168 [84.8]
Discontinued trial drug, n [%]	32 [16.2]	30 [15.2]
Withdrawals, n [%]	4 [2.0]	4 [2.0]
With BW measurement at week 56, n [%]	191 [96.5]	193 [97.5]
Sex, male, n [%]	90 [45.5]	99 [50.0]
Mean age, years	55.9 (11.3)	57.6 (10.4)
Race, White, n [%]	174 [87.9]	180 [90.9]
Mean body weight, kg	100.6 (20.8)	98.9 (19.9)
Mean BMI, kg/m^2	35.9 (6.5)	35.3 (5.8)
Mean HbA_{1c}, %	7.9 (1.1)	8.0 (1.0)
Mean diabetes duration, years	11.4 (6.8)	12.8 (6.9)
Mean daily insulin dose, U	38 (27)	38 (29)
Use of sulphonylureas, n [%]	66 [33.3]	70 [35.4]

Discontinued trial drug group includes randomised individuals who were not exposed to trial product. Data are mean (SD) unless otherwise stated. BMI, body mass index; BW, body weight; SD, standard deviation

- Mean estimated change in weight at 56 weeks was –5.8% and –1.5% with liraglutide 3.0 mg and placebo, respectively, corresponding to an estimated treatment difference (ETD) of –4.3% (95% confidence interval [CI]: –5.5; –3.2, p<0.0001) (Figure 2).
- The proportion of individuals achieving WL ≥5% was 51.8% with liraglutide 3.0 mg versus 24.0% with placebo (odds ratio [OR] 3.4, p<0.0001). Values for >10% WL were 22.8% and 6.6% (OR 4.2, p<0.0001), respectively (Table 2).
- Mean estimated change in HbA_{1c} at 56 weeks was –1.1% and –0.6% with liraglutide 3.0 mg and placebo, respectively (ETD: –0.5, 95% CI: –0.8; –0.3, p<0.0001) (Table 2).
- Outcome data for other glycaemic parameters are available from poster 575.[5]
- Treatment with liraglutide 3.0 mg resulted in a smaller increase in mean insulin dose requirement at 56 weeks versus placebo; +2.8U and +17.8U, respectively, from a baseline mean in both groups of 38U. This represented a relative difference of 15U (p<0.0001).
- Total number of hypoglycaemic events (on-drug) occurred at the respective rates of 742 and 938 events per 100 patient-years of exposure with liraglutide and placebo, with three and two severe events, respectively (Table 3).
- Adverse event incidence was similar for liraglutide 3.0 mg and placebo, except for gastrointestinal events (liraglutide 3.0 mg, 62.1%; placebo, 46.7%) (Table 3).

Figure 2: Change in body weight, over time (%)

Key result



Full analysis set. Over time graph is observed mean data ± SEM. SEM, standard error of the mean

Table 2: Endpoints at 56 weeks

	Liraglutide 3.0 mg (n=198)	Placebo (n=198)	ETD/OR* [95% CI]	p-value
Change in body weight from baseline (%)	–5.8	–1.5	–4.3 [–5.5; –3.2]	<0.0001
Percentage of ≥5% responders* (%)	51.8	24.0	3.4 [2.2; 5.3]	<0.0001
Percentage of >10% responders* (%)	22.8	6.6	4.2 [2.2; 8.2]	<0.0001
Change in waist circumference from baseline (cm)	–5.3	–2.6	–2.7 [–3.9; –1.5]	<0.0001
Change in HbA_{1c} from baseline (%)	–1.1	–0.6	–0.5 [–0.8; –0.3]	<0.0001
Change in heart rate (beats/min)	1.4	–0.2	1.5 [–0.2; 3.2]	NS
Change in systolic blood pressure (mmHg)	–5.6	–1.6	–4.0 [–6.4; –1.5]	0.0014
Change in diastolic blood pressure (mmHg)	–2.3	–0.9	–1.4 [–3.0; 0.2]	NS
Change in SF-36 Physical Functioning score from baseline	2.7	2.3	0.4 [–1.0; 1.8]	NS
Change in IWQOL-Lite-CT Physical Function domain score from baseline	8.2	5.7	2.5 [–1.5; 6.4]	NS

*The endpoint is analysed in a logistic regression model. CI, confidence interval; ETD, estimated treatment difference; IWQOL-Lite-CT, impact of weight on quality of life-lite clinical trial version; NS, non-significant; OR, odds ratio; SF-36, short-form 36

Table 3: Safety outcomes

	Liraglutide 3.0 mg			Placebo		
	N	(%)	E/100 yr	N	(%)	E/100 yr
Exposed to trial product, n	195	-	-	197	-	-
Adverse events	180	(92.3)	578.3	175	(88.8)	531.2
Serious	16	(8.2)	11.7	19	(9.6)	12.6
Fatal	0	(0.0)	-	0	(0.0)	-
Leading to discontinuation	15	(7.7)	8.6	6	(3.0)	3.0
Gastrointestinal disorders	121	(62.1)	207.1	92	(46.7)	101.9
Hypoglycaemic episodes*	140	(71.8)	742.3	140	(71.1)	937.9
Severe episodes	3	(1.5)	1.5	2	(1.0)	1.0
Documented symptomatic	92	(47.2)	336.1	102	(51.8)	411.7

Data are from individuals on-drug. *Hypoglycaemic episodes recorded in patient diaries and are based on the American Diabetes Association classification.[6] Documented symptomatic hypoglycaemia: measured plasma glucose concentration ≤3.9 mmol/L with typical symptoms of hypoglycaemia apparent. E/100 yr, event rate per 100 patient-years of exposure

Conclusions

- In individuals with overweight/obesity and insulin-treated T2D, liraglutide 3.0 mg was superior to placebo with respect to mean WL and the proportion of individuals achieving ≥5% and >10% WL at week 56.
- Additionally, liraglutide 3.0 mg was associated with significant improvements in glycaemic control, such as reduction in HbA_{1c} and a reduced need for basal insulin.
- More hypoglycaemic episodes were reported in individuals in the placebo versus liraglutide 3.0 mg group, and no new safety or tolerability issues were observed.
- Liraglutide 3.0 mg is effective for weight management, with an acceptable safety profile, in individuals with overweight/obesity and insulin-treated T2D.

The study was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT02963922).
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The authors are grateful to Sasha Walton, Watermeadow Medical, an Ashfield Company (supported by Novo Nordisk), for writing assistance.
Presented at the European Association for the Study of Diabetes, 55th Annual Meeting.
September 16–20, 2019, Barcelona, Spain.

References: (**1**) Pi-Sunyer. *Diabetes Care* 2005;28:1526–7; (**2**) Kenkre *et al. Expert Rev Clin Pharmacol* 2013;6:171–83; (**3**) Novo Nordisk. Saxenda® EU SmPC. https://www.ema.europa.eu/; (**4**) Davies *et al. JAMA* 2015;314:687–99; (**5**) Dicker *et al.* Poster 575. Presented at EASD 2019; (**6**) American Diabetes Association. *Diabetes Care* 2019;42:561–70.

Abstract

Poster presentation 756

Liraglutide and semaglutide improve cardiovascular and renal outcomes across baseline BP categories: analysis of LEADER and SUSTAIN 6

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- on behalf of the LEADER and SUSTAIN 6 investigators

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Background

- High blood pressure (BP) is prevalent in patients with type 2 diabetes (T2D) and is a risk factor for cardiovascular (CV) disease and microvascular complications.[1]
- In the LEADER[2] and SUSTAIN 6[3] CV outcomes trials, major adverse CV events (MACE) and renal events were evaluated in patients with T2D and high CV risk who received liraglutide or semaglutide versus placebo.
  - » Overall, in LEADER, there were 608 (13.0%) events of primary MACE with liraglutide and 694 (14.9%) events with placebo (hazard ratio [HR] 0.87; 95% confidence interval [CI] 0.78–0.97; p<0.001 for noninferiority; p=0.01 for superiority).[2] There were also 268 (5.7%) and 337 (7.2%) events of new or worsening nephropathy with liraglutide and placebo, respectively (HR 0.78; 95% CI 0.67–0.92; p=0.003).[2]
  - » In SUSTAIN 6 overall, there were 108 (6.6%) events of primary MACE with semaglutide and 146 (8.9%) events with placebo (HR 0.74; 95% CI 0.58–0.95; p<0.001 for noninferiority).[3] Additionally, there were 62 (3.8%) and 100 (6.1%) events of new or worsening nephropathy with semaglutide and placebo, respectively (HR 0.64; 95% CI 0.46–0.88; p=0.005).[3]
- Whether these cardiorenal benefits of liraglutide and semaglutide are consistent across patients within different BP categories is unknown.
- *Post hoc* analyses were performed on LEADER and SUSTAIN 6 data to evaluate cardiorenal efficacy by BP categories in patients with T2D and high CV risk.

Methods

- LEADER[2] and SUSTAIN 6[3] were global, double-blind, placebo-controlled, randomised CV outcomes trials of liraglutide and semaglutide, in 9340 and 3297 patients, respectively, with T2D and high CV risk.
- The primary composite outcome in both trials was the first occurrence of MACE (CV death, non-fatal myocardial infarction or non-fatal stroke).[2,3]
- The secondary outcomes included a composite renal outcome of new-onset persistent macroalbuminuria, persistent doubling of serum creatinine level, the need for continuous renal-replacement therapy or death from renal disease.[2,3]
- The effects of liraglutide and semaglutide on the primary CV and secondary renal outcomes were evaluated by baseline BP category.
  - » BP was categorised as normal (<120/80 mmHg), elevated (systolic 120–129 mmHg and diastolic <80 mmHg), stage 1 hypertension (systolic 130–139 mmHg or diastolic 80–89 mmHg), and stage 2 hypertension (systolic ≥140 mmHg or diastolic ≥90 mmHg) as per American College of Cardiology/American Heart Association clinical practice guidelines.[4]
- A Cox proportional hazards model, with treatment and BP category as factors and the interaction between BP category and treatment, was used to calculate the treatment HR and 95% CI, adjusted for baseline characteristics related to cardiorenal risk.
- Quadratic spline regression applied in a Cox regression was used to calculate the treatment HR in time to first MACE by systolic and diastolic BP on a *continuous* scale.

Results

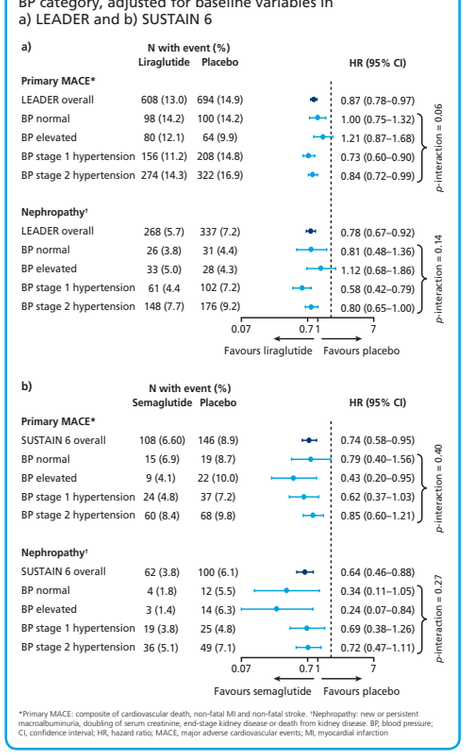
- In LEADER, 15%, 14%, 30% and 41% of patients had normal BP, elevated BP, stage 1 or stage 2 hypertension, respectively; proportions in SUSTAIN 6 were 13%, 13%, 31% and 43%, respectively (Table 1).
- The baseline characteristics were balanced across the treatment groups within each BP category.
- Liraglutide decreased the risk of both CV and renal endpoints across all four BP categories (Figure 1a). Semaglutide demonstrated a similar effect in SUSTAIN 6, even though the CIs were wider due to the small sample size (Figure 1b).
- No significant interactions (p<0.05) were found across risk groups for primary MACE or nephropathy with either treatment (Figure 1).
- Analysis of BP at baseline as a continuous variable revealed no indication of differential effect with either liraglutide or semaglutide, within the quartile boundaries, where 50% of the events occurred (Figure 2).A higher proportion of patients reported ≥1 treatment-emergent adverse event (AE) in the liraglutide group than the placebo group (66.3 vs 47.0%, respectively [Table 2]).
  - » Nausea was the most commonly reported AE (26.2% and 6.0% for liraglutide versus placebo, respectively) and was predominately early-onset and transient.
  - » The proportion of patients reporting hypoglycaemia was similar across liraglutide (8.9%) and placebo (8.0%) groups, and none of these episodes were severe (defined as requiring assistance from another person according to the American Diabetes Association criterion).[1]
  - » Serious AEs were reported by a low proportion of patients in both liraglutide (2.5%) and placebo (1.0%) groups and there were no fatalities, reports of acute renal failure, DKA, diabetic foot ulcers or amputations with liraglutide in combination with an SGLT2i.

Table 1: Proportion of patients at baseline in each blood pressure category

Blood pressure (mmHg)	LEADER, n (%) N=9340	SUSTAIN 6, n (%) N=3297
Normal (<120/80)	1397 (15)	436 (13)
Elevated (systolic 120–129 *and* diastolic <80)	1310 (14)	439 (13)
Stage 1 hypertension (systolic 130–139 *or* diastolic 80–89)	2806 (30)	1018 (31)
Stage 2 hypertension (systolic ≥140 *or* diastolic ≥90)	3827 (41)	1404 (43)

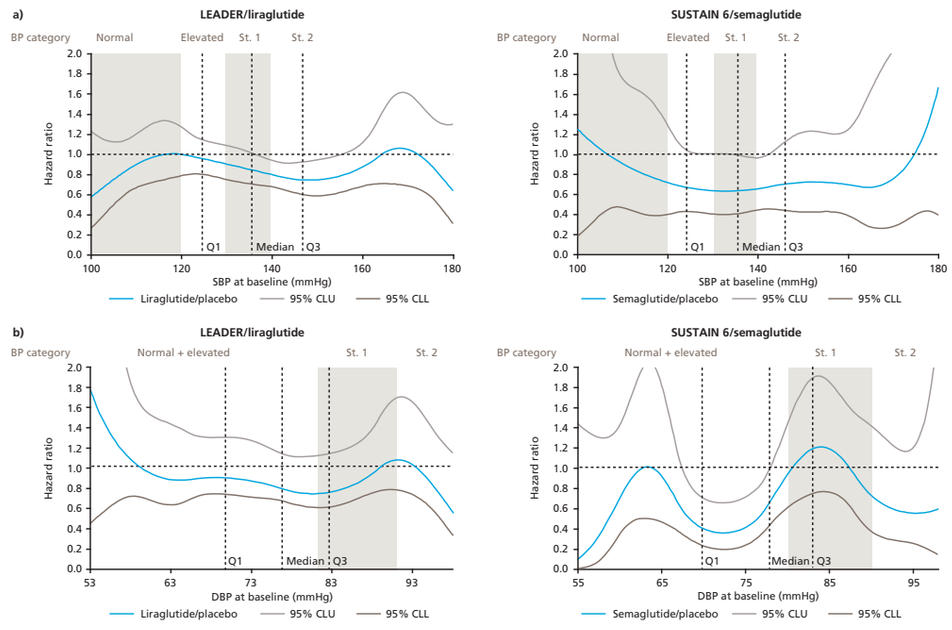
Figure 1: Cardiorenal outcomes by baseline BP category, adjusted for baseline variables in a) LEADER and b) SUSTAIN 6

Key result



*Primary MACE: composite of cardiovascular death, non-fatal MI and non-fatal stroke. †Nephropathy: new or persistent macroalbuminuria, doubling of serum creatinine, end-stage kidney disease or death from kidney disease. BP, blood pressure; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction

Figure 2: Treatment ratios (liraglutide or semaglutide vs placebo) in time to first MACE using quadratic spline regression according to a) SBP and b) DBP



Primary MACE: composite of cardiovascular death, non-fatal MI and non-fatal stroke. Q1, one quarter of patients with events had a lower BP value than this; median, half of patients with events had a lower BP value than this; Q3, three quarters of patients with events had a lower BP value than this. BP, blood pressure; CLL, confidence limit lower; CLU, confidence limit upper; DBP, diastolic blood pressure; MACE, major adverse cardiovascular events; MI, myocardial infarction; Q, quartile; SBP, systolic blood pressure; St., stage

Conclusions

- In LEADER and SUSTAIN 6, liraglutide and semaglutide demonstrated improvements in CV and renal outcomes irrespective of baseline BP categories.

The analysis was sponsored by Novo Nordisk. Both trials are registered with ClinicalTrials.gov (LEADER: NCT01179048; SUSTAIN 6: NCT01720446).
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Presented at the European Association for the Study of Diabetes, 55th Annual Meeting.
September 16–20, 2019, Barcelona, Spain.

References: (**1**) American Diabetes Association. *Diabetes Care* 2016;39 Suppl 1:S60–71; (**2**) Marso *et al. N Engl J Med* 2016;375:311–22; (**3**) Marso *et al. N Engl J Med* 2016;375:1834–44; (**4**) Whelton *et al. J Am Coll Cardiol* 2018;71:e127–248.

Abstract

Poster presentation 758

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Impact of microvascular disease on cardiorenal outcomes in type 2 diabetes: an analysis from the LEADER and SUSTAIN 6 clinical trials

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– on behalf of the LEADER and SUSTAIN 6 investigators

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Background

- Microvascular complications in type 2 diabetes (T2D) may increase the risk of cardiovascular (CV) complications,[1,2] but data from large-scale trials are lacking.
- Liraglutide and semaglutide are human glucagon-like peptide-1 analogues used for the treatment of patients with T2D.
- LEADER and SUSTAIN 6 were large-scale outcomes trials designed to assess the CV safety and efficacy of liraglutide and semaglutide, respectively.[3,4] Treatment with these GLP-1 analogues was shown to reduce the risk of CV events versus placebo in patients with T2D.[3,4]
- We present the results of *post hoc* analyses of LEADER and SUSTAIN 6 data evaluating cardiorenal risk, and the effects of liraglutide and semaglutide in patients with a history of microvascular disease.

Methods

Study design

- LEADER and SUSTAIN 6 were multinational, randomised, double-blind, CV outcomes trials of once-daily liraglutide (up to 1.8 mg) and once-weekly semaglutide (0.5–1.0 mg) respectively, versus placebo, in addition to standard of care therapy, in patients with T2D and at high risk of CV disease.[3,4] Median follow-up was 3.8 years in LEADER, and 2.1 years in SUSTAIN 6.[3,4]
- Both trials enrolled patients with glycated haemoglobin (HbA_{1c}) ≥7.0% who were aged ≥50 years with established CV disease/chronic renal failure, or aged ≥60 years with risk factors for CV disease.
- The primary outcome in LEADER and SUSTAIN 6 was time to first major cardiovascular event (MACE), a composite of CV death, non-fatal myocardial infarction (MI) or non-fatal stroke.
- Secondary endpoints included:
  - » Expanded MACE (MACE + coronary revascularisation, or hospitalisation for unstable angina pectoris or heart failure).
  - » A nephropathy composite endpoint (new onset of macroalbuminuria or doubling of serum creatinine level and an estimated glomerular filtration rate [eGFR] ≤45 mL/min/1.73 m^2, or the need for continuous renal-replacement therapy or death from renal disease).
- These endpoints were assessed by an independent event adjudication committee.

Statistical analysis

- We analysed time to first MACE, expanded MACE and the nephropathy composite endpoint according to history of microvascular disease at baseline, and concomitant microvascular and macrovascular disease at baseline.
- Microvascular disease at baseline was defined as an investigator-reported history of nephropathy (microalbuminuria, macroalbuminuria or overt proteinuria with normal serum creatinine/creatinine clearance; or chronic renal failure [elevated serum creatinine or reduced creatinine clearance]), retinopathy, or peripheral neuropathy.
- Macrovascular disease at baseline was defined as a history of MI, ≥50% coronary artery stenosis, percutaneous coronary intervention (PCI) or coronary artery bypass grafting, angina pectoris, asymptomatic cardiac ischaemia, stroke, transient ischaemic attack, or ≥50% intracranial, carotid or peripheral artery stenosis.
- Risk of CV events (hazard ratio [HR] and 95% confidence interval [CI]) by microvascular disease at baseline was calculated using a Cox proportional hazards model with risk group as a factor, adjusted for treatment.
- Treatment effects of liraglutide and semaglutide versus placebo, respectively, within risk groups were estimated using a Cox proportional hazards model with treatment, risk group, and the interaction of both as factors, adjusted for important CV risk factors.
  - » Furthermore, for SUSTAIN 6 the model was stratified for factors used for randomisation (CV disease status, insulin treatment and eGFR at screening).[3]

Results

- A history of microvascular disease at baseline was reported in 62% (5761/9340) patients in LEADER and 71% (2356/3297) patients in SUSTAIN 6 (Figure 1).
- Patients with microvascular disease at baseline were older, with a longer duration of diabetes, had more frequent insulin use, higher systolic blood pressure and a lower eGFR than those without (Table 1).
- Patients with ≥1 microvascular disease at baseline had a higher risk of MACE (HR [95% CI] in LEADER: 1.15 [1.03;1.29]; SUSTAIN 6: 1.56 [1.14;2.17]) and there was a stepwise increase in risk with increasing number of microvascular diseases (Figure 2).
  - » A similar effect was seen for expanded MACE and nephropathy.
- Compared with placebo, liraglutide and semaglutide reduced the risk of:
  - » MACE and expanded MACE in patients with and without microvascular disease (Figure 3).
  - » Nephropathy in patients with microvascular disease (Figure 3).
- A history of both microvascular and macrovascular disease at baseline was reported in 41% (3835/9340) patients in LEADER and 50% (1640/3297) patients in SUSTAIN 6.
- The risk of MACE was higher in patients with both microvascular and macrovascular disease, irrespective of treatment, compared with macrovascular disease alone: placebo event rates (per 100 patient-years observation) were 5.0 vs 3.8 in LEADER and 5.4 vs 4.1 in SUSTAIN 6.

