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Paper:
Vilsbøll, T., Bain, S., Leiter , L., Lingvay, I., Matthews , D., Simó , R., Carøe Helmark , I., Wijayasinghe , N. & Larsen , M. Semaglutide, reduction in HbA1c and the risk of diabetic retinopathy. *Diabetes, Obesity and Metabolism*

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Title: Semaglutide, reduction in HbA_{1c} and the risk of diabetic retinopathy

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Short running title: Semaglutide and diabetic retinopathy

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Summary (247/250 words, not including funding statement)

Aims

To evaluate diabetic retinopathy data from across the SUSTAIN clinical trial programme.

Materials and methods

The SUSTAIN clinical trial programme evaluated the efficacy and safety of semaglutide, a glucagon-like peptide-1 analogue, for the treatment of type 2 diabetes (T2D). In SUSTAIN 6 – a 2-year, preapproval cardiovascular outcomes trial – semaglutide was associated with a significant increase in the risk of diabetic retinopathy complications (DRC) versus placebo. Diabetic retinopathy (DR) data from across the SUSTAIN trials were evaluated and *post hoc* analyses of the SUSTAIN 6 data were conducted. These included subgroup analyses to identify at-risk patients and a mediation analysis with initial change in HbA_{1c} (percentage-points at Week 16) as a covariate, to examine the role of the magnitude of reduction in HbA_{1c} as an intermediate factor on risk of DRC.

Results

There was no imbalance in DR adverse events across the SUSTAIN 1–5 and Japanese trials. The majority of the effect with semaglutide versus placebo in SUSTAIN 6 may be attributed to the magnitude and rapidity of HbA_{1c} reduction during the first 16 weeks of treatment in patients with pre-existing DR, poor glycaemic control at baseline, and treated with insulin.

Conclusions

Early worsening of DR is a known phenomenon associated with the rapidity and magnitude of improvement in glycaemic control with insulin; the DRC findings in SUSTAIN 6 are consistent with this. Guidance regarding the early worsening of DR is recommended with insulin; similar recommendations may be appropriate for semaglutide.

Funding: Novo Nordisk A/S