Figure 1: Microvascular disease at baseline in LEADER and SUSTAIN 6

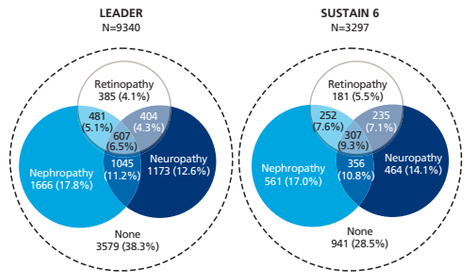
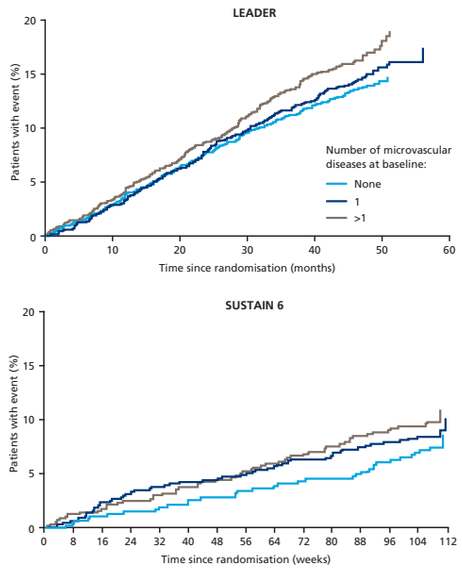


Table 1: Baseline characteristics by history of microvascular disease in LEADER and SUSTAIN 6

Characteristic	LEADER		SUSTAIN 6	
	≥1 microvascular disease (N=5761)	No microvascular disease (N=3579)	≥1 microvascular disease (N=2356)	No microvascular disease (N=941)
Age, years	64.9 ± 7.2	63.2 ± 7.2	65.1 ± 7.4	63.5 ± 7.2
Female	37%	35%	41%	35%
HbA_{1c}, %	8.8 ± 1.6	8.6 ± 1.5	8.7 ± 1.5	8.6 ± 1.4
Duration of T2D, years	14.0 ± 8.1	10.9 ± 7.4	14.9 ± 8.2	11.4 ± 7.2
Insulin use	50%	35%	52%	33%
BMI, kg/m^2	32.6 ± 6.3	32.4 ± 6.2	33.0 ± 6.3	32.3 ± 5.8
SBP, mmHg	136.6 ± 18.2	134.7 ± 16.9	136.4 ± 17.7	133.8 ± 15.6
DBP, mmHg	76.7 ± 10.4	77.7 ± 9.9	77.0 ± 10.2	77.2 ± 9.6
eGFR, mL/min/1.73m^2	76.1 ± 28.0	87.2 ± 24.8	72.2 ± 27.2	86.1 ± 22.0

Data are mean ± standard deviation, or proportion of patients (%). Microvascular disease at baseline: diabetic retinopathy, diabetic neuropathy or diabetic nephropathy. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; SBP, systolic blood pressure; T2D, type 2 diabetes

Figure 2: MACE by history of microvascular disease in LEADER and SUSTAIN 6

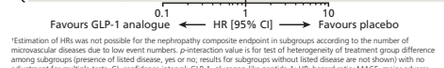


Cumulative incidences were estimated using the Kaplan–Meier method. Microvascular disease at baseline: diabetic retinopathy, diabetic neuropathy or diabetic nephropathy. MACE, major adverse cardiovascular events

Figure 3: Cardiorenal events with liraglutide and semaglutide, versus placebo, by history of microvascular disease

Key result

	Endpoint	History of microvascular disease	HR [95% CI]	*p*-interaction
LEADER	MACE	Total population	0.87 [0.78; 0.97]	–
		Retinopathy	0.86 [0.68; 1.08]	0.95
		Neuropathy	0.93 [0.78; 1.11]	0.33
		Nephropathy	0.82 [0.69; 0.97]	0.42
		None	0.87 [0.72; 1.04]	
		1 microvascular	0.85 [0.70; 1.02]	0.95
		>1 microvascular	0.88 [0.73; 1.08]	
	Expanded MACE	Total population	0.88 [0.81; 0.96]	–
		Retinopathy	0.85 [0.71; 1.03]	0.80
		Neuropathy	0.93 [0.81; 1.08]	0.25
		Nephropathy	0.84 [0.73; 0.96]	0.43
		None	0.84 [0.73; 0.97]	
		1 microvascular	0.91 [0.78; 1.06]	0.76
		>1 microvascular	0.88 [0.75; 1.03]	
	Nephropathy composite	Total population	0.78 [0.67; 0.92]	–
		Retinopathy	0.74 [0.55; 1.00]	0.83
		Neuropathy	0.73 [0.57; 0.92]	0.58
		Nephropathy	0.76 [0.63; 0.92]	0.93
		None	0.94 [0.64; 1.37]	
		1 microvascular	0.68 [0.51; 0.90]	0.41
		>1 microvascular	0.75 [0.60; 0.95]	
SUSTAIN 6	MACE	Total population	0.74 [0.58; 0.95]	–
		Retinopathy	0.51 [0.33; 0.78]	0.05
		Neuropathy	0.98 [0.69; 1.41]	0.02
		Nephropathy	0.91 [0.64; 1.29]	0.07
		None	0.41 [0.22; 0.74]	
		1 microvascular	0.90 [0.60; 1.33]	0.09
		>1 microvascular	0.78 [0.53; 1.15]	
	Expanded MACE	Total population	0.74 [0.62; 0.89]	–
		Retinopathy	0.60 [0.43; 0.84]	0.15
		Neuropathy	0.89 [0.67; 1.16]	0.08
		Nephropathy	0.88 [0.67; 1.15]	0.08
		None	0.56 [0.38; 0.82]	
		1 microvascular	0.87 [0.65; 1.17]	0.20
		>1 microvascular	0.76 [0.56; 1.03]	
	Nephropathy composite†	Total population	0.64 [0.46; 0.88]	–
		Retinopathy	0.51 [0.30; 0.87]	0.42
		Neuropathy	0.48 [0.29; 0.78]	0.19
		Nephropathy	0.58 [0.40; 0.84]	0.57



†Estimation of HRs was not possible for the nephropathy composite endpoint in subgroups according to the number of microvascular diseases due to low event numbers. *p*-interaction value is for test of heterogeneity of treatment group difference among subgroups (presence of listed disease, yes or no; results for subgroups without listed disease are not shown) with no adjustment for multiple tests. CI, confidence interval; GLP-1, glucagon-like peptide-1; HR, hazard ratio; MACE, major adverse cardiovascular events

Conclusions

- In this *post hoc* analysis of data from LEADER and SUSTAIN 6, patients with a history of microvascular disease were:
  - » Older, with a longer duration of T2D and lower eGFR, and used insulin more frequently.
  - » At higher risk of cardiorenal events.
- The risk of CV events, irrespective of treatment, was higher in patients with microvascular and macrovascular disease versus macrovascular disease alone.
- Liraglutide and semaglutide reduced the risk of cardiorenal events versus placebo, irrespective of microvascular disease at baseline.

The analysis was sponsored by Novo Nordisk. Both trials are registered with ClinicalTrials.gov (LEADER: NCT01179048; SUSTAIN 6: NCT01720446).
Presenter Bernard Zinman reports consulting fees from Merck, Novo Nordisk, Sanofi-Aventis, Eli Lilly, AstraZeneca, Janssen, and Boehringer Ingelheim.
The authors are grateful to Watermeadow Medical, an Ashfield Company (supported by Novo Nordisk), for writing assistance.
Presented at the European Association for the Study of Diabetes, 55th Annual Meeting.
September 16–20, 2019, Barcelona, Spain.

References: (**1**) Beckman *et al. Circ Res* 2016;118:1771–85; (**2**) Brownrigg *et al. Lancet Diabetes Endocrinol* 2016;4:588–97; (**3**) Marso *et al. N Engl J Med* 2016;375:1834–44; (**4**) Marso *et al. N Engl J Med* 2016;375:311–22.

Abstract

Poster presentation 998

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Estimated GFR (eGFR) loss with glucagon-like peptide-1 (GLP-1) analogue treatment: data from SUSTAIN 6 and LEADER

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- on behalf of the LEADER and SUSTAIN 6 investigators

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Introduction and aims

- Type 2 diabetes (T2D) is associated with long-term complications, including chronic kidney disease (CKD) and cardiovascular disease (CVD).[1]
- CKD occurs in approximately 40% of adults with T2D,[2] and represents a significant burden for patients and healthcare providers.[2] Currently, blockade of the renin-angiotensin-aldosterone system is the only approved therapy to reduce CKD progression,[3] and a great unmet need for more effective treatment remains.
- A decline in estimated glomerular filtration rate (eGFR) has been shown to predict the risk of kidney failure, cardiovascular (CV) events and mortality.[4,5]
- Treatment with glucagon-like peptide-1 (GLP-1) analogues has proven to be an effective approach to improving glycaemic levels in patients with T2D. Additionally, data have suggested that GLP-1 analogues may delay CKD progression.[6-10]
- In the SUSTAIN 6[7] and LEADER[8] trials, renal events were evaluated as part of a pre-specified secondary renal outcome in patients with T2D and high CV risk who received the GLP-1 analogues semaglutide or liraglutide versus placebo, both in addition to standard of care.
- This *post hoc* analysis of SUSTAIN 6 and LEADER trial data investigated the effects of semaglutide and liraglutide on the rate of loss of kidney function, evaluated as total eGFR slope.

Methods

Study design

- SUSTAIN 6 and LEADER were global, double-blind, randomised, placebo-controlled cardiovascular outcomes trials that assessed CV, renal and safety outcomes with semaglutide (0.5 mg or 1.0 mg) and liraglutide (up to 1.8 mg) versus placebo when added to standard of care in 3297 and 9340 patients, respectively. Median follow-up was 2.1 and 3.8 years in SUSTAIN 6 and LEADER, respectively.
- Major inclusion criteria were:
  - T2D with glycated haemoglobin (HbA_{1c}) ≥7.0%;
  - Age ≥50 years with at least one coexisting CV condition, one of which being eGFR <60 mL/min/1.73 m^2;
  - Alternatively, age ≥60 years with at least one CV risk factor.
- Major exclusion criteria were:
  - Type 1 diabetes;
  - Use of GLP-1 analogues, dipeptidyl peptidase-4 inhibitors, pramlintide or rapid-acting insulin;
  - A familial or personal history of multiple endocrine neoplasia type 2 or medullary thyroid cancer;
  - The occurrence of an acute coronary or cerebrovascular event within 14 days before screening.
- The primary composite outcome in both trials was the occurrence of first major adverse CV events. Secondary outcomes included a composite renal outcome of new-onset persistent macroalbuminuria, persistent doubling of serum creatinine level and the need for continuous renal-replacement therapy or death from renal disease.
- In the current analysis, the annual eGFR change was evaluated by overall population and baseline eGFR subgroup (<60 vs ≥60 mL/min/1.73 m^2) for semaglutide (0.5 mg and 1.0 mg) and liraglutide, compared with placebo.

Statistical analysis

- Annual change in eGFR and estimated treatment differences in the rate of eGFR change over time (total eGFR slope) were analysed using in-trial data from baseline to end-of-treatment for SUSTAIN 6 and LEADER, respectively, by overall population and by baseline eGFR subgroup (<60 vs ≥60 mL/min/1.73 m^2) using a linear random regression model with random intercept and time slope.
- A *p*-value of <0.05 was considered significant.
- To further illustrate the eGFR decline over time, the eGFR by visit was estimated using a mixed model for repeated measures (MMRM) analysis for the overall population and by subgroup.

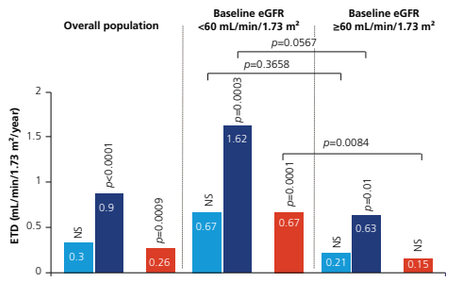
Table 1: Patients' baseline characteristics

	SUSTAIN 6 (N = 3297*)			LEADER (N = 9340*)	
	Semaglutide 0.5 mg (n=825)	Semaglutide 1.0 mg (n=821)	Placebo (n=1648)	Liraglutide 1.8 mg (n=4512)	Placebo (n=4498)
Age, years	64.6 ± 7.3	64.6 ± 7.1	64.6 ± 7.5	64.1 ± 7.2	64.4 ± 7.2
Sex, male, N (%)	494 (59.9)	517 (63.0)	988 (60.0)	2915 (64.6)	2884 (64.1)
Body weight, kg	91.8 ± 20.3	92.9 ± 21.1	91.9 ± 20.6	91.9 ± 21.2	91.5 ± 20.5
Diabetes duration, years	14.3 ± 8.2	14.1 ± 8.2	13.6 ± 8.0	12.7 ± 7.9	12.8 ± 8.0
Glycated haemoglobin (HbA_{1c}), %	8.7 ± 1.4	8.7 ± 1.5	8.7 ± 1.5	8.7 ± 1.6	8.6 ± 1.5
Systolic blood pressure, mmHg	136.1 ± 17.9	135.9 ± 16.9	135.3 ± 16.8	135.9 ± 17.7	136.0 ± 17.7
Diastolic blood pressure, mmHg	77.1 ± 9.8	76.9 ± 10.2	77.1 ± 10.0	77.3 ± 10.3	77.0 ± 10.1
RAAS inhibitor use, N (%)	673 (81.6)	665 (81.0)	1327 (80.5)	3633 (80.5)	3598 (80.0)
Renal function, N (%)					
eGFR[†] ≥60	613 (74.3)	617 (75.2)	1221 (74.1)	3544 (78.5)	3593 (79.9)
eGFR[†] <60	212 (25.7)	204 (24.8)	427 (25.9)	968 (21.5)	905 (20.1)
Albuminuria status					
Normoalbuminuria	472 (58.3)	476 (59.0)	986 (60.8)	2820 (63.6)	2737 (62.3)
Microalbuminuria	235 (29.0)	237 (29.4)	412 (30.9)	1168 (26.4)	1185 (27.0)
Macroalbuminuria	102 (12.6)	94 (11.6)	224 (16.8)	443 (10.0)	474 (10.8)

*These values represent the total number of patients recruited into SUSTAIN 6 and LEADER, respectively; only patients with eGFR at baseline and at least one post-baseline eGFR measurement have been included in this analysis. Normoalbuminuria defined as UACR <30 mg/g; microalbuminuria defined as UACR ≥30 to 300 mg/g; macroalbuminuria defined as UACR >300 mg/g. Full analysis set. Data are means ± standard deviation unless otherwise indicated. Renal function is calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. †mL/min/1.73 m^2. eGFR, estimated glomerular filtration rate; N, number of patients; RAAS, renin-angiotensin-aldosterone system; UACR, urinary albumin-to-creatinine ratio

Key results

Figure 1: Annual change in eGFR and ETD in SUSTAIN 6 and LEADER



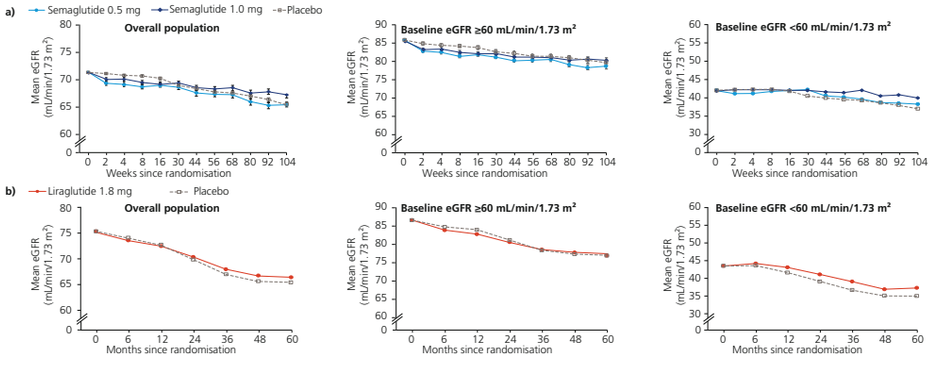
Annual eGFR change (mL/min/1.73 m²)/year	Estimate [95% CI]; *p*-value				
	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	Liraglutide 1.8 mg	Placebo
Overall population	N=825 −1.59 [−1.95; −1.23]	N=821 −1.05 [−1.41; −0.69]	N=1648 −1.92 [−2.18; −1.67]	N=4512 −1.72 [−1.84; −1.61]	N=4498 −1.98 [−2.10; −1.87]
<60 mL/min/1.73 m²	N=212 −1.20 [−1.90; −0.49]	N=204 −0.25 [−0.97; 0.48]	N=427 −1.87 [−2.37; −1.36]	N=968 −1.44 [−1.68; −1.19]	N=905 −2.11 [−2.37; −1.85]
≥60 mL/min/1.73 m²	N=613 −1.73 [−2.15; −1.32]	N=617 −1.31 [−1.72; −0.90]	N=1221 −1.94 [−2.24; −1.64]	N=3544 −1.80 [−1.92; −1.67]	N=3593 −1.95 [−2.08; −1.83]

SUSTAIN 6
Semaglutide 0.5 mg vs placebo
Semaglutide 1.0 mg vs placebo

LEADER
Liraglutide 1.8 mg vs placebo

p-values above bracketed lines are *p*-values for treatment by subgroup interaction; *p*-values directly above bars in graph are *p*-values for the ETD. A positive ETD value indicates less reduction in eGFR with semaglutide or liraglutide versus placebo. eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; N, number of patients; NS, non-significant

Figure 2: eGFR by visit by treatment group in the overall population, and subgroups by eGFR at baseline, in a) SUSTAIN 6 and b) LEADER



Estimates are from an MMRM with treatment / treatment by subgroup interaction and baseline value as fixed effects, embedded within visit. Analysis is done on log-transformed eGFR values and backtransformed to original scale. eGFR, estimated glomerular filtration rate

Results

- Patient demographic and clinical characteristics at baseline were comparable across treatment groups (Table 1).
- Of the 3297 patients in SUSTAIN 6, 3294 with baseline and post-baseline eGFR measurements are included in this analysis:
  - 2451 (74.4%) patients had a preserved eGFR of ≥60 mL/min/1.73 m^2 and 1934 (59.7%) had normoalbuminuria (UACR <30 mg/g).
- Of the 9340 patients in LEADER, 9010 with baseline and post-baseline eGFR measurements are included in this analysis:
  - 7137 (79.2%) patients had a preserved eGFR of ≥60 mL/min/1.73 m^2 and 5557 (63.0%) had normoalbuminuria (UACR <30 mg/g).
- Mean duration of T2D was 13.9 years and 12.8 years in SUSTAIN 6 and LEADER, respectively. The mean HbA_{1c} was 8.7% in both trials.
- In the SUSTAIN 6 overall population, a significantly slower rate of annual eGFR decline was observed with semaglutide 1.0 mg versus placebo (*p*<0.0001); a lower rate was also observed with 0.5 mg versus placebo, but this was not significant (*p*=0.1382) (Figure 1).
- In the SUSTAIN 6 subgroup analysis by baseline eGFR <60 or ≥60 mL/min/1.73 m^2 (Figure 1):
  - Semaglutide 1.0 mg significantly slowed the rate of annual eGFR decline compared with placebo, with a trend towards a larger treatment difference in those with eGFR <60 mL/min/1.73 m^2 (*p*-value for interaction=0.0567);
  - A similar effect was not seen with semaglutide 0.5 mg and there was no effect of subgroup on the treatment difference (*p*-value for interaction=0.3658).
- In the overall LEADER population, the annual rate of decline in eGFR was significantly slower for liraglutide than for placebo (*p*=0.0009) (Figure 1).
  - In the subgroup analysis, the effect was more marked in patients with baseline eGFR <60 mL/min/1.73 m^2 than for the ≥60 mL/min/1.73 m^2 subgroup (*p*-value for interaction=0.0084).
- eGFR by treatment group in the overall population and subgroups by eGFR at baseline are shown in Figure 2.

Conclusions

- The annual rate of decline in renal function among patients with T2D (and at high CV risk) was slower over the trial duration in patients treated with semaglutide 1.0 mg or liraglutide when compared with placebo.
- The benefit of semaglutide and liraglutide treatment appears to be more pronounced in patients with reduced kidney function (eGFR <60 mL/min/1.73 m^2).
- Total eGFR slope has been shown to correlate with hard renal outcomes, and the effects observed in the current analysis are potentially clinically important, suggesting a renal benefit with semaglutide and liraglutide.

The analysis was sponsored by Novo Nordisk. Both trials are registered with ClinicalTrials.gov (LEADER: NCT01179048; SUSTAIN 6: NCT01720446).
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Presented at the European Association for the Study of Diabetes, 55th Annual Meeting.
September 16–20, 2019, Barcelona, Spain.

References: (**1**) Wu *et al. BMJ Open Diabetes Res Care* 2016;4:e000154; (**2**) Yee. *Diabetes Spectr* 2008;21:8–10; (**3**) Inket *et al. Am J Kidney Dis* 2014;201;63:713–5; (**4**) Coresh *et al. JAMA* 2014;311:2518–31; (**5**) Heerspink *et al. Lancet Diabetes Endocrinol* 2019;7:128–39; (**6**) Zelniker *et al. Circulation* 2019;139:2022–31; (**7**) Marso *et al. N Engl J Med* 2016;375:1834–44; (**8**) Marso *et al. N Engl J Med* 2016;375:311–22; (**9**) Vilsbøll *et al. Diabetes* 2018;67(Suppl 1):1084–P; (**10**) Mann *et al. N Eng J Med* 2017; 377:839–48.

Abstract

Poster presentation 1164

1164

Liraglutide and semaglutide improve cardiovascular and renal outcomes across most BMI categories in type 2 diabetes: results of the LEADER and SUSTAIN 6 trials

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- on behalf of the LEADER and SUSTAIN 6 investigators
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Background

- In the LEADER[1] and SUSTAIN 6[2] cardiovascular (CV) outcomes trials, major adverse CV events (MACE) and renal events were evaluated in patients with type 2 diabetes (T2D) and at high CV risk who were randomised to receive liraglutide or semaglutide versus placebo.
  - Both liraglutide (in LEADER) and semaglutide (in SUSTAIN 6) resulted in fewer MACE compared with placebo. For liraglutide versus placebo, the hazard ratio (HR) was 0.87 (95% confidence interval [CI] 0.78–0.97), which demonstrated superiority (p=0.01).[1] A statistically significant reduction in MACE with semaglutide was shown *post hoc* (HR 0.74; 95% CI 0.58–0.95; p=0.02).[2]
  - Similar results were obtained in both trials for new or worsening nephropathy events (LEADER: HR 0.78; 95% CI 0.67–0.92; p=0.003,[1] SUSTAIN 6: HR 0.64; 95% CI 0.46–0.88; p=0.005).[2]
- Whether these cardiorenal benefits of liraglutide and semaglutide are consistent across patients within different body mass index (BMI) categories is unknown.
- We performed *post hoc* analyses on LEADER and SUSTAIN 6 data to evaluate cardiorenal efficacy by BMI categories in patients with T2D and high CV risk.

Methods

- LEADER[1] and SUSTAIN 6[2] were global, randomised, double-blind, placebo-controlled, CV outcomes trials of liraglutide and semaglutide, in 9340 and 3297 patients, respectively, with T2D and high CV risk.[1,2]
- In both trials, the first occurrence of MACE (CV death, non-fatal myocardial infarction or non-fatal stroke) was the primary composite outcome.[1,2]
- Secondary outcomes included a composite renal outcome of new-onset persistent macroalbuminuria, persistent doubling of serum creatinine level, the need for continuous renal-replacement therapy or death from renal disease.[1,2]
- The effects of liraglutide and semaglutide on time to first primary CV and secondary renal outcomes were evaluated by baseline BMI category.
  - BMI was categorised as <25 kg/m², ≥25 to <30 kg/m², ≥30 to <35 kg/m² and ≥35 kg/m².
- The HR and 95% CI for treatment versus placebo were calculated using Cox regression with treatment and BMI category as fixed factors and the interaction between both, adjusted for baseline characteristics related to cardiorenal risk.
- Quadratic spline regression applied in a Cox regression was used to analyse the treatment differences in time to first MACE by continuous BMI.
- No adjustments for multiple testing were performed.

Results

- In LEADER, 9%, 29%, 32% and 30% of patients had a baseline BMI of <25 kg/m², ≥25 to <30 kg/m², ≥30 to <35 kg/m² and ≥35 kg/m², respectively; proportions for SUSTAIN 6 were 8%, 28%, 33% and 31% (Table 1).
- The baseline characteristics were mostly balanced across the trial groups within each BMI category (Table 1).

Table 1: Proportion of patients at baseline in each BMI category

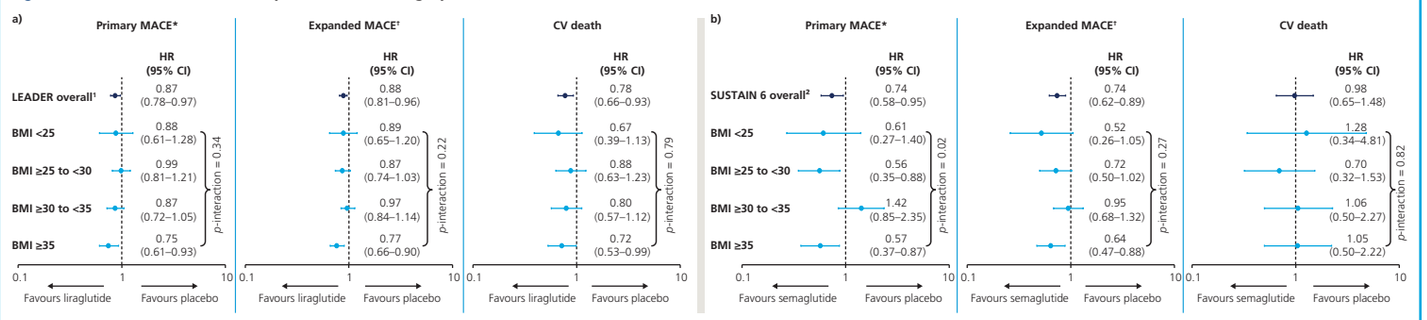
	LEADER, n (%) N=9340				SUSTAIN 6, n (%) N=3297			
BMI (kg/m²)	**<25**	**≥25 to <30**	**≥30 to <35**	**≥35**	**<25**	**≥25 to <30**	**≥30 to <35**	**≥35**
n (%)	832 (9)	2684 (29)	2993 (32)	2822 (30)	254 (8)	926 (28)	1080 (33)	1030 (31)
Age, years	64.7 ± 7.8	65.4 ± 7.4	64.4 ± 7.2	63.0 ± 6.7	65.6 ± 7.7	65.6 ± 7.6	64.6 ± 7.2	63.7 ± 7.1
Male, n (%)	578 (69.5)	1868 (69.6)	1995 (66.7)	1559 (55.2)	159 (62.6)	637 (68.8)	670 (62.0)	529 (51.4)
HbA_{1c}, %	9.0 ± 1.8	8.6 ± 1.5	8.6 ± 1.5	8.7 ± 1.5	9.0 ± 1.7	8.7 ± 1.5	8.6 ± 1.4	8.7 ± 1.5
Duration of diabetes, years	14.2 ± 8.9	13.5 ± 8.2	12.5 ± 7.8	12.1 ± 7.7	15.6 ± 8.1	15.1 ± 8.5	13.3 ± 8.1	13.1 ± 7.7
Insulin use at baseline, n (%)	304 (36.5)	1161 (43.3)	1348 (45.0)	1351 (47.9)	139 (54.7)	520 (56.2)	615 (56.9)	636 (61.7)
Established CV disease, n (%)	673 (80.9)	2154 (80.3)	2459 (82.2)	2304 (81.6)	200 (78.7)	748 (80.0)	915 (84.7)	866 (84.1)
eGFR, mL/min/1.73 m²	82.1 ± 29.4	80.2 ± 27.1	80.1 ± 26.6	80.3 ± 27.8	77.5 ± 29.9	77.0 ± 27.3	76.5 ± 25.4	74.6 ± 26.2

CV, cardiovascular; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin

- In LEADER, the mean diabetes duration was longest in the <25 kg/m² BMI category (14.2 years) and slightly shorter (12.1–13.5 years) in the other three BMI categories. A similar trend was seen in SUSTAIN 6, with the mean diabetes duration being 15.6 years, 15.1 years, 13.3 years and 13.1 years in the <25 kg/m², ≥25–<30 kg/m², ≥30–<35 kg/m² and ≥35 kg/m² BMI categories, respectively.
- There were 608 (13.0%) events of primary MACE with liraglutide and 694 (14.9%) events with placebo in LEADER.[1] Due to the smaller trial size, these numbers were lower in SUSTAIN 6, with 108 (6.6%) events of primary MACE with semaglutide and 146 (8.9%) events with placebo.[2]

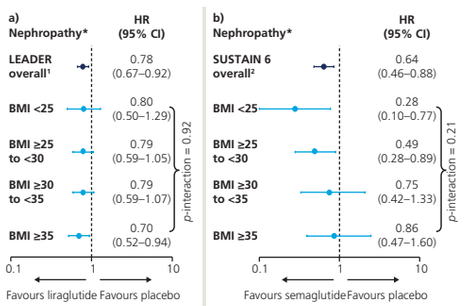
Figure 1: Cardiovascular outcomes by baseline BMI category in a) LEADER and b) SUSTAIN 6

Key result



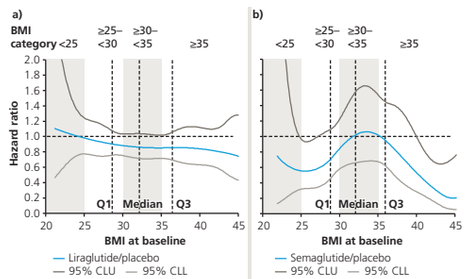
*Primary MACE: composite of CV death, non-fatal MI and non-fatal stroke. †Expanded MACE: components of primary MACE plus coronary revascularisation or hospitalisation for unstable angina pectoris or heart failure. BMI, body mass index (kg/m²); CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction

Figure 2: Renal outcomes by baseline BMI category in a) LEADER and b) SUSTAIN 6



*New or worsening nephropathy: new or persistent macroalbuminuria, doubling of serum creatinine, end-stage kidney disease or death from kidney disease. BMI, body mass index (kg/m²); CI, confidence interval; HR, hazard ratio

Figure 3: Treatment difference in time to first MACE across continuous BMI using spline regression in a) LEADER and b) SUSTAIN 6



Primary MACE: composite of CV death, non-fatal MI and non-fatal stroke. Q1, one quarter of patients with events had a lower BMI value; median, half of patients with events had a lower BMI value; Q3, three quarters of patients with events had a lower BMI value. BMI, body mass index (kg/m²); CLL, confidence limit lower; CLU, confidence limit upper; CV, cardiovascular; MACE, major adverse cardiovascular events; MI, myocardial infarction; Q, quartiles for patients with an event

- Overall, liraglutide reduced the risk of CV and renal endpoints across BMI categories (Figures 1 and 2). The analysis of SUSTAIN 6 data demonstrated a similar effect with semaglutide, even though the CIs were wider due to the small sample size.
- In addition to the improvements in MACE and new or worsening nephropathy outcomes, more weight loss was observed with liraglutide at year 3 (<25 kg/m²: −0.85 kg; ≥25–<30 kg/m²: −1.93 kg; ≥30–<35 kg/m²: −2.06 kg; ≥35 kg/m²: −3.25 kg; p-interaction: <0.001) and semaglutide at week 104 (<25 kg/m²: −3.13 kg; ≥25–<30 kg/m²: −2.89 kg; ≥30–<35 kg/m²: −3.96 kg; ≥35 kg/m²: −3.99 kg; p-interaction: 0.14) versus placebo.
- When analysing BMI at baseline as a continuous linear variable, there was no indication of a differential effect with liraglutide or semaglutide, within the quartile boundaries, where 50% of the events occurred (Figure 3). Again, there was greater variability in the semaglutide than liraglutide HRs due to the small number of MACE analysed in SUSTAIN 6.

Conclusions

- The *post hoc* analyses from LEADER and SUSTAIN 6 show that the CV and renal benefits of liraglutide and semaglutide versus placebo are consistent across baseline BMI categories.
- These data reaffirm the cardioprotective role of liraglutide and semaglutide in patients with T2D, irrespective of baseline BMI.

The analysis was sponsored by Novo Nordisk. Both trials are registered with ClinicalTrials.gov (LEADER: NCT01179048; SUSTAIN 6: NCT01720446).
Presenter Lawrence A. Leiter reports consultant and/or speaker fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk A/S, Sanofi and Servier; and research grants or support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Novo Nordisk A/S and Sanofi.
The authors are grateful to Emre Yildirim, Novo Nordisk, for review of and input to the poster, and to Melanie Francis, MSc, of Watermeadow Medical (supported by Novo Nordisk), for writing assistance.
Presented at the European Association for the Study of Diabetes, 55th Annual Meeting.
September 16–20, 2019, Barcelona, Spain.

References: (**1**) Marso *et al. N Engl J Med* 2016;375:311–22; (**2**) Marso *et al. N Engl J Med* 2016;375:1834–44.

Abstract

Weight loss induced by semaglutide once weekly contributes to improved health-related quality of life and treatment satisfaction

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Aim

- Semaglutide (Novo Nordisk, Denmark) is a glucagon-like peptide-1 (GLP-1) analogue approved for the once-weekly subcutaneous treatment of type 2 diabetes (T2D),[1] and has shown reductions in HbA_{1c} and body weight across the SUSTAIN clinical trial programme.[2–7]
- Health-related quality of life (HRQoL) and treatment satisfaction were evaluated in the SUSTAIN 2–5 and 7 trials using the Short Form-36 Health Survey version 2® (SF-36v2®) and Diabetes Treatment Satisfaction Questionnaire status version (DTSQs), respectively.[3–7]
- Studies have suggested that weight loss in patients with T2D may be associated with an increase in HRQoL.[8,9]
- The aim of this *post hoc* analysis was to assess if weight loss was associated with improvements in patient-reported HRQoL and treatment satisfaction in SUSTAIN 2–5 and 7.

Methods

- Changes in HRQoL (SF-36v2®) and treatment satisfaction scores (DTSQs) were evaluated in subjects who achieved ≥5% and ≥10% weight loss ('responders') vs those who did not ('non-responders') at end of treatment (30, 40, or 56 weeks) in SUSTAIN 2–5 and 7.
- The weight-loss responders were chosen to represent meaningful changes at the individual level, as weight losses of ≥5% and ≥10% are known to be clinically meaningful.[10] Estimated responder differences are evaluated in this analysis.
- Data were pooled across the trials (N=2,808; comparator data not evaluated), and presented by dose (semaglutide 0.5 mg or 1.0 mg) and overall.

Patient-reported outcome (PRO) scales

- Norm-based scoring was used for the SF-36v2®, setting the general population mean to 50 for each domain; higher and increasing scores indicate better health.
  - » Scores from the Physical Component Summary (PCS), Mental Component Summary (MCS), and all subdomains were analysed.
- The standard DTSQs scales range from 0 to 6 on a 7-point Likert scale, where 6 indicates the highest treatment satisfaction and 0 the lowest, with the exception of questions on the perception of hyperglycaemia and hypoglycaemia, where 6 indicates the lowest treatment satisfaction and 0 the highest.
  - » The overall treatment satisfaction is the sum of all scores, excluding the perception of hyperglycaemia and hypoglycaemia.

Statistical analysis

- Body weight and PROs were analysed using 'on-treatment without rescue medication' data.
  - » Missing body weight (kg) data were imputed from a mixed model for repeated measurements with treatment, region and stratum as fixed factors, and baseline value as covariate, all nested within visit.
  - » PRO data were analysed using an analysis of covariance controlled for treatment strata, and baseline values of body weight, and PROs.
- Safety was assessed using 'on-treatment' data.

Results

Baseline characteristics and demographics

- Subject disposition and baseline characteristics for SUSTAIN 2–5 and 7 are shown in Table 1.

Table 1: Subject disposition and baseline characteristics and demographics in SUSTAIN 2–5 and 7

	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Semaglutide pooled (0.5 mg and 1.0 mg)
Subject disposition, n (%)			
Randomised	1,205	1,610	2,815
Exposed*	1,204 (99.9)	1,604 (99.6)	2,808 (99.8)
Trial completers*	1,128 (93.6)	1,510 (93.8)	2,638 (93.7)
Treatment completers†	1,041 (86.5)	1,339 (83.5)	2,380 (84.8)
Subjects who discontinued treatment prematurely‡	163 (13.5)	265 (16.5)	428 (15.2)
Baseline characteristics§			
Male, n (%)	647 (53.7)	845 (52.7)	1,492 (53.1)
Diabetes duration, years	7.9 (5.8)	8.6 (6.5)	8.3 (6.2)
HbA_{1c}, %	8.2 (0.9)	8.2 (0.9)	8.2 (0.9)
Body weight, kg	93.0 (21.8)	93.5 (21.9)	93.3 (21.8)
BMI, kg/m²	33.0 (6.5)	33.1 (6.7)	33.1 (6.6)

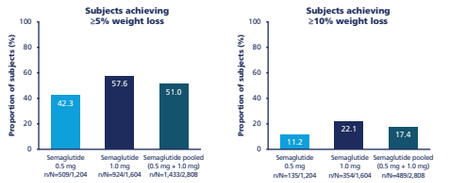
*Denominator for the percentage is the number of subjects randomised. †Denominator for the percentage is the full analysis set. §Baseline characteristics are calculated using full analysis set data; values are mean (SD) unless otherwise indicated. BMI, body mass index; n, number of subjects; SD, standard deviation.

- Overall, 82.7% of subjects receiving semaglutide completed all questions in the SF-36v2® questionnaire.
- Overall, 81.5% of subjects receiving semaglutide reported a treatment satisfaction score, and completed the perception of hyperglycaemia and perception of hypoglycaemia questions of the DTSQs.

Efficacy

- Overall, 51.0% and 17.4% of subjects achieved ≥5% and ≥10% weight loss with semaglutide, respectively (Figure 1).
- Significantly greater improvements in the overall PCS score and most of its components were reported in responders vs non-responders in the semaglutide 1.0 mg and pooled groups (Figure 2A).
- Overall treatment satisfaction was improved in responders vs non-responders in the semaglutide 1.0 mg and pooled groups (Figure 2B).
- Perception of hyperglycaemia, but not hypoglycaemia, improved in responders vs non-responders with both doses of semaglutide and in the pooled groups (Figure 2C).

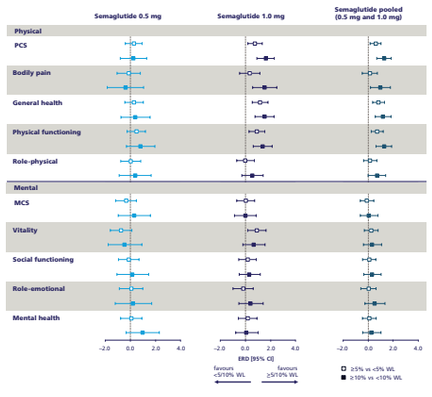
Figure 1: Proportions of subjects achieving weight-loss responses in SUSTAIN 2–5 and 7



Observed 'on-treatment without rescue medication' data with missing body weight (kg) values imputed from a mixed model for repeated measurements with treatment, region, and stratum as fixed factors and baseline value as covariate, all nested within visit. All imputed continuous data were dichotomised. N, number of subjects contributing to the analysis; n, number of subjects responding.

Figure 2: Estimated responder differences for HRQoL and treatment satisfaction in SUSTAIN 2–5 and 7

Key results



Observed 'on-treatment without rescue medication' and mixed model for repeated measurements imputed data were included. PROs at end of treatment were analysed by trial using an analysis of covariance with study-specific strata and responder as fixed factors, and baseline PROs and baseline body weight as covariates. Estimates are weighted means of individual trials with weight 1/SE^2. The individual DTSQs scales are not shown. CI, confidence interval; DTSQs, Diabetes Treatment Satisfaction Questionnaire status version; ERD, estimated responder difference; HRQoL, health-related quality of life; MCS, Mental Component Summary; PCS, Physical Component Summary; PRO, patient-reported outcome; SE, standard error; SF-36v2®, Short Form-36 Health Survey version 2®; WL, weight loss.

Safety

- Overall, across SUSTAIN 2–5 and 7, similar proportions of subjects experienced adverse events (AEs) in both the semaglutide 0.5 mg and 1.0 mg dose groups.
- AEs were experienced by 70.9% and 71.7% of semaglutide 0.5 mg and 1.0 mg dose groups, respectively; 71.4% in the pooled dose group.
- The most frequent AEs were gastrointestinal, and occurred in 44.5% of subjects in the pooled treatment groups. Nausea was the most frequently reported gastrointestinal AE, followed by vomiting and constipation (occurring in 19.9%, 8.9% and 13.5% of subjects in the pooled treatment groups, respectively).
- The incidence of severe or blood glucose-confirmed hypoglycaemia was low, and occurred in 3.9% of subjects in the pooled treatment groups.
- The incidence of serious AEs was low, with similar proportions of subjects reporting them in both dose groups (7.0% in the pooled dose group).

Discussion

- This analysis found that weight loss was associated with improvements in the PCS score of SF-36v2®, overall treatment satisfaction and perception of hyperglycaemia in subjects achieving weight-loss responses vs those not achieving these responses.
  - » This association appeared to be dose-dependent for the PCS score and overall treatment satisfaction. The changes observed in the pooled semaglutide group were driven by the semaglutide 1.0 mg data.
- In all semaglutide groups, there was a significant association between weight loss and the perception of hyperglycaemia. There was no difference in the perception of hypoglycaemia, potentially due to the low rate of hypoglycaemia observed in the SUSTAIN trials.
- The safety profile of semaglutide in the SUSTAIN 2–5 and 7 trials was consistent with that of other GLP-1 receptor agonists (GLP-1RAs).[11,12]
- GLP-1RAs may offer HRQoL and treatment satisfaction benefits, which are often associated with the drugs' effects on weight.[13]
- PROs are assessed by patients, and subjective interpretations may confound results; therefore, it can be difficult to infer how changes in HRQoL are influenced by AEs.
- The results of this analysis may be also confounded in part by the greater numbers of responders in the semaglutide 1.0 mg groups than in the semaglutide 0.5 mg groups.
- The focus of this analysis was the effect of weight loss on treatment satisfaction; it did not compare the 10% vs 5% responder groups.
- The results in the present analysis are clinically relevant as they suggest that weight loss can be a driver for treatment satisfaction and improved HRQoL.

Conclusion

- Weight loss was associated with improvements in the PCS score of the SF-36v2®, overall treatment satisfaction, and the perception of hyperglycaemia across the SUSTAIN 2–5 and 7 trials.
- These data suggest that weight loss may be an important factor affecting HRQoL and treatment satisfaction improvements during T2D treatment with semaglutide.

These studies were sponsored by Novo Nordisk and are registered with ClinicalTrials.gov (NCT01930188; NCT01885208; NCT02128932; NCT02305381; NCT02648204).
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References: (**1**) Novo Nordisk. Ozempic® (semaglutide) Prescribing Information 2019. Available at: https://www.novo-pi.com/ozempic.pdf. Accessed August 2019; (**2**) Sorli C et al. Lancet Diabetes Endocrinol 2017;5:251–60; (**3**) Ahrén B et al. Lancet Diabetes Endocrinol 2017;5:341–54; (**4**) Ahmann AJ et al. Diabetes Care 2018;41:258–66; (**5**) Aroda VR et al. Lancet Diabetes Endocrinol 2017;5:355–66; (**6**) Rodbard HW et al. J Clin Endocrinol Metab 2018;103:2291–301; (**7**) Pratley RE et al. Lancet Diabetes Endocrinol 2018;6:275–86; (**8**) Ridderstråle M et al. Health Qual Life Outcomes 2016;14:13; (**9**) Wharton S et al. Can J Diabetes 2015;39(Suppl. 1):S35; (**10**) Jensen MD et al. Obesity 2014;22(Suppl. 2):S5–S39; (**11**) Russell-Jones D et al. Diabetologia 2009;52:2046–55; (**12**) Diamant M et al. Lancet Diabetes Endocrinol 2014;2:464–73; (**13**) Billings LK et al. J Manag Care Spec Pharm 2018;24(Suppl. 9-a):S30–S41.

Abstract

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The effect of once-weekly semaglutide on MACE, blood pressure and lipids by race and ethnicity: a SUSTAIN 6 *post hoc* analysis

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(qrs.ly/e5abn8z)

Aim

- Semaglutide (Novo Nordisk, Denmark) is a glucagon-like peptide-1 (GLP-1) analogue approved for the once-weekly (OW) subcutaneous treatment of type 2 diabetes (T2D).[1]
- In SUSTAIN 6, semaglutide OW added to standard of care significantly reduced the risk of major adverse cardiovascular (CV) events (MACE: nonfatal myocardial infarction [MI], nonfatal stroke or CV death) vs placebo. The hazard ratio (HR) [95% confidence interval (CI)] was 0.74 [0.58;0.95]; p<0.001 for noninferiority, p=0.02 for superiority.[2]
- Fewer Caucasians are diagnosed with T2D than Black/African American, Asian or Hispanic adults.[3] There is also an increased incidence of CV disease in Black/African American patients with T2D, compared with Caucasians.[4]
- The aim of this *post hoc* analysis was to assess the effect of semaglutide OW vs placebo on MACE, blood pressure (BP) and lipid levels in race and ethnicity subgroups in SUSTAIN 6.

Methods

SUSTAIN 6 trial design

- The SUSTAIN 6 trial design has been reported previously.[2]
  - Subjects with T2D and an HbA_{1c} ≥7.0% on 0–2 oral antidiabetic drugs, basal or premixed insulin with no concomitant GLP-1 receptor agonist (GLP-1RA) therapy were eligible.
  - Subjects were randomised (1:1:1:1) to semaglutide 0.5 mg, semaglutide 1.0 mg, or volume-matched placebo for 104 weeks.
  - The primary composite outcome was time to first occurrence of MACE.

Post hoc analysis

- In this *post hoc* analysis, treatment groups (semaglutide 0.5 mg and 1.0 mg, or placebo 0.5 mg and 1.0 mg) were pooled and analysed in subgroups of race (Caucasian, Black/African American, Asian or Other) and ethnicity (Hispanic or non-Hispanic).
  - The Other race subgroup comprised all subjects in the 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander' or 'Other' subgroups.
- MACE and each of its components were evaluated in race and ethnicity subgroups.
- The following secondary endpoints were also assessed in race and ethnicity subgroups:
  - Changes from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at week 104.
  - Estimated treatment ratios (ETRs), defined as the relative levels of each parameter in the semaglutide vs placebo groups, of lipids (total cholesterol, low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], free fatty acids [FFAs] and triglycerides) at week 104.
  - Adverse events (AEs) throughout the trial.

Statistical analysis

- MACE and its components were analysed using a Cox proportional hazards model, with treatment and subgroup as fixed factors.
- Changes in SBP were analysed using an analysis of covariance. Changes in DBP were analysed using a mixed model for repeated measurements (MMRM) with interaction between subgroup, randomised treatment and baseline value as covariates, all interacting with visit. ETRs were also analysed using an MMRM with treatment and stratification as fixed factors and baseline value as covariate.
- MACE, BP and lipid data were observed without imputation, irrespective of subjects' adherence to treatment (in-trial). AE data are from the period when subjects were exposed to the study drug (on-treatment).

Results

Baseline characteristics and demographics

- Overall, 3,297 subjects with T2D were randomised to semaglutide 0.5 mg or 1.0 mg, or placebo 0.5 mg or 1.0 mg.[2]
- Subject disposition and baseline characteristics by race and ethnicity are shown in Table 1.
- In general, baseline characteristics were similar across subgroups. However, mean baseline body weight was lower in the Asian subgroup than in other subgroups in both treatment groups.

Table 1: Subject disposition and baseline characteristics by race and ethnicity

	Semaglutide (pooled)						Placebo (pooled)					
	Race				Ethnicity		Race				Ethnicity	
	Caucasian	Black/ African American	Asian	Other	Hispanic	Non-Hispanic	Caucasian	Black/ African American	Asian	Other	Hispanic	Non-Hispanic
Subject disposition												
Full analysis set, n	1,384	108	121	35	256	1,392	1,352	113	152	32	254	1,395
Trial completers, n (%)	1,364 (82.8)	105 (6.4)	120 (7.3)	34 (2.1)	253 (15.4)	1,370 (83.1)	1,321 (80.1)	104 (6.3)	152 (9.2)	32 (1.9)	251 (15.2)	1,358 (82.4)
Treatment completers, n (%)	1,091 (66.2)	72 (4.4)	109 (6.6)	25 (1.5)	215 (13.0)	1,082 (65.7)	1,100 (66.7)	75 (4.5)	138 (8.4)	26 (1.6)	211 (12.8)	1,128 (68.4)
Baseline characteristics*												
Male, n (%)	871 (62.9)	46 (42.6)	73 (60.3)	23 (65.7)	151 (59.0)	862 (61.9)	811 (60.0)	55 (48.7)	105 (69.1)	18 (56.3)	137 (53.9)	852 (61.1)
Age, years	64.9 (7.2)	63.3 (7.3)	63.5 (7.2)	63.0 (7.4)	64.3 (7.3)	64.7 (7.2)	65.2 (7.5)	61.9 (7.6)	61.8 (6.8)	63.7 (6.5)	63.8 (7.6)	64.8 (7.5)
Diabetes duration, years	13.8 (8.2)	16.2 (9.4)	15.7 (7.1)	15.6 (7.0)	15.7 (8.7)	13.9 (8.1)	13.4 (7.9)	14.3 (8.4)	15.0 (8.4)	14.1 (8.3)	16.0 (8.5)	13.2 (7.9)
HbA_{1c}, %	8.7 (1.4)	9.0 (1.5)	8.9 (1.4)	9.4 (2.3)	8.9 (1.7)	8.7 (1.4)	8.6 (1.4)	9.1 (1.8)	9.2 (1.6)	8.9 (1.8)	8.9 (1.6)	8.7 (1.5)
FPG, mmol/L	10.4 (3.7)	9.6 (4.0)	9.4 (3.4)	9.2 (2.8)	9.7 (4.2)	10.3 (3.6)	10.4 (3.6)	10.4 (3.9)	9.5 (3.9)	9.9 (3.4)	9.9 (3.6)	10.3 (3.7)
Body weight, kg	93.8 (20.1)	97.5 (23.9)	74.3 (14.7)	82.2 (15.2)	84.0 (18.4)	93.9 (20.7)	93.4 (20.1)	97.4 (22.7)	74.5 (13.1)	89.6 (19.8)	82.5 (16.2)	93.6 (20.8)

*Values are mean (SD) unless otherwise indicated. Data were pooled for both the semaglutide groups and for the placebo groups. Trial completers were subjects who either attended the last follow-up visit or died while considered an active trial participant. Treatment completers were subjects who were exposed and did not discontinue treatment prematurely, did not withdraw from trial and were not lost to follow-up before the last treatment visit. FPG, fasting plasma glucose; n, number of subjects; SD, standard deviation.

Time to first occurrence of MACE

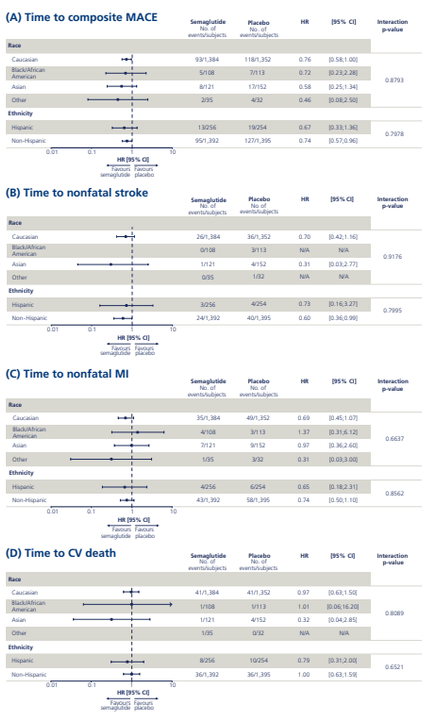
- The HRs for the time to composite MACE were <1 in each race and ethnicity subgroup (Figure 1A).
- The HRs for the individual components of MACE were <1 in each race and ethnicity subgroup, except in Black/African American subjects for nonfatal MI and CV death, and in non-Hispanics for CV death (Figure 1B–D).
- All interaction p-values were nonsignificant (p>0.05).

Change in SBP and DBP from baseline

- Reductions in SBP with semaglutide were consistent across most subgroups (Figure 2A), except in Black/African American subjects.
  - In Black/African American subjects, the increase was driven by a 1.9 mmHg increase with semaglutide 0.5 mg (n=54; data not shown).
  - SBP decreased by 2.0 mmHg in Black/African American subjects with semaglutide 1.0 mg (n=54; data not shown).
  - In SUSTAIN 1–5 and 7, SBP was reduced in Black/African American subjects (data not shown).
- Changes in DBP with semaglutide were consistent across all subgroups (Figure 2B).

Key result

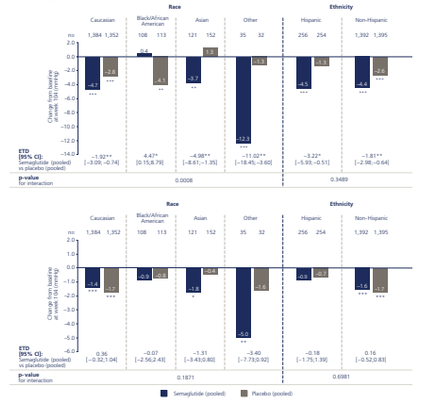
Figure 1: Time to composite MACE and its individual components by race and ethnicity



Data are from the in-trial observation period from the full analysis set, and were pooled for both the semaglutide groups and for the placebo groups. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; N/A, not available.

- The greatest reductions in SBP and DBP were observed in the Other subgroup. It should be noted that the subject numbers in this group were low.
- All interaction p-values were nonsignificant (p>0.05), with the exception of the treatment effect of semaglutide on SBP by race (p=0.0008).

Figure 2: Change in (A) SBP and (B) DBP from baseline by race and ethnicity



*p<0.05, **p<0.01, ***p<0.001. Data are estimated mean changes from baseline or ETD [95% CI] from the in-trial observation period from the full analysis set, and were pooled for the semaglutide groups and for the placebo groups. CI, confidence interval; DBP, diastolic blood pressure; ETD, estimated treatment difference; SBP, systolic blood pressure.

ETRs for total cholesterol, LDL-C, HDL-C, FFAs and triglycerides

- Most ETRs were <1 for total cholesterol, LDL-C, FFAs and triglycerides in all race and ethnicity subgroups (data not shown).
  - Exceptions were ETRs for LDL-C and total cholesterol in Black/African Americans (1.08 and 1.02, respectively); and total cholesterol, FFAs and triglycerides in Asians (1.01, 1.02 and 1.01, respectively) (data not shown).
- Most ETRs were >1 for HDL-C in all race and ethnicity subgroups, except for the Other subgroup (ETR: 0.98).
- All interaction p-values were nonsignificant (p>0.05).

Safety

- Semaglutide was well tolerated in all race and ethnicity subgroups (Table 2), and had a safety profile similar to that of other GLP-1RAs.[5,6]
- A greater proportion of Caucasian and Black/African American subjects discontinued treatment due to AEs with semaglutide, compared with subjects in other race subgroups.
- A slightly lower proportion of Asian subjects reported gastrointestinal AEs with semaglutide compared with subjects in other race and ethnicity subgroups.
- The overall incidence of severe hypoglycaemia with semaglutide was low.

Table 2: Adverse events by race and ethnicity

	Semaglutide (pooled)						Placebo (pooled)					
	Race				Ethnicity		Race				Ethnicity	
	Caucasian	Black/ African American	Asian	Other	Hispanic	Non-Hispanic	Caucasian	Black/ African American	Asian	Other	Hispanic	Non-Hispanic
All AEs	1,230 (89.3)	98 (90.7)	95 (78.5)	31 (88.6)	231 (90.9)	1,223 (88.1)	1,196 (88.8)	101 (89.4)	127 (83.6)	29 (90.6)	229 (90.9)	1,224 (87.9)
Serious AEs	420 (30.5)	34 (31.5)	40 (33.1)	10 (28.6)	54 (21.3)	450 (32.4)	478 (35.5)	42 (37.2)	43 (28.3)	11 (34.4)	66 (26.2)	508 (36.5)
AEs leading to premature treatment discontinuation	189 (13.7)	15 (13.9)	7 (5.8)	3 (8.6)	20 (7.9)	194 (14.0)	94 (7.0)	8 (7.1)	4 (2.6)	4 (12.5)	13 (5.2)	97 (7.0)
GI AEs	718 (52.1)	55 (50.9)	52 (43.0)	16 (45.7)	118 (46.5)	723 (52.1)	482 (35.8)	34 (30.1)	36 (23.7)	12 (37.5)	77 (30.6)	487 (35.0)
Severe hypoglycaemia*	14 (1.0)	2 (1.9)	6 (5.0)	1 (2.9)	5 (2.0)	18 (1.3)	23 (1.7)	3 (2.7)	0 (0.0)	0 (0.0)	3 (1.2)	23 (1.7)
Severe or BG-confirmed symptomatic hypoglycaemia*	300 (21.8)	25 (23.1)	23 (19.0)	9 (25.7)	71 (28.0)	286 (20.6)	277 (20.6)	21 (18.6)	32 (21.1)	3 (9.4)	65 (25.8)	268 (19.3)

*Defined as an episode that is severe according to the ADA classification.[7] Defined as an episode that is severe (according to the ADA classification) or BG-confirmed (plasma glucose value <3.1 mmol/L [56 mg/dL]) with symptoms consistent with hypoglycaemia). Data are number (percentage) of subjects experiencing ≥1 event, for the on-treatment observation period and from the safety analysis set, and were pooled for both the semaglutide groups and for the placebo groups. ADA, American Diabetes Association; AE, adverse event; BG, blood glucose; GI, gastrointestinal.

Discussion

- This *post hoc* analysis assessed the effects of semaglutide vs placebo on MACE and its components, BP and lipid levels in race and ethnicity subgroups.
- The effect of semaglutide vs placebo on MACE and its individual components was largely consistent across all race and ethnicity subgroups.
- The effects of semaglutide on MACE shown here align with analyses from the LEADER and REWIND CV outcomes trials, which showed that the respective effects of liraglutide and dulaglutide vs placebo on MACE were consistent, irrespective of race or ethnicity.[7,8]
- SBP was reduced with semaglutide in all subgroups except in Black/African American subjects, although this was unlikely to be clinically meaningful.
  - Only the interaction p-value for the effect of semaglutide on SBP by race was statistically significant. This could be due to the large decrease and the heterogeneity observed in the Other subgroup in which the 95% CI was broad.
- Despite minor variations in all subgroups, the absence of significant interaction p-values suggests there was no differential effect of semaglutide on lipids across race and ethnicity subgroups.
- An association between the occurrence of severe hypoglycaemia and risk of MACE was demonstrated in the LEADER trial.[9]
  - In this study, HRs for nonfatal MI and CV death in Black/African American subjects slightly favoured placebo; however, the variation was large and there did not appear to be an imbalance in severe hypoglycaemia across race and ethnicity subgroups.

Conclusion

- In this *post hoc* analysis of the SUSTAIN 6 trial, there appeared to be no heterogeneity in the effect of semaglutide vs placebo on MACE, BP and lipid levels in race and ethnicity subgroups.
- The safety profile in each subgroup was similar to that of all subjects in the SUSTAIN clinical trial programme.[10]

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Presented at the 55th Annual Meeting of the European Association for the Study of Diabetes, 16–20 September 2019, Barcelona, Spain.

References: (**1**) Novo Nordisk. Ozempic® (semaglutide) Prescribing Information 2019. Available at: https://www.novo-pi.com/ozempic.pdf. Accessed August 2019; (**2**) Marso SP et al. N Engl J Med 2016;375:1834–44; (**3**) National Diabetes Statistics Report, 2017. Available at: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed August 2019; (**4**) Osei K, Gaillard T. Front Endocrinol (Lausanne) 2017;8:204; (**5**) Ahmann AJ et al. Diabetes Care 2018;41:258–66; (**6**) Pratley RE et al. Lancet Diabetes Endocrinol 2018;6:275–86; (**7**) Marso SP et al. N Engl J Med 2016;375:311–22; (**8**) Gerstein HC et al. Lancet 2019;394:121–30; (**9**) Zinman B et al Diabetes Care 2018;41:1783–91; (**10**) Aroda VR et al. Diabetes Metab 2019 Jan 4. doi: 10.1016/j.diabet.2018.12.001 [Epub ahead of print].

Abstract

Efficacy and safety of semaglutide by baseline BMI in SUSTAIN 1–5 and 7

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(qrs.ly/e5abn8z)

Aim

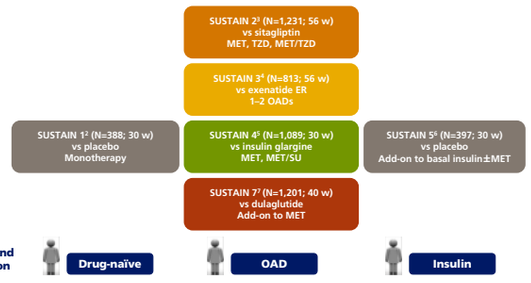
- Semaglutide (Novo Nordisk, Denmark) is a glucagon-like peptide-1 (GLP-1) analogue approved for the once-weekly subcutaneous treatment of type 2 diabetes (T2D).[1]
- The efficacy and safety of semaglutide were evaluated in the SUSTAIN clinical trial programme, which covered the continuum of care in T2D, including in drug-naïve subjects and those on background medication with oral antidiabetic drugs±insulin.[2–7]
- Across the SUSTAIN trials, semaglutide showed superior reductions in HbA_{1c} and body weight vs placebo and all active comparators (sitagliptin, exenatide extended release, insulin glargine, dulaglutide), and enabled a greater proportion of subjects to achieve clinically meaningful (≥5%) weight-loss responses.[2–7]
  - A higher body mass index (BMI) at baseline was generally associated with greater weight loss during semaglutide therapy.[8,9]
- As exposure to a drug may be affected by body weight,[10] the aim of this *post hoc* analysis was to assess if reductions in HbA_{1c} were affected by baseline BMI in the SUSTAIN trials.

Methods

SUSTAIN 1–5 and 7 trial designs

- In SUSTAIN 1–5 and 7, adults with T2D (HbA_{1c} 7.0–10.0% for SUSTAIN 1, 4, and 5, or 7.0–10.5% for SUSTAIN 2, 3, and 7) were randomised to semaglutide 0.5 mg or 1.0 mg, placebo or active comparator (Figure 1).[2–7]

Figure 1: SUSTAIN 1–5 and 7 trials



SUSTAIN 6 was a cardiovascular outcomes trial in subjects at high risk of cardiovascular disease and, as such, was not included in the present analysis. Exenatide ER, exenatide extended release; MET, metformin; N, number of randomised subjects; OAD, oral antidiabetic drug; SU, sulphonylurea; TZD, thiazolidinedione; w, weeks.

- All semaglutide-treated subjects followed a fixed dose-escalation regimen:[2–7]
  - The semaglutide 0.5 mg maintenance dose was reached after 4 weeks of semaglutide 0.25 mg once weekly; the semaglutide 1.0 mg maintenance dose was reached after an additional 4 weeks of semaglutide 0.5 mg once weekly.
- Key endpoints were similar across trials:[2–7]
  - The primary endpoint was the change in HbA_{1c} from baseline to end of treatment.
  - The confirmatory secondary endpoint was the change in body weight from baseline to end of treatment.

Post hoc analysis

- For this *post hoc* analysis of data from the SUSTAIN 1–5 and 7 trials:
  - Subjects were grouped by baseline BMI (<25, 25 to <30, 30 to <35, and ≥35 kg/m²).
  - Change in HbA_{1c} was evaluated for semaglutide vs placebo or active comparator by trial for SUSTAIN 1–5 and 7 in a mixed model for repeated measurements, with treatment, BMI subgroup, and HbA_{1c} at baseline as covariates, and interaction between treatment and BMI subgroups at baseline.
  - Safety data were pooled and analysed by a Cochran–Mantel–Haenszel analysis stratified by trial.

Results

Baseline characteristics and demographics

- Baseline characteristics were broadly consistent across SUSTAIN 1–5 and 7, with mean baseline HbA_{1c} and body weight values ranging from 8.1% to 8.4% and 89.5 kg to 95.8 kg, respectively (Table 1).
- Diabetes duration at baseline ranged from 4.2 years to 13.3 years, reflecting the continuum of T2D care covered by the SUSTAIN trials (Table 1).

Table 1: Baseline characteristics and demographics by trial

		SUSTAIN 1[2] vs placebo	SUSTAIN 2[3] vs sitagliptin	SUSTAIN 3[4] vs exenatide ER	SUSTAIN 4[5] vs IGlar	SUSTAIN 5[6] vs placebo	SUSTAIN 7[7] vs dulaglutide
Age, years		53.7 (11.3)	55.1 (10.0)	56.6 (10.7)	56.5 (10.4)	58.8 (10.1)	56.0 (10.6)
Diabetes duration, years		4.2 (5.5)	6.6 (5.1)	9.2 (6.3)	8.6 (6.3)	13.3 (7.8)	7.4 (5.7)
HbA_{1c}	%	8.1 (0.9)	8.1 (0.9)	8.3 (1.0)	8.2 (0.9)	8.4 (0.8)	8.2 (0.9)
	mmol/mol	64.5 (9.3)	64.8 (10.1)	67.7 (10.4)	65.8 (9.7)	67.9 (9.2)	66.4 (10.0)
Body weight, kg		91.9 (23.8)	89.5 (20.3)	95.8 (21.5)	93.5 (21.8)	91.7 (21.0)	95.2 (22.6)
BMI, kg/m²		32.9 (7.7)	32.5 (6.2)	33.8 (6.7)	33.0 (6.5)	32.2 (6.2)	33.5 (6.8)

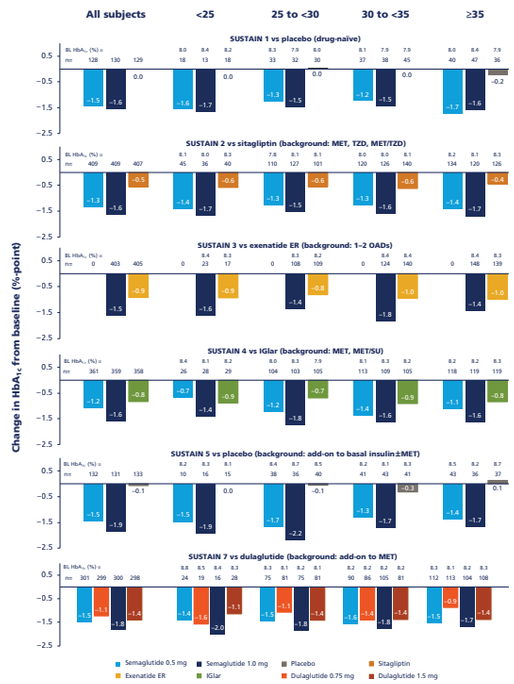
Values are mean (SD). BMI, body mass index; exenatide ER, exenatide extended release; IGlar, insulin glargine; SD, standard deviation.

Glycaemic control

- Reductions in mean HbA_{1c} (%) from baseline were generally greater with semaglutide vs placebo or active comparator in all BMI subgroups (Figure 2).
  - The only exception was in the <25 kg/m² BMI subgroup, for semaglutide 0.5 mg vs insulin glargine (–0.7% vs –0.9%, respectively) and for semaglutide 0.5 mg vs dulaglutide 0.75 mg (–1.4% vs –1.6%, respectively).
- There were no significant interactions between treatment and BMI, with the exception of semaglutide 0.5 mg in SUSTAIN 7.

Figure 2: Estimated change in HbA_{1c} by baseline BMI

Key result



Values shown are estimated mean changes from baseline for subjects on treatment without rescue medication. BL, baseline; BMI, body mass index; exenatide ER, exenatide extended release; IGlar, insulin glargine; MET, metformin; OAD, oral antidiabetic drug; SU, sulphonylurea; TZD, thiazolidinedione.

Safety

- In all treatment arms, adverse events (AEs) occurred in similar proportions of subjects across BMI subgroups (Table 2).
- The proportion of subjects with gastrointestinal AEs was higher with semaglutide vs placebo or active comparators; however, these events generally decreased with increasing baseline BMI.
- Premature treatment discontinuation due to AEs:
  - Decreased with increasing baseline BMI, potentially reflecting the trend in gastrointestinal AEs.
  - Was higher in all BMI subgroups with semaglutide vs placebo or active comparators.

Table 2: Adverse events by baseline BMI

	Semaglutide 0.5 mg				Semaglutide 1.0 mg				Comparator			
Baseline BMI subgroup, kg/m²	**<25**	**25 to <30**	**30 to <35**	**≥35**	**<25**	**25 to <30**	**30 to <35**	**≥35**	**<25**	**25 to <30**	**30 to <35**	**≥35**
All AEs	89 (71.8)	249 (69.0)	284 (70.6)	313 (70.0)	96 (72.2)	337 (69.9)	375 (68.9)	413 (72.1)	111 (66.0)	365 (67.0)	448 (69.9)	462 (68.6)
Serious AEs	5 (3.9)	19 (5.2)	31 (7.7)	29 (6.4)	4 (3.6)	29 (6.0)	36 (6.6)	58 (10.2)	6 (3.4)	26 (5.2)	46 (6.9)	53 (7.6)
AEs leading to premature treatment discontinuation	16 (13.5)	38 (10.5)	22 (5.7)	15 (3.4)	23 (18.0)	44 (9.2)	42 (7.7)	39 (6.9)	15 (8.3)	29 (4.6)	24 (3.7)	15 (2.3)
GI AEs	59 (47.8)	155 (43.2)	155 (38.8)	171 (38.4)	65 (50.5)	210 (43.7)	212 (39.0)	228 (39.9)	40 (21.2)	152 (25.8)	191 (28.9)	184 (25.5)

On-treatment data for number of subjects in the safety analysis set (% of total subjects) experiencing >1 event. Comparators were: placebo (SUSTAIN 1 and 5), sitagliptin (SUSTAIN 2), exenatide extended release (SUSTAIN 3), insulin glargine (SUSTAIN 4), and dulaglutide (SUSTAIN 7). AE, adverse event; BMI, body mass index; GI, gastrointestinal.

Discussion

- Achieving glycaemic control in T2D is challenging, and responsiveness to therapy is important.[11]
- In this *post hoc* analysis of the SUSTAIN 1–5 and 7 trials, the estimated treatment differences in mean HbA_{1c} for semaglutide vs placebo or active comparators did not appear to be influenced by baseline BMI, indicating a consistent effect of semaglutide.
  - A previous analysis of SUSTAIN 1–5 data, showing change in HbA_{1c} against change in body weight with semaglutide, resulted in similar findings.[12]
- Reductions in mean HbA_{1c} from baseline were generally greater with semaglutide vs placebo or active comparators in all BMI subgroups.
- AEs occurred in a similar proportion of subjects in all treatment arms and across BMI subgroups.
- Gastrointestinal AEs generally decreased with increasing BMI in subjects receiving semaglutide.

Conclusion

- Semaglutide consistently reduced HbA_{1c} vs placebo or active comparators in subjects with T2D regardless of their baseline BMI.
- Semaglutide had an acceptable safety profile in all BMI subgroups.

These studies were sponsored by Novo Nordisk and are registered with ClinicalTrials.gov (NCT02054897; NCT01930188; NCT01885208; NCT02128932; NCT02305381; NCT02648204).
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Presented at the 55th Annual Meeting of the European Association for the Study of Diabetes, 16–20 September 2019, Barcelona, Spain.

References: (**1**) Lau J et al. J Med Chem 2015;58:7370–80; (**2**) Sorli C et al. Lancet Diabetes Endocrinol 2017;5:251–60; (**3**) Ahrén B et al. Lancet Diabetes Endocrinol 2017;5:341–54; (**4**) Ahmann AJ et al. Diabetes Care 2018;41:258–66; (**5**) Aroda VR et al. Lancet Diabetes Endocrinol 2017;5:355–66; (**6**) Rodbard HW et al. J Clin Endocrinol Metab 2018;103:2291–301; (**7**) Pratley RE et al. Lancet Diabetes Endocrinol 2018;6:275–86; (**8**) Leiter LA et al. Presented at the 77th Scientific Sessions of the American Diabetes Association, 9–13 June 2017, San Diego, CA, USA. Poster 1105-P; (**9**) Viljoen A et al. Presented at the 78th Scientific Sessions of the American Diabetes Association, 22–26 June 2018, Orlando, FL, USA. Poster 1083-P; (**10**) Carlsson Petri KC et al. Diabetes Ther 2018;9:1533–47; (**11**) Fonseca VA et al. Diabetes Care 2009;32:S151–6; (**12**) Rodbard HW et al. Presented at the 77th Scientific Sessions of the American Diabetes Association, 9–13 June 2017, San Diego, CA, USA. Poster 1124-P.

Abstract

Efficacy and safety of once-weekly semaglutide low dose 0.5 mg vs once-weekly dulaglutide high dose 1.5 mg in type 2 diabetes: a *post hoc* analysis of SUSTAIN 7

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Aim

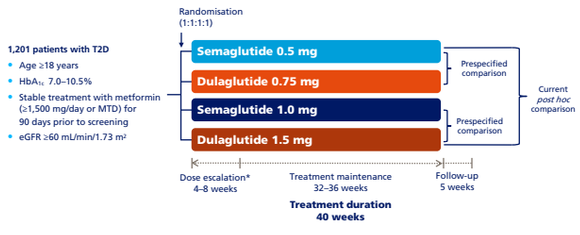
- Semaglutide (Novo Nordisk, Denmark) is a glucagon-like peptide-1 analogue indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes (T2D).[1]
- In SUSTAIN 7, an international, open-label, parallel-group trial, adults with inadequately controlled T2D were randomised (1:1:1:1) to receive subcutaneous semaglutide once weekly or dulaglutide once weekly at low (0.5 vs 0.75 mg, respectively) or high (1.0 vs 1.5 mg, respectively) doses.[2]
  - » Semaglutide provided superior glycaemic control and reductions in body weight vs dulaglutide at both low- and high-dose drug comparisons.[2]
- The aim of this *post hoc* analysis was to compare the effects of semaglutide low (0.5 mg) vs dulaglutide high (1.5 mg) dose at week 40.
  - » This comparison was **not prespecified** in the primary analysis of SUSTAIN 7.[2]
  - » This comparison was implemented to reflect options available in clinical practice and to ensure a thorough assessment of clinical efficacy and safety.

Methods

SUSTAIN 7 trial design (Figure 1)

- Data were collected from all patients randomised and exposed to treatment (full analysis set), and the data analysed in this *post hoc* analysis were prior to use of any rescue medication.

Figure 1: SUSTAIN 7 trial design[2]



*Semaglutide dose escalation from starting dose of 0.25 mg once weekly, dose doubled every 4 weeks until trial maintenance dose reached. Dulaglutide 0.75 mg and 1.5 mg dosed once weekly without dose escalation. eGFR, estimated glomerular filtration rate; MTD, maximum tolerated dose.

Results

Baseline characteristics and demographics

- Baseline characteristics were broadly consistent between semaglutide and dulaglutide (Table 1).
  - » Mean age was 56 years. Baseline HbA_{1c} was 8.2–8.3%; diabetes duration 7.6–7.7 years.

Table 1: Baseline characteristics and demographics

		Low-dose semaglutide 0.5 mg (n=301)	High-dose dulaglutide 1.5 mg (n=299)
Male, n (%)		169 (56.1)	171 (57.2)
Female, n (%)		132 (43.9)	128 (42.8)
Age, years		56 (10.9)	56 (10.6)
Diabetes duration, years		7.7 (5.9)	7.6 (5.6)
HbA_{1c}	%	8.3 (1.0)	8.2 (0.9)
	mmol/mol	67.5 (10.5)	66.1 (9.7)
FPG	mg/dL	176.3 (45.7)	172.5 (41.2)
	mmol/L	9.8 (2.5)	9.6 (2.3)
Body weight, kg		96.4 (24.4)	93.4 (21.8)
BMI, kg/m²		33.7 (7.1)	33.1 (6.6)
SBP, mmHg		134 (14.8)	132 (13.6)
DBP, mmHg		81 (9.0)	80 (8.7)

Values are mean (SD) unless otherwise indicated. BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; SBP, systolic blood pressure; SD, standard deviation.

Change in HbA_{1c} and body weight from baseline, and proportions of subjects achieving targets

- Low-dose semaglutide 0.5 mg resulted in similar improvements in glycaemic control and significantly greater weight loss vs high-dose dulaglutide 1.5 mg at week 40 (Figure 2).
- Similar proportions of subjects achieved HbA_{1c} <7.0% and ≤6.5%, but with low-dose semaglutide 0.5 mg, significantly larger proportions of subjects achieved weight loss ≥5% and ≥10% compared with high-dose dulaglutide 1.5 mg (Figure 3).

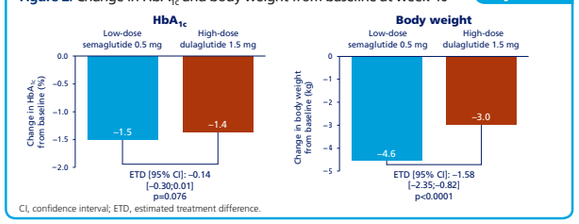
Change in systolic and diastolic blood pressure from baseline

- There were no significant differences in change from baseline in systolic and diastolic blood pressure between low-dose semaglutide 0.5 mg and high-dose dulaglutide 1.5 mg (Table 2).

Safety

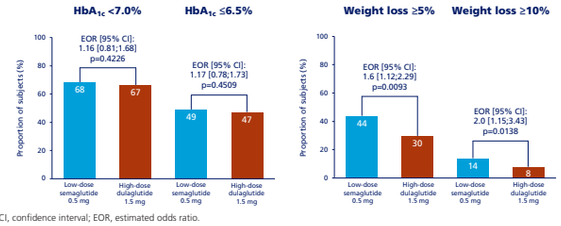
- The rate of adverse events (AEs) and serious AEs overall was similar for low-dose semaglutide 0.5 mg and high-dose dulaglutide 1.5 mg (Table 3).
- The rate of gastrointestinal (GI) AEs was similiar for low-dose semaglutide 0.5 mg and high-dose dulaglutide 1.5 mg; the GI AEs were mainly mild or moderate for both treatment groups (Table 3).
- The proportions of subjects discontinuing treatment due to any AE or due to GI AEs were similar for low-dose semaglutide 0.5 mg and high-dose dulaglutide 1.5 mg (Table 3).

Figure 2: Change in HbA_{1c} and body weight from baseline at week 40 — **Key result**



CI, confidence interval; ETD, estimated treatment difference.

Figure 3: Proportion of subjects achieving targets at week 40



CI, confidence interval; EOR, estimated odds ratio.

Table 2: Change in systolic and diastolic blood pressure from baseline at week 40

		Low-dose semaglutide 0.5 mg	High-dose dulaglutide 1.5 mg
SBP	Baseline, mmHg	134 (14.8)	132 (13.6)
	Change from baseline at week 40, mmHg	−2.4 (0.8)	−2.9 (0.8)
	ETD [95% CI]	0.42 [−1.68;2.52]	
	p-value	0.697	
DBP	Baseline, mmHg	81 (9.0)	80 (8.7)
	Change from baseline at week 40, mmHg	−0.6 (0.5)	−0.0 (0.5)
	ETD [95% CI]	0.54 [−1.86;0.79]	
	p-value	0.426	

Values are mean (SD) unless otherwise indicated. CI, confidence interval; DBP, diastolic blood pressure; ETD, estimated treatment difference; SBP, systolic blood pressure; SD, standard deviation.

Table 3: Adverse events by treatment

	Low-dose semaglutide 0.5 mg				High-dose dulaglutide 1.5 mg			
	n	%	E	R	n	%	E	R
All AEs	**204**	**68**	**966**	**412.7**	**221**	**74**	**957**	**402.6**
Serious AEs	**17**	**6**	**23**	**9.8**	**22**	**7**	**33**	**13.9**
Fatal events *†	**1**	**<1**	**1**	**0.4**	**2**	**1**	**5**	**2.0**
AEs leading to premature treatment discontinuation	**24**	**8**	**46**	**19.7**	**20**	**7**	**51**	**21.5**
GI AEs leading to premature treatment discontinuation	16	5	27	11.5	14	5	37	15.6
GI AEs	**129**	**43**	**394**	**168.3**	**143**	**48**	**393**	**165.4**
Mild	108	36	317	135.4	125	42	300	126.2
Moderate	40	13	57	24.4	39	13	80	33.7
Severe	9	3	20	8.5	8	3	13	5.5
Most frequent GI AEs								
Nausea	68	23	145	62.0	60	20	108	45.4
Diarrhoea	43	14	79	33.8	53	18	75	31.6
Vomiting	31	10	51	21.8	29	10	40	16.8

AEs include events that had an onset, or increase in severity, from first exposure to the planned follow-up visit scheduled 5 weeks (+7-day visit window) after the end of treatment visit at week 40 (on-treatment data). *AEs include events that had an onset, or increase in severity, from randomisation to the end of trial regardless of treatment or rescue medication status (in-trial data). †One subject receiving dulaglutide 1.5 mg had four events resulting in a fatal outcome. AE, adverse event; E, events; GI, gastrointestinal; R, rate of events per 100 patient-years.

Discussion

- In the original SUSTAIN 7 study, semaglutide was superior to dulaglutide at both low- and high-dose drug comparisons in improving glycaemic control and reducing body weight, and had a similar safety profile, in subjects with T2D.
- In this *post hoc* analysis of the SUSTAIN 7 trial, the comparison of low-dose semaglutide 0.5 mg vs high-dose dulaglutide 1.5 mg showed a similar glycaemic control, but with more weight loss and more subjects achieving ≥5% and ≥10% weight loss with low-dose semaglutide 0.5 mg vs high-dose dulaglutide 1.5 mg after 40 weeks, with a similar safety profile in subjects with T2D.
- These results suggest that the low dose of semaglutide 0.5 mg can provide greater weight-loss benefit to patients with T2D vs high-dose dulaglutide 1.5 mg, alongside similar glycaemic control and a similar safety profile.

Conclusion

- Subcutaneous low-dose semaglutide 0.5 mg once weekly showed greater weight loss and similar improvements in glycaemic control vs subcutaneous high-dose dulaglutide 1.5 mg once weekly at week 40, and with a similar safety profile in subjects with T2D, previously uncontrolled on metformin treatment.

This study was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT02648204).
Presenter Richard Pratley has received consulting fees from AstraZeneca, GlaxoSmithKline, Glytec LLC, Janssen, Ligand Pharmaceuticals, Lilly, Merck, Mundipharma, Novo Nordisk, Pfizer, and Sanofi;
has received grants from Lexicon Pharmaceuticals, Ligand Pharmaceuticals, Lilly, Merck, Novo Nordisk, and Sanofi; and lecture and other fees from AstraZeneca and Novo Nordisk. All honoraria and fees were directed to AdventHealth, a non-profit organisation.
The authors are grateful to Emre Yildirim, Novo Nordisk, for review of and input to the poster, and to Heather Mittman, AXON Communications (supported by Novo Nordisk), for writing assistance.
Presented at the 55th Annual Meeting of the European Association for the Study of Diabetes, 16–20 September 2019, Barcelona, Spain.

References: (**1**) Novo Nordisk. Ozempic® (semaglutide) Prescribing Information 2019. Available at: https://www.novo-pi.com/ozempic.pdf. Accessed August 2019; (**2**) Pratley RE et al. Lancet Diabetes Endocrinol 2018;6:275–86.

Abstract

Efficacy and safety of semaglutide by background sodium–glucose co-transporter-2 inhibitor: a *post hoc* analysis of SUSTAIN 9

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(qrs.ly/e5abn8z)

Aim

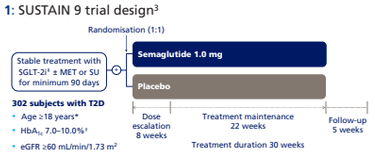
- Treatment guidelines recommend glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose co-transporter-2 inhibitors (SGLT-2is) for use after metformin in patients with type 2 diabetes (T2D) and established cardiovascular disease.[1,2]
- However, clinical trial data on the efficacy and safety of the concomitant use of GLP-1RAs and SGLT-2is in the management of T2D are scarce.
- The SUSTAIN 9 trial showed that, in subjects with T2D inadequately controlled with SGLT-2i therapy with or without metformin or a sulphonylurea, the addition of the GLP-1RA semaglutide once weekly (Novo Nordisk, Denmark) improved glycaemic control, lowered body weight, and was generally well tolerated.[3]
- The aim of this *post hoc* analysis of SUSTAIN 9 was to assess whether the efficacy and safety of semaglutide vs placebo were consistent in subjects on different background SGLT-2is.

Methods

SUSTAIN 9 trial design

- SUSTAIN 9 was a randomised, double-blind, placebo-controlled, multinational trial (Figure 1).[3]
- Subjects were randomised to semaglutide 1.0 mg or placebo, both subcutaneous once weekly, as an add-on to SGLT-2i therapy, with or without metformin or a sulphonylurea.[3]
- Semaglutide dosing began at 0.25 mg, doubling every 4 weeks until the maintenance dose was reached.[3]
- The primary and confirmatory secondary endpoints were change in HbA_{1c} and body weight, respectively, from baseline to week 30.[3]

Figure 1: SUSTAIN 9 trial design[3]



*Japan: minimum age for enrolment ≥20 years. †53–86 mmol/mol. ‡Stable treatment with SGLT-2i was defined as having started SGLT-2i treatment ≥90 days before screening. eGFR, estimated glomerular filtration rate; MET, metformin; SGLT-2i, sodium–glucose co-transporter-2 inhibitor; SU, sulphonylurea.

Statistical analysis

- In this *post hoc* analysis of SUSTAIN 9, changes in HbA_{1c} and body weight from baseline to week 30 were analysed by background SGLT-2i: canagliflozin; dapagliflozin (includes dapagliflozin and dapagliflozin propanediol monohydrate); empagliflozin; or other (ipragliflozin L-proline, luseogliflozin, and tofogliflozin; drugs available only in Japan) using an analysis of covariance.
- Proportions of subjects achieving HbA_{1c} targets (<7.0% and ≤6.5%), weight-loss responses (≥5% and ≥10%), and the triple composite endpoint of HbA_{1c} <7.0%, no weight gain, and no severe or blood glucose-confirmed hypoglycaemia were analysed by background SGLT-2i using a logistic regression model.
- A test for interaction was used to evaluate any impact of background SGLT-2i on treatment effect.

Results

Baseline characteristics and demographics

- A total of 302 subjects with T2D, on stable treatment with SGLT-2i with or without metformin or a sulphonylurea, were randomised to receive either semaglutide or placebo; one subject was assigned to semaglutide but did not receive treatment.[3]
- Baseline characteristics for subjects enrolled in SUSTAIN 9 were similar across SGLT-2i subgroups (Table 1).[3]

Table 1: Baseline characteristics and demographics by background SGLT-2i

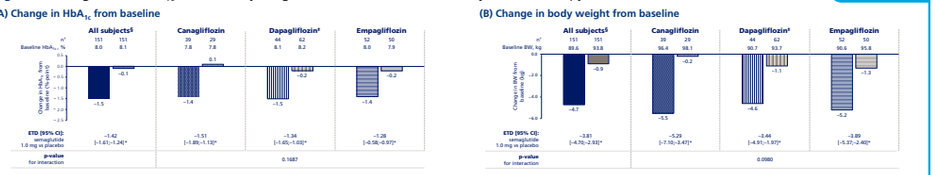
	All subjects*		Canagliflozin		Dapagliflozin†		Empagliflozin	
	Semaglutide 1.0 mg (n=150)	Placebo (n=151)	Semaglutide 1.0 mg (n=39)	Placebo (n=29)	Semaglutide 1.0 mg (n=44)	Placebo (n=62)	Semaglutide 1.0 mg (n=52)	Placebo (n=50)
Age, years	57.5 (8.9)	56.6 (10.1)	55.2 (10.1)	54.3 (8.7)	56.5 (9.2)	56.1 (10.7)	59.6 (7.5)	57.7 (10.9)
Diabetes duration, years	9.8 (6.3)	9.6 (5.9)	11.1 (8.0)	7.1 (3.8)	8.0 (4.6)	10.2 (6.2)	9.4 (5.0)	9.7 (6.1)
HbA_{1c}, %	8.0 (0.8)	8.1 (0.8)	7.8 (0.8)	7.8 (0.8)	8.1 (0.9)	8.2 (0.9)	8.0 (0.7)	7.9 (0.8)
FPG, mmol/L	9.1 (2.1)	8.9 (2.2)	8.5 (1.9)	8.8 (2.6)	9.3 (2.1)	9.3 (2.4)	9.5 (2.4)	8.7 (1.7)
BMI, kg/m²	31.1 (6.2)	32.7 (6.9)	33.9 (7.2)	35.4 (7.0)	32.1 (5.6)	32.9 (6.0)	30.2 (4.6)	32.3 (7.3)
eGFR, mL/min/1.73 m²	94.5 (15.3)	96.0 (15.1)	96.0 (13.3)	98.4 (14.5)	95.0 (15.7)	95.9 (15.7)	92.1 (16.0)	94.2 (15.8)

*25 subjects who received other SGLT-2is were randomised to receive semaglutide 1.0 mg (n=15) or placebo (n=10); data not presented owing to small number of subjects. †Includes subjects receiving dapagliflozin or dapagliflozin propanediol monohydrate. Values are mean (SD). BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; SD, standard deviation; SGLT-2i, sodium–glucose co-transporter-2 inhibitor.

Glycaemic control and body weight

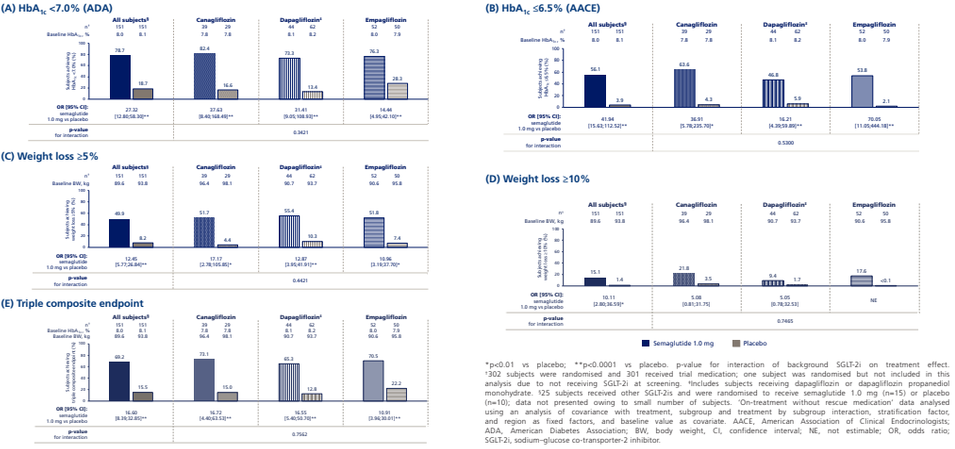
- At 30 weeks, there was no significant interaction between background SGLT-2i and treatment effect for any of the endpoints (interaction p>0.05 for all; Figures 2 and 3).
- Across background SGLT-2i groups, reductions in HbA_{1c} (Figure 2A) and body weight (Figure 2B) were significantly greater with semaglutide vs placebo.
- The proportions of subjects achieving American Diabetes Association and American Association of Clinical Endocrinologists HbA_{1c} targets of <7.0% and ≤6.5%, respectively, weight-loss responses of ≥5%, and the composite endpoint of HbA_{1c} <7.0% without weight gain or blood glucose-confirmed symptomatic hypoglycaemia, were also significantly greater for semaglutide vs placebo, with a similar pattern for all SGLT-2is (Figure 3A–C, E).

Figure 2: Change in (A) HbA_{1c} and (B) body weight from baseline at 30 weeks by SGLT-2i therapy



*p<0.0001 vs placebo. p-value for interaction of background SGLT-2i on treatment effect. ‡302 subjects were randomised and 301 received trial medication; one subject was randomised but not included in this analysis due to not receiving SGLT-2i at screening. †Includes subjects receiving dapagliflozin or dapagliflozin propanediol monohydrate. ‡25 subjects received other SGLT-2is and were randomised to receive semaglutide 1.0 mg (n=15) or placebo (n=10); data not presented owing to small number of subjects. §On-treatment without rescue medication' data analysed using an analysis of covariance with treatment, subgroup and treatment by subgroup interaction, stratification factor, and region as fixed factors, and baseline value as covariate. Mean baseline values and mean changes from baseline are shown. BW, body weight; CI, confidence interval; ETD, estimated treatment difference; SGLT-2i, sodium–glucose co-transporter-2 inhibitor.

Figure 3: Proportion of subjects achieving, at 30 weeks, (A) HbA_{1c} <7.0%, (B) HbA_{1c} ≤6.5%, (C) weight loss ≥5%, (D) weight loss ≥10%, (E) triple composite of HbA_{1c} <7.0% without weight gain and no severe or blood glucose-confirmed symptomatic hypoglycaemia



*p<0.01 vs placebo; **p<0.0001 vs placebo. p-value for interaction of background SGLT-2i on treatment effect. ‡302 subjects were randomised and 301 received trial medication; one subject was randomised but not included in this analysis due to not receiving SGLT-2i at screening. †Includes subjects receiving dapagliflozin or dapagliflozin propanediol monohydrate. ‡25 subjects received other SGLT-2is and were randomised to receive semaglutide 1.0 mg (n=15) or placebo (n=10); data not presented owing to small number of subjects. §On-treatment without rescue medication' data analysed using an analysis of covariance with treatment, subgroup and treatment by subgroup interaction, stratification factor, and region as fixed factors, and baseline value as covariate. AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; BW, body weight, CI, confidence interval; NE, not estimable; OR, odds ratio; SGLT-2i, sodium–glucose co-transporter-2 inhibitor.

Key results

- The proportion of subjects achieving a weight-loss response of ≥10% was significantly greater for semaglutide vs placebo for all subjects, but there was no significant difference between the treatment arms when analysed by individual SGLT-2i group (Figure 3D).
- Results for subjects who received other SGLT-2is (n=25; data not shown) were similar to those for subjects receiving canagliflozin, dapagliflozin, or empagliflozin.

Safety

- No new safety concerns were identified when adding semaglutide to SGLT-2i therapy.
- Reported adverse events by treatment arm were similar between the SGLT-2i subgroups (Table 2). Results for subjects who received other SGLT-2is (n=25; data not shown) were similar to those for subjects receiving canagliflozin, dapagliflozin, or empagliflozin.

Table 2: Adverse events by background SGLT-2i

	All subjects*		Canagliflozin		Dapagliflozin†		Empagliflozin	
	Semaglutide 1.0 mg (n=150)	Placebo (n=151)	Semaglutide 1.0 mg (n=39)	Placebo (n=29)	Semaglutide 1.0 mg (n=43)	Placebo (n=62)	Semaglutide 1.0 mg (n=52)	Placebo (n=50)
All AEs	104 (69.3)	91 (60.3)	34 (87.2)	21 (72.4)	29 (67.4)	33 (53.2)	35 (67.3)	32 (64.0)
Serious AEs	7 (4.7)	6 (4.0)	3 (7.7)	1 (3.4)	1 (2.3)	1 (1.6)	3 (5.8)	4 (8.0)
AEs leading to premature treatment discontinuation	13 (8.7)	3 (2.0)	4 (10.3)	1 (3.4)	3 (7.0)	2 (3.2)	5 (9.6)	0
GI AEs	56 (37.3)	20 (13.2)	14 (35.9)	4 (13.8)	18 (41.9)	8 (12.9)	21 (40.4)	6 (12.0)
Severe or BG-confirmed‡ symptomatic hypoglycaemia	4 (2.7)	0	2 (5.1)	0	1 (2.3)	0	1 (1.9)	0
Infections and infestations	34 (22.7)	31 (20.5)	13 (33.3)	5 (17.2)	11 (25.6)	16 (25.8)	10 (19.2)	10 (20.0)

*25 subjects who received other SGLT-2is were randomised to receive semaglutide 1.0 mg (n=15) or placebo (n=10); data not presented owing to small number of subjects. †Includes subjects receiving dapagliflozin or dapagliflozin propanediol monohydrate. ‡ADA classified, including hypoglycaemia episodes classified as severe, documented symptomatic, asymptomatic, probable symptomatic, and pseudo-hypoglycaemia. Severe or BG-confirmed hypoglycaemia defined as a plasma glucose value below 3.1 mmol/L (55.8 mg/dL) with symptoms consistent with hypoglycaemia. AEs include events that had onset, or increase in severity, from first exposure to the planned follow-up visit scheduled 5 weeks (with a 7-day visit window) after end-of-treatment visit at 30 weeks (on-treatment data). All AEs coded using version 21.0 of the Medical Dictionary for Regulatory Activities. Values are number (percentage) of subjects experiencing ≥1 event. ADA, American Diabetes Association; AE, adverse event; BG, blood glucose; GI, gastrointestinal; SGLT-2i, sodium–glucose co-transporter-2 inhibitor.

Discussion

- This *post hoc* analysis of the SUSTAIN 9 trial shows that, when once-weekly semaglutide is used as an add-on to SGLT-2i therapy, no interaction is observed between the individual SGLT-2is and treatment effect. This indicates that the same efficacy can be expected with semaglutide, regardless of background SGLT-2i.
- Reductions in HbA_{1c} and body weight with semaglutide, compared with placebo, were significant and clinically relevant. These findings are consistent with those of previous SUSTAIN trials.[4–10]

Conclusion

- In this *post hoc* analysis of SUSTAIN 9, in subjects with T2D already receiving an SGLT-2i, semaglutide once weekly resulted in superior HbA_{1c} and body weight reductions vs placebo; effects were consistent across SGLT-2i subgroups.
- No new safety concerns were identified.

This study was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT03086330).
Presenter Bernhard Ludvik has received grants from Novo Nordisk.
The authors are grateful to Gabriel Hoppen and Fraser Harris, AXON Communications (supported by Novo Nordisk), for writing assistance.
Presented at the 55th Annual Meeting of the European Association for the Study of Diabetes, 16–20 September 2019, Barcelona, Spain.

References: (**1**) Davies MJ et al. Diabetes Care 2018;41:2669–701; (**2**) No authors listed. Diabetes Care 2019;42(Suppl 1):S1–52; (**3**) Zinman B et al. Lancet Diabetes Endocrinol 2019;7:356–67; (**4**) Sorli C et al. Lancet Diabetes Endocrinol 2017;5:251–60; (**5**) Ahrén B et al. Lancet Diabetes Endocrinol 2017;5:341–54; (**6**) Ahmann AJ et al. Diabetes Care 2018;41:258–66; (**7**) Aroda VR et al. Lancet Diabetes Endocrinol 2017;5:355–66; (**8**) Rodbard HW et al. J Clin Endocrinol Metab 2018;103:2291–301; (**9**) Marso SP et al. N Engl J Med 2016;375:1834–44; (**10**) Pratley RE et al. Lancet Diabetes Endocrinol 2018;6:275–86.

Abstract

Cost-Effectiveness of Once-Weekly Semaglutide versus Empagliflozin in People with Type 2 Diabetes and Inadequate Glycemic Control in Sweden

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grs.ly/e5abn8z

Background and aims

Background

- Once-weekly semaglutide is a glucagon-like peptide (GLP-1) analogue. It was judged as the most cost effective glucagon-like peptide-1 receptor agonist (GLP-1RA) by The Dental and Pharmaceutical Benefits Agency, TLV, and therefore gained reimbursement in Sweden in 2018.[1]
- GLP-1RAs and sodium-glucose cotransporters 2 inhibitors (SLGT-2i) are both antidiabetic agents for treatment of type 2 diabetes (T2D). Both treatment options exert their effectiveness through distinct but different physiologic, metabolic and molecular mechanisms.[2–5] (Figure 1)
- The role of increased HbA1c as a strong association for cardiovascular outcomes highlights the importance to lower HbA1c.[6,7]
- These glucose lowering treatments have been compared from an efficacy perspective, however this is the first assessment of the cost-effectiveness (CEA) of semaglutide vs. empagliflozin from a Swedish societal perspective.[8]

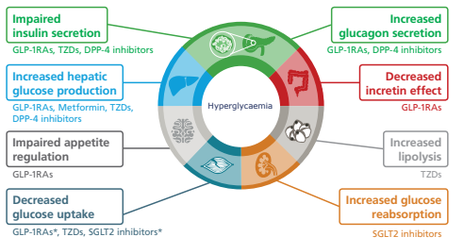
Aim

To estimate the cost-effectiveness of once-weekly semaglutide 1 mg vs. empagliflozin 25 mg in patients with T2D inadequately controlled with metformin monotherapy from a Swedish societal perspective.

Materials and methods

- This cost-effectiveness analysis (CEA) was made using the Institutet för Hälso- och Sjukvårdsekonomi (IHE) Diabetes Cohort Model.[9]
- The model is based on metabolic risk equations from the Swedish National Diabetes Register and UKPDS, and does not regard any plausible cardiovascular benefits in addition to what's already captured through changes in the traditional risk factors (including HbA1c, BMI, lipids, blood pressure, age) in these equations. Treatment effects are applied to the biomarkers (HbA1c, blood pressure, lipids and BMI) and the evolution of biomarkers and hypoglycaemia is simulated annually. The progression of the cohort between different health states is predicted by the risk equations.
- Analyses were conducted from a Swedish societal perspective spanning over 40 years.
- Input data for the analyses on the differences in HbA1c decline and weight reduction between the treatments were obtained from a published network meta-analysis investigating the differences in glycemic control between once-weekly semaglutide and once-daily empagliflozin, where semaglutide reached significantly better improvements in both endpoints.[8] (Table 1)
- Baseline patient characteristics were obtained from the SUSTAIN 7 clinical trial.[10]
- Both treatments result in decreased HbA1c, but due to the progressive nature of the disease HbA1c will eventually increase again and intensification will be needed. Data on this increase (0.14 percent units per year) were taken from the ADOPT study.[11] Treatment intensification was made in two steps – basal insulin and basal-bolus insulin – when HbA1c reached the baseline value. Insulin doses and efficacy of the treatment intensification data were obtained from a published source.[12]
- The cost of pharmaceuticals and self-monitored blood glucose tests (SMBG) were based on the pharmacy selling price (Apotekens utpris, AUP, www.TLV.se) in April 2019. The costs of long-term diabetes-related complications were identified from a literature review made for a published cost-effectiveness analysis, and adjusted to the current price level.[13]
- Baseline values of HbA1c, BMI and age were varied over a number of hypothetical sensitivity analyses to identify cost-effectiveness in different patient groups.

Figure 1: GLP-1RA, SGLT2i and other treatments target different pathophysiologic defects of T2D



Adapted from DeFronzo RA. 2009[2]; 2015[3]; 2017[4] and Ahrén B. 2017[5]
*Indirectly, weight loss enhances both muscle and hepatic sensitivity to insulin. DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium glucose co-transporter-2 inhibitor; TZD, thiazolidinedione.

Table 1: Relative treatment effects of semaglutide 1.0 mg vs. empagliflozin 25 mg[8]

	Mean difference and 95% CI
HbA1c (%)	-0.80 (-1.04, -0.58)
HbA1c (mmol/mol)	-8.5 (-11.2, -6.0)
Weight (kg)	-2.05 (-2.94, -1.15)

Results

- Our results shows that semaglutide is a cost-effective treatment option compared to empagliflozin in patients with inadequate control on metformin. (Table 2)
- Semaglutide imposed a higher total cost and more quality-adjusted life-years (QALYs) in all analyses vs. empagliflozin with a cost difference of SEK 3 300–55 700 over a 40-year perspective and a QALY gain of 0.137–0.242.
- Cost per QALY varied from SEK 16 000–407 000, where the lowest cost per QALY was found in patients with higher baseline HbA1c and lower age (Table 2), while baseline BMI did not have any significant impact on the results. A diabetes treatment is valued cost-effective in Sweden if cost per QALY is below SEK 500 000.
- Time to insulin initiation was 13 years for semaglutide and 8 years for empagliflozin, based on the initial HbA1c reduction, which was significantly higher for semaglutide as compared to empagliflozin.[8]
- Our results are largely driven by the reduction in complications due to the HbA1c decline with semaglutide compared to empagliflozin. As an example, the result including a breakdown of costs over 40 years, for the analysis with baseline values: 56 years, HbA1c 60 mmol/mol and BMI 30 is presented in Table 3.

Table 2: Cost/QALY (SEK) depending on baseline HbA1c, age and BMI

		HbA1c			
Age	BMI	55 mmol/mol (7.2%)	60 mmol/mol (7.65%)	65 mmol/mol (8.1%)	70 mmol/mol (8.55%)
56 years	28	224 000	142 000	50 000	16 000
	30	226 000	143 000	52 000	18 000
	34	232 000	148 000	56 000	23 000
66 years	28	389 000	290 000	186 000	156 000
	30	394 000	293 000	188 000	158 000
	34	407 000	302 000	193 000	162 000

(€ 1 = SEK 10.47, 19MAR2019)

Discussion

- This CEA indicates that semaglutide is a cost-effective treatment option vs. empagliflozin in patients with T2D inadequately controlled with OADs from a Swedish societal perspective.
- The results suggest that semaglutide could be initiated early to target optimal HbA1c level. Lowest cost per QALY was found in patients with higher baseline HbA1c and lower age. The reason for this is that the absolute risk for complications is higher at higher HbA1c levels, so even though the incremental difference in HbA1c between treatments is kept constant, the total number of predicted complications is increased.
- Baseline BMI had little impact on the results, indicating that it is equally cost-effective to use either semaglutide or empagliflozin in patients with baseline BMI 28 or 34.
- In this simulation model, initial cost for semaglutide is higher compared to empaglifozin, however the long term costs for microalbumuria, macroalbumuria, end stage renal disease and retinopathy are lower due to more pronounced effect on HbA1c.
- As a standard in CEA, a long-term perspective is used in order to be able to follow patients over their full life span. In T2D, this implies modelling over at least 40 years, as in this analysis. However, the last 20 years of analysis did not affect the overall conclusions.

Table 3: Results, including breakdown of costs (SEK) over 40 years, an example from the analysis with baseline values: 56 years, HbA1c 60 mmol/mol and BMI 30

	Semaglutide 1.0 mg	Empagliflozin 25 mg	Increment
QALYs	8,445	8,226	0,219
Costs			
Anti-Hyperglycaemic Treatment	174 225	97 314	76 911
Hypoglycaemia	2 355	3 032	-677
Dyslipidemia Treatment	24 367	24 287	80
Retinopathy	6 069	8 729	-2 660
Neuropathy	113 949	116 156	-2 206
Nephropathy	83 271	113 310	-30 039
IHD	41 836	42 634	-798
MI	27 874	28 748	-874
Stroke	23 330	23 744	-414
CHF	40 283	41 958	-1 675
Indirect cost	342 985	349 325	-6 340
Total Direct Costs	537 560	499 913	37 647
Total Costs	880 545	849 238	31 307
Cost/QALY			
Health care perspective	-	-	172 020
Societal Perspective	-	-	143 051

(€ 1 = SEK 10.47, 19MAR2019)

Conclusion

Using modelling based on metabolic risk equations, semaglutide was cost-effective in all subgroups analysed, while the lowest cost per QALY was found in patients with higher baseline HbA1c and lower age.

The study was sponsored by Novo Nordisk. Presenter Magnus Löndahl has received grant support, lecture fees or advisory board fees from Abbott, Amgen, AstraZeneca, Boehringer-Ingelheim, Merch Sharp & Dome, Novo Nordisk, ReApplix AS, Rubin Medical and Sanofi. Presented at EASD, 17th of September 2019, Barcelona, Spain.

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Abstract

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Oral semaglutide reduces appetite and energy intake and improves control of eating in subjects with type 2 diabetes

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https://qrs.ly/qjabn92

Background and aims

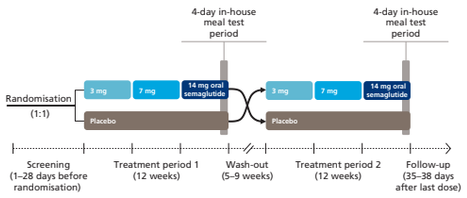
- Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue that has previously been shown to increase fullness, and reduce hunger and energy intake in subjects with obesity after subcutaneous administration.[1]
- An oral formulation of semaglutide has been developed, in which semaglutide is co-formulated with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC).[2]
- This trial was conducted to evaluate the extent to which oral semaglutide affects appetite and energy intake in subjects with type 2 diabetes (T2D).

Materials and methods

Trial design

- Phase 1, placebo-controlled, double-blind, two-period crossover trial conducted at a single site in the UK.
- There were two treatment periods (Figure 1); after the first 12 weeks of treatment, subjects crossed over to whichever treatment they did not previously receive for a further 12 weeks.
- At the end of each treatment period was a 4-day in-house meal test period, during which subjects received a standardised breakfast (standard on day 2, fat-rich on day 4), lunch and evening meal (both *ad libitum* on day 2), and *ad libitum* evening snack box on day 2.

Figure 1 Trial design.



Eligibility criteria

- Male or female, aged 18–75 years, T2D ≥90 days, treated with diet and exercise and/or stable dose of metformin ≥30 days, HbA_{1c} 6.0–9.0%, body mass index 20–38 kg/m², and stable body weight (<3 kg body weight change during 3 months prior to screening).

Assessments

- Appetite and palatability ratings were measured using a 100 mm visual analogue scale (VAS)[3] on days 2 and 4 of the standardised meal test periods.
- Control of eating and cravings were evaluated using the Control of Eating Questionnaire (CoEQ)[4] on day 3 of the standardised meal test periods.
- Changes in body weight and composition were assessed by air displacement plethysmography in both treatment periods; data are reported for treatment period 1 only, due to a possible rebound effect in subjects crossing-over from oral semaglutide to placebo.

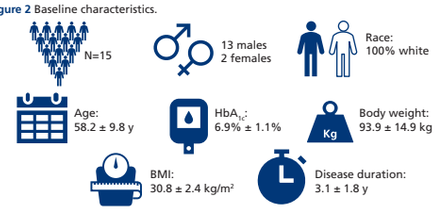
Statistical analysis

- The difference between oral semaglutide and placebo for each outcome was estimated together with the corresponding two-sided 95% confidence interval (CI) and P value for the test of no difference.
- Safety endpoints (adverse events [AE]) were analysed descriptively.

Results

- Fifty-three subjects were screened, of whom 15 were enrolled; two subjects withdrew before the end of the trial. Baseline characteristics are shown in Figure 2.

Figure 2 Baseline characteristics.



Data are mean ± standard deviation unless otherwise stated. BMI, body mass index.

Energy intake

- ***Ad libitum* energy intake** was lower when receiving oral semaglutide vs placebo at each meal, leading to a **38.9% lower total daily energy intake** (Figure 3).

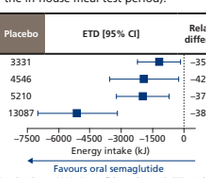
Appetite and palatability

- There were **no significant differences** between treatments in **overall appetite** ratings pre-meal (in a fasting state) or during the standard breakfast (data not shown).
- After the fat-rich breakfast, there were **statistically significant differences** in favour of oral semaglutide vs placebo for the **mean postprandial overall appetite score** as well as all four individual mean postprandial ratings of appetite (satiety, fullness, hunger and prospective food consumption; Figure 4).
  - **Mean postprandial increment for fullness** after a fat-rich breakfast was **significantly greater** during treatment with oral semaglutide vs placebo.
- **Palatability** (taste, visual appearance and overall pleasantness) of the standard breakfast, *ad libitum* lunch and evening meal, and evening snack box appeared **similar** for oral semaglutide and placebo.
- No mean VAS scores of <50 mm were reported for palatability with either treatment, indicating **no food aversion**.

Figure 3 *Ad libitum* energy intake (*ad libitum* meals [lunch, evening meal and snack box] on day 2 of the in-house meal test period).

Key results

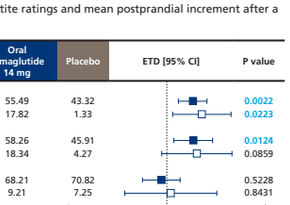
Energy intake, kJ	Oral semaglutide 14 mg	Placebo	ETD [95% CI]	Relative difference	P value
Lunch meal	2133	3331		–35.9%	0.0257
Evening meal	2620	4546		–42.4%	0.0263
Snack box	3237	5210		–37.9%	0.0058
Total daily intake	7991	13087		–38.9%	0.0001



Relative difference: ETD / estimated mean for placebo x 100%. CI, confidence interval; ETD, estimated treatment difference.

Figure 4 Mean postprandial appetite ratings and mean postprandial increment after a fat-rich breakfast.

Parameter, VAS (mm)	Oral semaglutide 14 mg	Placebo	ETD [95% CI]	P value
Fullness				
Mean postprandial rating	55.49	43.32		0.0022
Mean postprandial increment	17.82	1.33		0.0223
Satiety				
Mean postprandial rating	58.26	45.91		0.0124
Mean postprandial increment	18.34	4.27		0.0859
Well-being				
Mean postprandial rating	68.21	70.82		0.5228
Mean postprandial increment	9.21	7.25		0.8431
Hunger				
Mean postprandial rating	31.99	45.26		0.0133
Mean postprandial increment	–3.69	8.42		0.1894
Prospective food consumption				
Mean postprandial rating	42.05	52.98		0.0414
Mean postprandial increment	–3.32	–2.27		0.9157
Overall appetite score				
Mean postprandial rating	40.07	52.27		0.0059
Mean postprandial increment	–10.79	0.15		0.0722
Thirst				
Mean postprandial rating	37.88	39.80		0.5362
Mean postprandial increment	–2.13	–6.75		0.4830
Nausea				
Mean postprandial rating	10.91	5.78		0.1059
Mean postprandial increment	–12.90	–0.88		0.1322



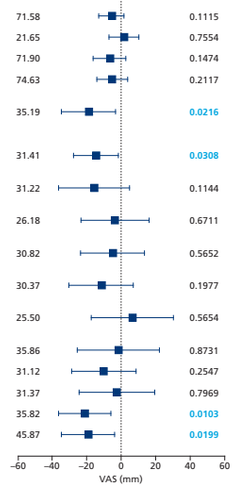
Mean postprandial rating = $AUC_{15-480min}$ / 465 minutes (postprandial time span). Mean postprandial increment = $iAUC_{15-480min}$ / 465 minutes (postprandial time span). Overall appetite score = ([100-satiety] + [100-fullness] + hunger + prospective food consumption) / 4. AUC, area under the curve; CI, confidence interval; ETD, estimated treatment difference; iAUC, incremental area under the curve; VAS, visual analogue scale.

Control of eating and cravings

- Control of eating (evaluated with the CoEQ) assessed after a standard breakfast indicated **fewer food cravings**, **better control** of eating and **less difficulty resisting food** when receiving oral semaglutide vs placebo (Figure 5).

Figure 5 Control of Eating Questionnaire scores.

CoEQ item*, VAS (mm)	Oral semaglutide 14 mg	Placebo	ETD [95% CI]	P value
1. How hungry have you felt?	29.59	41.24		0.0618
2. How full have you felt?	68.07	62.22		0.4983
3. How strong was your desire to eat sweet foods?	29.67	45.60		0.0862
4. How strong was your desire to eat savoury (non-sweet) foods?	35.70	37.50		0.8215
5. How happy have you felt?	65.83	71.58		0.1115
6. How anxious have you felt?	22.91	21.65		0.7554
7. How alert have you felt?	65.10	71.90		0.1474
8. How contented have you felt?	69.32	74.63		0.2117
9. During the last 7 days how often have you had food cravings?	15.94	35.19		0.0216
10. How strong have any food cravings been?	16.64	31.41		0.0308
11. How difficult has it been to resist any food cravings?	15.23	31.22		0.1144
12. How often have you eaten in response to food cravings?	22.27	26.18		0.6711
13. Cravings for chocolate or chocolate flavoured foods	25.89	30.82		0.5652
14. Cravings for other sweet foods	18.60	30.37		0.1977
15. Cravings for fruit or fruit juice	31.92	25.50		0.5654
16. Cravings for dairy foods	34.07	35.86		0.8731
17. Cravings for starchy foods	20.87	31.12		0.2547
18. Cravings for savoury foods	28.76	31.37		0.7969
19. Difficulty in controlling eating	14.66	35.82		0.0103
21. Difficulty in resisting this food during last 7 days	26.52	45.87		0.0199



*Question 20 was open-ended and thus not rated using the VAS. CI, confidence interval; CoEQ, Control of Eating Questionnaire; ETD, estimated treatment difference; VAS, visual analogue scale.

Body weight and composition

- For subjects who received oral semaglutide in treatment period 1, a rebound in body weight was observed during the wash-out period.
- Weight loss with oral semaglutide was due to a **reduction in whole body fat mass**; whole body lean mass was not substantially affected (Table 1).

Table 1 Change from baseline in body composition at the end of treatment period 1.

	Oral semaglutide 14 mg		Placebo	
	N	Mean ± SD	N	Mean ± SD
Whole body fat mass, kg	7	–2.7 ± 2.5	7	–1.2 ± 3.0
Whole body lean mass, kg	7	–0.2 ± 2.3	7	0.0 ± 1.1
Fat percentage, %	7	–2.0 ± 2.0	7	–0.9 ± 2.4
Body weight, kg	7	–2.9 ± 4.2	7	–1.2 ± 3.1

SD, standard deviation.

Safety

- **More AEs** were reported in subjects when receiving oral semaglutide vs placebo (93 events in 14 [93.3%] subjects vs 51 events in 13 [92.9%] subjects, respectively).
- Typical of the GLP-1 receptor agonist class, **gastrointestinal AEs** were most frequently reported.
- Most AEs during oral semaglutide treatment were considered possibly related to trial product.
- There was **one serious AE** (acute myocardial infarction) during oral semaglutide treatment, considered possibly related to trial product and leading to withdrawal. This serious AE was severe; all other AEs reported were of mild or moderate severity. **No deaths** were reported.

Conclusions

***Ad libitum* energy intake** throughout the day was **lower** during treatment with oral semaglutide vs placebo, resulting in a **greater reduction in body weight** after 12 weeks of treatment, mainly driven by a reduction in whole body fat mass.

Hunger was reduced, and satiety and fullness increased during treatment with oral semaglutide vs placebo after a fat-rich breakfast, whereas there was no difference in appetite after a standard breakfast.

Control of eating was improved during treatment with oral semaglutide compared with placebo. This did not appear to be related to increased food aversion.

This trial was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT02773381).
The authors acknowledge the medical writing assistance of Sophie Walton of Spirit Medical Communications Group Ltd.
Presented at the 55th Annual Meeting of the European Association for the Study of Diabetes (EASD), Barcelona, Spain, 16–20 September 2019.

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Abstract

Poster presentation 777

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Background and aims

- Semaglutide is a glucagon-like peptide-1 analogue formulated both as an approved once-weekly subcutaneous (s.c.) injection and a once-daily oral tablet in development for the treatment of type 2 diabetes (T2D).[1,2]
- The s.c. and oral formulations have been studied across a series of clinical trials in the SUSTAIN and PIONEER programmes, respectively.[3–12]
- The long half-life and daily dosing with oral semaglutide mitigate variability in absorption, leading to stable steady-state exposure levels. Nevertheless, the plasma concentrations are more variable with oral compared with s.c. administration.[1]
- Using population data from the SUSTAIN and PIONEER trials, we analysed whether the route of administration affected the efficacy and gastrointestinal (GI) tolerability vs exposure for semaglutide.

Materials and methods

Population data

- Response data were compared from:
  - Four trials (SUSTAIN 1, 2, 3 and SUSTAIN-Japan) of once-weekly s.c. semaglutide 0.5 and 1.0 mg evaluated after 30 weeks.[3–6]
  - Six trials (PIONEER 1, 2, 3, 5, 8 and 9 [PIONEER 9 conducted in Japan]) of once-daily oral semaglutide 3, 7 or 14 mg given for 26 weeks.[7–12]

Population pharmacokinetic model

- A population pharmacokinetic (PK) model was developed for each PIONEER and SUSTAIN dataset.[13]

Exposure–response models for efficacy and tolerability

- For HbA_{1c} and body weight change from baseline, the data were adequately described by maximum response (E_{max}) models with baseline HbA_{1c}, sex and trial population as main influential factors, and additional effects of diabetes duration, race and ethnicity.
- For binary safety endpoints (proportions of patients with nausea and vomiting, respectively), linear models on the logit scale were used. The main influential factors were sex and trial population.

Propensity score matching

- Overall the PIONEER and SUSTAIN exposure–response populations were similar, with the main difference being the inclusion of a dedicated study of patients with moderate renal impairment and a trial with concomitant insulin treatment in the PIONEER programme.
- Propensity score matching was used to analyse the effect of balancing the differences between the SUSTAIN and PIONEER populations based on baseline HbA_{1c}, trial population, diabetes duration, race, ethnicity and sex (Figure 1).

Results

- Before matching, data from 1552 patients from SUSTAIN and 3003 patients from PIONEER were included. After matching, both datasets contained 1551 patients with well-matched characteristics, although the SUSTAIN population contained more Asian patients and more patients with mild renal impairment (Table 1).
- Population PK analysis indicated dose-proportional PK profiles for both oral and s.c. semaglutide, with body weight the main factor influencing exposure.
- The exposure range was wider with oral vs s.c. administration, but with considerable overlap between oral semaglutide 7 and 14 mg, and s.c. semaglutide 0.5 and 1.0 mg, indicating consistent exposure across formulations.
- Exposure–response analyses showed greater HbA_{1c} and body weight reductions, and more GI side effects, with increasing semaglutide exposure.
- Exposure–response relationships for efficacy and safety were consistent across the SUSTAIN and PIONEER datasets, and even more consistent with overlapping 95% confidence intervals when propensity matching was used (Figure 2 and key result panel).

Conclusions

Oral and s.c. semaglutide have **consistent efficacy and GI safety profiles** vs exposure

Propensity matching helped to confirm that **the differences between trial populations did not influence** the exposure–response evaluation

Increasing semaglutide exposure is associated with **greater efficacy** and **an increased proportion of patients reporting GI side effects**

These trials were sponsored by Novo Nordisk and are registered with ClinicalTrials.gov (NCT02054897 [SUSTAIN 1], NCT01930188 [SUSTAIN 2], NCT01885208 [SUSTAIN 3], NCT02254291 [SUSTAIN-Japan], NCT02906930 [PIONEER 1], NCT02863328 [PIONEER 2], NCT02607865 [PIONEER 3], NCT02827708 [PIONEER 5], NCT03021187 [PIONEER 8], NCT03018028 [PIONEER 9]).
The authors acknowledge the medical writing assistance of Stephen Purver of Spirit Medical Communications Group Ltd.
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https://qrs.ly/qjabn92

Similar efficacy and gastrointestinal tolerability versus exposure for oral and subcutaneous semaglutide

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Novo Nordisk A/S, Søborg, Denmark

Key results

Change from baseline in HbA_{1c} in the propensity score matched population.

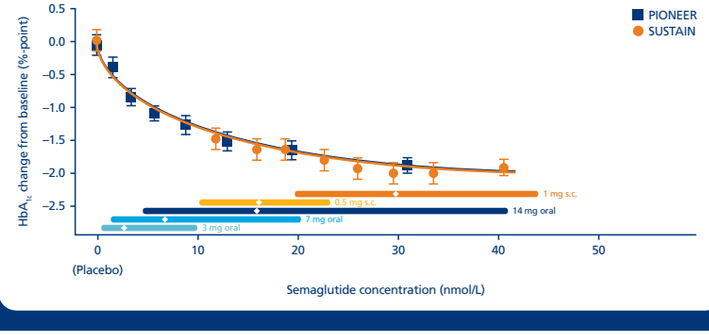


Figure 1 Propensity score matching – illustrative principle.

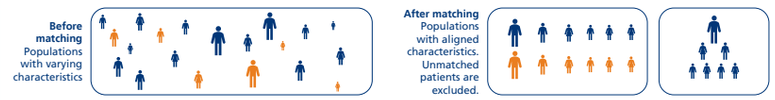
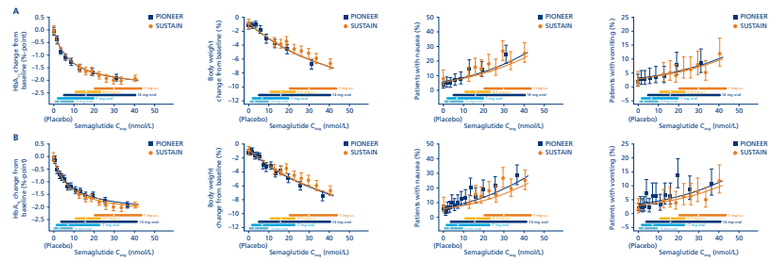


Figure 2 Efficacy and GI side effects by semaglutide exposure: **A**, propensity score matched populations; **B**, unmatched populations.



Data (circles and squares) are means and 95% CIs at week 26 for PIONEER and week 30 for SUSTAIN. Exposure is presented as ten quantiles of C_{avg} for semaglutide and one quantile for placebo (at C_{avg} of 0 nmol/L). The fitted solid line represents covariate-adjusted, model-derived relations for each programme. The horizontal lines along the x-axes represent medians and 90% exposure ranges with the median exposure represented by a diamond. Data from SUSTAIN 1, 2, 3, SUSTAIN-Japan and PIONEER 1, 2, 3, 5, 8 and 9. C_{avg}, median semaglutide concentration; CI, confidence interval; GI, gastrointestinal; HbA_{1c}, glycated haemoglobin; s.c., subcutaneous.

Table 1 Patient baseline characteristics.

Category		PIONEER		SUSTAIN (N=1551)
		Unmatched (N=3003)	Matched (N=1551)	
Age, years		59.4 (10.9)	57.3 (10.5)	56.0 (10.6)
Female		1345 (44.8)	653 (42.1)	658 (42.4)
Race				
White, other		2034 (67.7)	971 (62.6)	834 (53.8)
Asian		779 (25.9)	487 (31.4)	647 (41.7)
Black or African American		190 (6.3)	93 (6.0)	70 (4.5)
Renal function				
Normal		1809 (60.2)	1099 (70.9)	1024 (66.0)
Mild impairment		865 (28.8)	415 (26.8)	502 (32.4)
Moderate impairment		329 (11.0)	37 (2.4)	25 (1.6)
HbA_{1c}, %		8.1 ± 0.8	8.1 ± 0.9	8.1 ± 0.9
Body weight, kg		88.2 ± 21.9	87.2 ± 22.4	86.3 ± 22.7
Diabetes duration, years		9.5 ± 7.9	7.3 ± 6.3	7.2 ± 6.0
Background therapy				
1–2 OADs		1335 (44.5)	994 (64.1)	1077 (69.4)
Monotherapy		703 (23.4)	431 (27.8)	345 (22.2)
Insulin		845 (28.1)	12 (0.8)	–
Diet and exercise		120 (4.0)	114 (7.4)	129 (8.3)
Maintenance dose				
Placebo		572 (19.0)	191 (12.3)	129 (8.3)
0.5 mg s.c.		–	–	556 (35.8)
1.0 mg s.c.		–	–	866 (55.8)
3 mg oral		629 (20.9)	345 (22.2)	–
7 mg oral		620 (20.6)	331 (21.3)	–
14 mg oral		1182 (39.4)	684 (44.1)	–

Data are n (%) or mean ± SD. HbA_{1c}, glycated haemoglobin; OAD, oral antidiabetic drug; s.c., subcutaneous; SD, standard deviation.

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Abstract

795

Improved insulin adherence after introduction of a smart connected insulin pen

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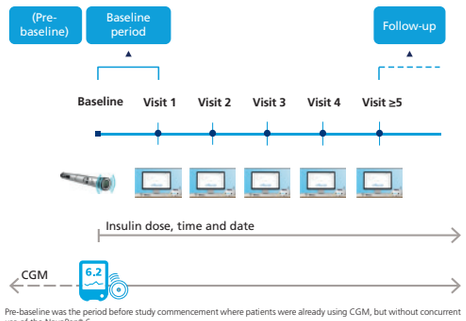
qrs.ly/jdabn99

Background

- The association between missed insulin injections and the impact on HbA_{1c} levels in insulin-dependent diabetes is well established, with the unwanted effect of increasing the risk of diabetes-related complications.[1–4]
- The smart connected NovoPen® 6 collects and stores data on the date and time of insulin injections and the number of units administered. These data are then downloaded using near field connectivity to a centralised database. This allows healthcare professionals (HCPs) and patients to look at injection data together when discussing insulin treatment. If the injection data are further combined with glucose/continuous glucose monitoring (CGM) data the potential to improve patient-HCP dialogue is thought to be even greater.
- The possibility to have a combined view of insulin injections and CGM data and the potential for improved dialogue between patients and HCPs can eliminate any guessing about doses taken, missed doses and optimal injection time in relation to meals.
- An engaging and open patient-HCP dialogue has been identified as highly important for optimal disease management, and could reduce the number of missed insulin injections to improve treatment adherence.[5,6] It is therefore of interest to assess whether use of the NovoPen® 6 can reduce the number of missed injections in everyday clinical use.

Figure 1: Study design

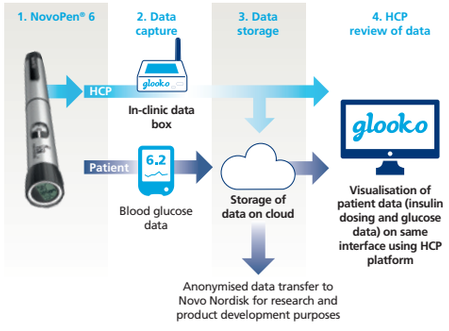


Pre-baseline was the period before study commencement where patients were already using CGM, but without concurrent use of the NovoPen® 6.
CGM, continuous glucose monitoring.

Aim

- To investigate whether the use of NovoPen® 6 can influence the behaviour of patients with type 1 diabetes (T1D) in terms of change in numbers of missed bolus dose (MBD) injections.

Figure 2: Using NovoPen® 6 with the Glooko/Diasend® system

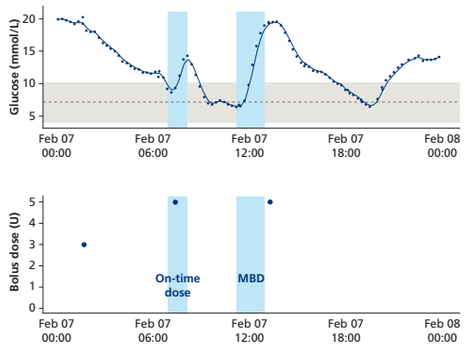


HCP, healthcare professional.

Methods

- This pilot study was a prospective, non-interventional study running from May 2017–Nov 2018. Twelve diabetes clinics from different parts of Sweden participated. Patients with T1D using CGM were included if their treating physicians decided to offer them a NovoPen® 6.
- At baseline, patients received a NovoPen® 6 for basal and/or bolus insulin injections. Baseline was then followed by a baseline period between pen introduction and visit 1, during which the patient started to use the NovoPen® 6 but without access to downloads of injection data. The first data download occurred at visit 1, using the Glooko/Diasend® in-clinic system to transfer data from the pen to the Glooko/Diasend® server. From here the data were accessed via the Glooko/Diasend® HCP web portal and the patient and HCP had the first chance to look at the data together.
- Hereafter, the study continued with HCP visits according to clinical practice. At each visit, pen data were available for download and use by the patient and HCP during the consultation (Figures 1 and 2).
- With this study design, it was possible to compare the number of MBD injections between the baseline and follow-up periods. CGM and dosing data from the first 14 days following a clinic visit were used in the analyses. The 14-day time period was chosen to be in line with the international consensus on the use of CGM.[7] Visit 5 was chosen as the earliest point for follow-up, as patients would on average have been in the study for ≥180 days, allowing for sufficient interaction with HCPs and discussion of available pen data.
- MBDs were identified using the clinically validated Glucose Rate Increase Detector (GRID) algorithm[8] to detect meals from the CGM signal. An MBD was defined as an occasion where no bolus injection had occurred within −15 to +60 minutes from the start of a meal, as detected by the algorithm (Figure 3).

Figure 3: Detection of missed bolus insulin doses by the GRID algorithm



Example of a day with two meals detected. The solid dark blue line represents the CGM signal and the light blue shaded areas each represent a detected meal. The grey dashed line represents a glucose level of 7.2 mmol/L and the grey shaded area represents a target glycaemic range of 3.9–10.0 mmol/L, as previously reported.[8] Meals are detected when the CGM signal is ≥7.2 mmol/L and increases steeply over 30–45 minutes. A bolus dose within 15 minutes before to 60 minutes after a meal starts is considered 'on-time', whereas a dose outside of this time window is considered an MBD. Male patient, aged 30 at baseline.
CGM, continuous glucose monitoring; GRID, Glucose Rate Increase Detector; MBD, missed bolus dose.

Statistical analyses

- Pen and CGM data for each patient were linked based on patient IDs. Data from days with unacceptable CGM coverage (<70%) or where bolus injections were not available, were excluded.
- Each day was aggregated to the number of MBD meals, the number of on-time meals and total number of meals.
- A generalised linear mixed model based on the Poisson distribution was applied with visit number (baseline, 1, 2, 3, 4, 5+) as fixed effect and patient and visit nested within patient as random effects. The model allows for unbalanced and missing data.
- The estimated difference between the follow-up period (visits ≥5) and the baseline period was obtained on the logarithmic-scale. Estimates and 95% confidence intervals were converted to the original scale.

Results

- Eighty-one adults with T1D with a mean [min; max] age of 39.2 years [18; 83] were included in these analyses. A total of 1892 days were analysed.
- A significant decrease of 43.1% in the average daily number of MBD injections was observed from the baseline period to the follow-up period, from 0.74 (95% CI [0.62; 0.88]) to 0.42 (95% CI [0.30; 0.60]) (p=0.002) (Figure 4 and Table 1).
- Based on the assumption that patients have three main meals per day, this corresponded to a decrease from 24.7% (95% CI [20.8; 29.4]) to 14.1% (95% CI [9.9; 19.9]) in MBD injections (Table 1).

Table 1: Mean number of daily meals and dosing behaviours from the baseline period to the follow-up period

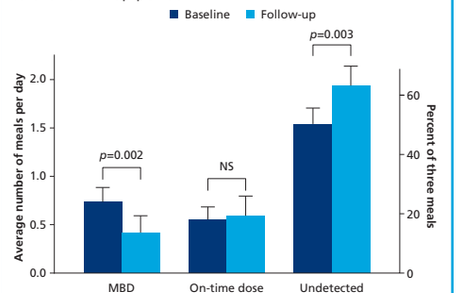
	Estimated relative change [95% CI]	Baseline level [95% CI]		Follow-up level [95% CI]		*P* value
		Daily meals (n)	Proportion of 3 meals	Daily meals (n)	Proportion of 3 meals	
MBD	–43.1% [–60.5; –18.0]	0.74 [0.62; 0.88]	24.7% [20.8; 29.4]	0.42 [0.30; 0.60]	14.1% [9.9; 19.9]	0.002
On-time dose	2.7% [–24.7; 40.2]	0.57 [0.48; 0.69]	19.1% [15.9; 23.0]	0.59 [0.43; 0.80]	19.6% [14.5; 26.7]	0.865
Undetected meals*	25.4% [8.7; 43.5]	1.54 [1.37; 1.70]	51.5% [45.6; 56.7]	1.94 [1.69; 2.14]	64.6% [56.4; 71.2]	0.003

Mean and 95% CI based on a mixed Poisson model, with visit number (baseline, 1, 2, 3, 4, 5+) as fixed effect and patient and visit nested in patient as random effects.
*Assuming 3 meals per day on average. CI, confidence interval; MBD, missed bolus dose; n, number.

- A significant increase in the number of daily, undetected meals was observed from the baseline period to the follow-up period, from 1.54 (95% CI [1.37; 1.70]) to 1.94 (95% CI [1.69; 2.14]) (Figure 4 and Table 1).
- These results indicate that patients achieved more well-dosed meals, as indicated by the slight increase in the number of on-time doses observed in the follow-up period compared with the baseline period (Table 1). The increase was not statistically significant, however, because well-dosed meals tend to have a lower CGM response and are as such undetected by the GRID algorithm (Figure 3).

Figure 4: Mean number of daily meals and dosing behaviours from the baseline period to the follow-up period

Key result



Estimated mean number of daily meals with 95% confidence intervals. MBD are meals with missed bolus doses. On-time doses are meals where a bolus dose is taken. Undetected are meals that are not detected by the CGM signal, assuming an average of three meals per day.
CGM, continuous glucose monitoring; MBD, missed bolus dose; NS, not significant.

Conclusions

- These real-world findings confirm that missed bolus dose injections are the reality for patients with T1D and that the smart connected NovoPen® 6 can support good injection behaviour, with fewer missed and more well-dosed mealtime injections.
- This could subsequently lead to better glycaemic control and thus lower the risk of diabetes-related complications.

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Presenter Niels Vaever Hartvig is an employee of, and holds stocks and/or shares in, Novo Nordisk A/S.
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Presented at the European Association for the Study of Diabetes, 55th Annual Meeting.
September 16–20, 2019, Barcelona, Spain.

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Abstract

Poster presentation 796

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Increased time in range observed after introduction of a connected insulin pen

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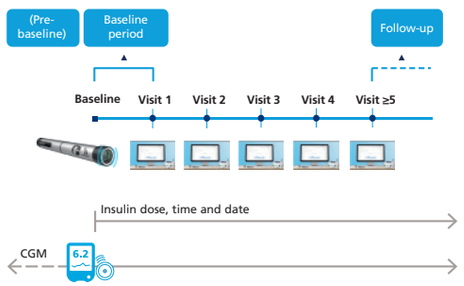
qrs.ly/jdabn99

Background

- Insulin pens have become the most widely used devices for delivering insulin. Despite their convenience, however, there are shortcomings. In particular, poor documentation of insulin therapy can result in inadequate glycaemic control for patients with diabetes. Smart insulin pens offer automatic access to insulin injection data, and could help overcome barriers of poor adherence, clinical inertia and incorrect dosing.[1]
- The smart connected NovoPen® 6 collects and stores data on the date and time of insulin injections and the number of units administered. These data are then downloaded using near field connectivity to a centralised database. This allows healthcare professionals (HCPs) and patients to look at injection data together when discussing insulin treatment. If the injection data are further combined with glucose/continuous glucose monitoring (CGM) data the potential to improve patient-HCP dialogue is thought to be even greater.
- The possibility to have a combined view of insulin injections and CGM data gives the HCP and the patient a more complete picture of current glycaemic status. Thus, both patient-HCP dialogue and treatment approaches can be improved.
- An engaging and open patient-HCP dialogue has been identified as highly important for optimal disease management. Therefore, the NovoPen® 6 has the potential to improve glycaemic control.[2,3]

Figure 1: Study design

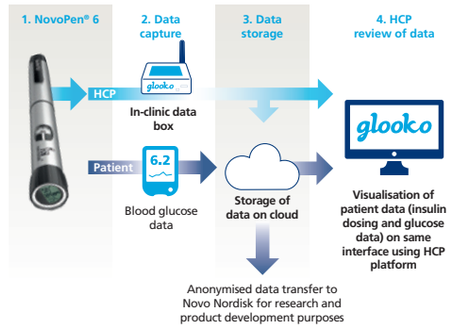


Pre-baseline was the period before study commencement where patients were already using CGM, but without concurrent use of the NovoPen® 6.
CGM, continuous glucose monitoring.

Aim

- The objective of this non-interventional study was to investigate how a smart connected insulin pen (NovoPen® 6) influences glycaemic control in patients with type 1 diabetes (T1D) in a real world setting.

Figure 2: Using NovoPen® 6 with the Glooko/Diasend® system



HCP, healthcare professional.

Methods

- This pilot study was a prospective, non-interventional study running from May 2017–Nov 2018. Twelve diabetes clinics from different parts of Sweden participated. Patients with T1D using CGM were included if their treating physicians decided to offer them a NovoPen® 6.
- At baseline, patients received a NovoPen® 6 for basal and/or bolus insulin injections. Baseline was then followed by a baseline period between pen introduction and visit 1, during which the patient started to use the NovoPen® 6 but without access to downloads of injection data. The first data download occurred at visit 1, using the Glooko/Diasend® in-clinic system to transfer data from the pen to the Glooko/Diasend® server. From here the data were accessed via the Glooko/Diasend® HCP web portal and the patient and HCP had the first chance to look at the data together.
- Hereafter, the study continued with HCP visits according to clinical practice. At each visit, pen data were available for download and use by the patient and HCP during the consultation (Figures 1 and 2).
- This study design permitted comparison between the baseline and follow-up periods. CGM and dosing data from the first 14 days following a clinic visit were used in the analyses. The 14-day period was chosen to be in line with the international consensus on the use of CGM.[4] Visit 5 was chosen as the earliest point for follow-up, as patients would on average have been in the study for ≥180 days, allowing for sufficient interaction with HCPs and discussion of available pen data. Time in range (TIR), time spent in hyperglycaemia and time spent in L1 (3.0–<3.9 mmol/L) and L2 hypoglycaemia (<3.0 mmol/L) were compared between the baseline and follow-up periods, which was defined as any point after the fifth HCP visit.

Table 1: Baseline levels and estimated changes to follow up of key glycaemic parameters

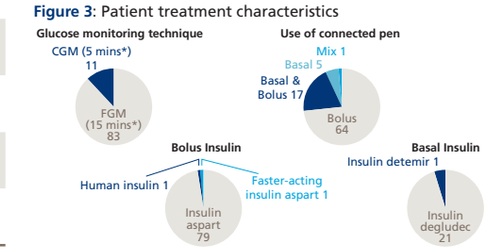
	Baseline level [95% CI]	Estimated mean change [95% CI]	*p*-value
TIR (3.9–10.0 mmol/L) (hours)	9.19 [8.28; 10.10]	1.89 [0.79; 2.99]	0.0009
TIHyper (>10.0 mmol/L) (hours)	11.80 [10.81; 12.79]	–1.78 [–2.96; –0.60]	0.003
TIHypo L1 (3.0–<3.9 mmol/L) (hours)	0.69 [0.55; 0.83]	–0.15 [–0.36; 0.07]	0.181
TIHypo L2 (<3.0 mmol/L) (hours)	0.47 [0.32; 0.61]	–0.33 [–0.56; –0.10]	0.005
Mean glucose (mmol/L)	11.09 [10.53; 11.64]	–0.34 [–0.96; 0.28]	0.279
Coefficient of variation (%)	35.89 [34.33; 37.45]	–3.84 [–6.12; –1.56]	0.001

Estimated mean baseline level and change between the follow-up period (visits ≥5) and the baseline period with 95% CI. Linear mixed model, with visit number (baseline, 1, 2, 3, 4, 5+) as fixed effect, patient and visit nested in patient as random effects, and with exponential covariance function. N=94, visits=231, CGM days=2552.
CGM, continuous glucose monitoring; CI, confidence interval; TIR, time in range; TIHyper, time in hyperglycaemia; TIHypo L1, time in L1 hypoglycaemia; TIHypo L2, time in L2 hypoglycaemia.

Results

- Ninety-four adults with T1D with a mean [min; max] age of 40.1 years [18; 83] were included in the analyses. A total of 64 patients used NovoPen® 6 for bolus insulin only, 17 for basal and bolus insulin and 5 for basal insulin only. For the majority, insulin degludec was the basal insulin and insulin aspart was the bolus insulin. Seven patients did not have connected pen data in the 14-day periods studied and 1 patient used biphasic insulin aspart 30, neither bolus nor basal insulin (Figure 3).
- A significant increase of 1.9 hours per day (~21% of the baseline level) in mean TIR from the baseline period to the follow-up period was observed (p=0.0009; Figure 4 and Table 1).
- Accordingly, a significant reduction in mean time spent in hyperglycaemia (>10.0 mmol/L) and L2 hypoglycaemia (<3.0 mmol/L) of –1.8 hours per day (p=0.003) and –0.3 hours per day (p=0.005), respectively, was also observed (Figure 4 and Table 1).
- There was no significant change in mean time spent in L1 hypoglycaemia (3.0–<3.9 mmol/L; p=0.181; Figure 4 and Table 1).
- While the mean glucose level did not change significantly, the coefficient of variation was reduced by 3.8% from the initial level of 35.9% (Table 1). This shows that the improved TIR is obtained primarily by more stable glucose levels over the day.
- In terms of bolus insulin dose (n=81), a significant increase from the baseline period to the follow-up period of 28%, to a dose of 32.1 U/day was observed. There was no significant change in mean basal insulin dose (n=22).

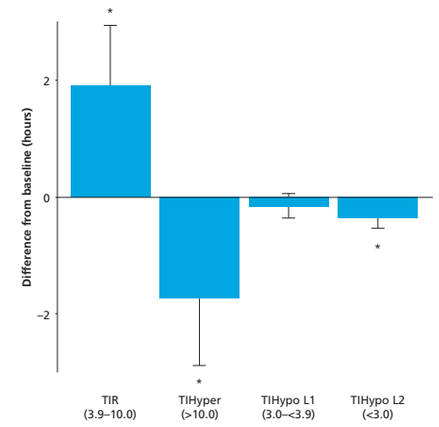
Figure 3: Patient treatment characteristics



*Interval between CGM readings. Numbers indicate numbers of patients. Seven patients did not have connected pen data at any of the CGM days studied. One patient used biphasic insulin aspart 30 that is neither considered bolus nor basal insulin in the analysis.
CGM, continuous glucose monitoring, FGM, flash glucose monitoring.

Figure 4: Mean difference in the time spent in glycaemic ranges from the baseline period to the follow-up period

Key result



*p<0.05. Estimated mean difference in time spent in glycaemic ranges with 95% CI. The difference is observed between the baseline period and the follow-up period (≥5 visits). Baseline is the period after treatment initation but before the first visit. Analysis is based on CGM data from a 14-day interval after each visit (≥70% coverage).
CGM, continuous glucose monitoring; CI, confidence interval; TIR, time in range; TIHyper, time in hyperglycaemia; TIHypo L1, time in L1 hypoglycaemia; TIHypo L2, time in L2 hypoglycaemia. Patients above 18 years (n=94) are included.

Conclusion

- These real-world findings in patients with T1D highlight the potential benefit to glycaemic control when connected pen data contribute to the patient-HCP dialogue.
- Patients with a smart connected pen obtained more stable CGM profiles, with more time in range and less time spent in hyperglycaemia and hypoglycaemia.

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September 16–20, 2019, Barcelona, Spain.

References: (**1**) Klonoff and Kerr. *J Diabetes Sci Technol* 2018;12:551–3; (**2**) Heisler *et al. J Gen Intern Med* 2002;17:243–52; (**3**) Ritholz *et al. Chronic Illn* 2014;10:303–13; (**4**) Danne *et al. Diabetes Care* 2017;40:1631–40.

Abstract

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Non-Severe Hypoglycemia Predicts Increased Risk of Subsequent Serious Adverse Events in Patients With Type 2 Diabetes

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Aim

- It is well-known that higher rates of non-severe hypoglycemic episodes (NSHEs) associate with a greater risk of severe hypoglycemic episodes in patients with type 1 diabetes. [1]
- We aimed to investigate whether a similar association existed in patients with type 2 diabetes (T2D).
- We also aimed to investigate the association between non-severe hypoglycemia and other adverse events: time to first Major Adverse Cardiovascular Event (MACE†), time to cardiovascular (CV) death, and time to all-cause mortality.

Methods

- We used data from the LEADER trial; a cardiovascular outcomes trial with patients randomized to either the GLP1-RA liraglutide or placebo.
- The LEADER trial included 9340 T2D patients at high risk of cardiovascular events; pre-existing CV-disease (81%) or risk factors for CV-disease (19%). [Table 1] The trial information and baseline data has previously been published in details.[2,3]
- During the total trial period of 35,563 patient years of observation (median follow-up of 3.8 years), a total of 27,933 NSHEs were registered (BS <3.1 mmol/L). There was 433 severe hypoglycemic episodes, 1,302 first 3-point-MACEs, 497 cases of CV death and 828 cases of 'all-cause mortality'.
- In this secondary analysis we explored if the annual rate of NSHEs was associated with time to first severe hypoglycemic episode, time to first MACE, time to CV-death and time to all cause mortality.
- A Cox proportional hazards model was used, adjusted for randomized treatment arm, and annual rate of NSHE as a time-dependent covariate with three levels;
  - Group A: <2 NSHEs per year (reference)
  - Group B: 2-11 NSHEs per year
  - Group C: ≥12 NSHEs per year
- The time-dependent covariate was updated at each NSHE event time. The association between NSHE and outcome is estimated with Hazard ratios (HR).
- The robustness of the results was investigated with three sensitivity analysis:

1. adjusting the primary analysis for baseline information (sex, baseline HbA_{1c}, diabetes duration, age and insulin treatment)
2. Rather than updating the time-dependent covariate at the time of each event it is updated in windows of size 100 days. The NSHE event rate at the closure of each window is used as covariate value for the following window. The HR for each value of the time-dependent covariate is used to investigate the association.
3. The first year of observation is used to categorize all patients according to group A-C. The subsequent follow-up time beyond the first year is used to investigate the association with a Cox regression model with two covariates with constant values.

- The first sensitivity analysis investigated if a high annual NSHE event rate can be moderated through selected baseline characteristics.
- The second sensitivity analysis investigated the dependence of the results toward the method of accounting for the dynamic NSHE rate. The analysis was performed with a range of window sizes.
- The third sensitivity analysis was performed to avoid the time-dependent covariate but instead categorize patients at a given follow-up time and use this as constant covariate throughout the analysis. In this analysis the number of events (severe hypoglycemia, MACE; CV-deaths) is notably reduced.

Results

- Baseline characteristics according to an exclusive A-C grouping where patients are categorized according to their highest observed annual NSHE rate is similar with regard to age, BMI and gender distribution. Patients with risk time in group C had lower baseline HbA_{1c}, longer duration of diabetes and less likely to be insulin naïve. [Table 1]

Table 1 Baseline characteristics

	Overall	Group A	Group B	Group C
N	9340	6723	1509	1101
Age, years	64.3 (7.2)	64.19 (7.26)	64.67 (7.21)	64.36 (7.02)
BMI, kg/m²	32.5 (6.3)	32.79 (6.35)	31.9 (6.01)	31.54 (6.17)
HbA1c (%)	8.7 (1.5)	8.72 (1.55)	8.73 (1.52)	8.48 (1.38)
Female sex (%)	36%	35%	36%	37%
Diabetes duration, years	12.8 (8.0)	11.9(7.6)	14.5(8.4)	16.2(8.5)
Existing CVD/CKD†(%)	81%	80%	83%	85%
CVD risk factors (%)	19%	20%	17%	15%
Insulin naive (%)	55.5%	61%	44%	36%

Table notes: Baseline characteristics for the total trial population and those experiencing a NSHE annual event rate >12 (group C), for those experiencing an annual event rate>2 but not >12 at any time during trial (group B) and for with n annual event rate <=2 during trial (group A). Due to incomplete baseline information 7 subjects were not included in the table.

Key Result

Figure 2 Hazard ratios (95% CI) for severe hypoglycemia, MACE, CV death and all-cause death by NSHE rate groups.

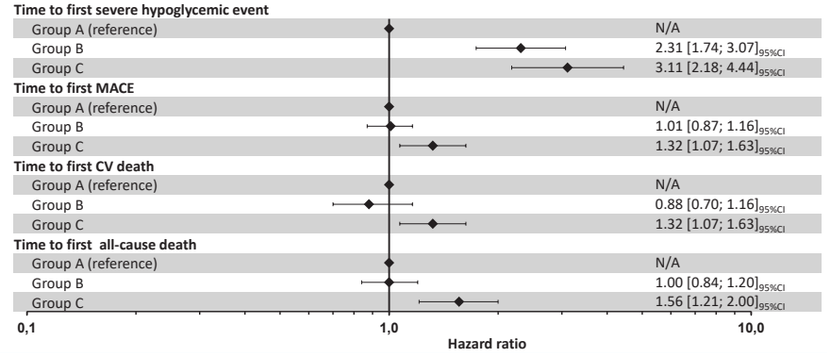
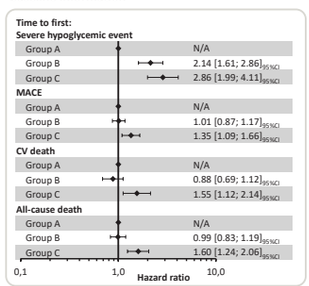
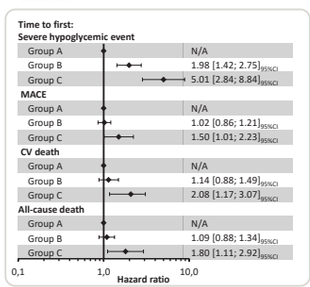


Figure 3 Sensitivity analysis (1-3)

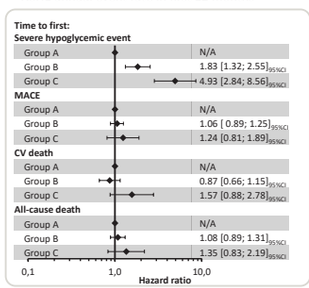
Sensitivity analysis 1: primary analysis adjusted for baseline information



Sensitivity analysis 2: 100 days of observation "windows"



Sensitivity analysis 3: Patients categorized by NSHE annual event rate in first 12 months



- Higher rates of NSHE was associated with a higher rate of severe hypoglycemia, MACE, CV death and all-cause death in patients with T2D. [Figure 2]
- For MACE, CV-death and all-cause mortality the association was driven by patients with an annual event ≥12.
- The rate for severe hypoglycemia was increased - also when the annual NSHE event rate was ≥ 2 per year.
- The sensitivity analyses support the primary findings. In the third sensitivity analysis the total number of events is notably reduced, which affects the CI but the point estimates are consistent. [Figure 3]

Discussion

- There is an increasing amount of evidence pointing to hypoglycaemia as a detrimental factor in development of complications to both type 1 and type 2 diabetes.[4]
- Previously a number of effect pathways has been demonstrated, one being that even non-severe hypoglycemia is associated with acute and persistent prothrombotic effects illustrating a possible mechanism by which hypoglycemia can increase CV risk.[5]
- Moreover secondary analysis of a number of large landmark trials has consistently shown the association between hypoglycemia and increased CV risk. [6]
- As the findings are limited to observational associations it is therefore continuously discussed if hypoglycemia is a marker or mediator of the associated CV risk.
- Our results supports the findings that there is a strong association between the rate of non-severe hypoglycemia and adverse outcomes, consistent within multiple sensitivity analysis.
- Independent of causality, reducing the risk of any hypoglycemia by lifestyle intervention or pharmacological solutions may be beneficial for any patient – including those at high CV risk.

Conclusion

- Higher rates of NSHE was associated with a higher rate of severe hypoglycemia, MACE, CV death and all-cause death in patients with T2D (Figure 2-3);
- Our results suggest that in this T2DM population, a high rate of NSHEs is associated with serious adverse events and should be avoided.

†3-point MACE (CV death, non-fatal MI, non-fatal stroke)

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Presented at the European Association for the Study of Diabetes, 55th Annual Meeting.
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References: **(1)** Kovatchev et al, Diabetes Care 21:1870-1875, 1998 **(2)** Marso et al. Am Heart J. 2013 Nov;166(5):823-30 **(3)** Marso et al. N Engl J Med 2016; 375:311-322 **(4)** International Hypoglycaemia Study Group. Lancet Diabetes Endocrinol 7:385-396, 2019 **(5)** Chow et al. Diabetes Care 41:2625-2633, 2018 (6) Bonds et al. BMJ 340:b4909, 2010

Abstract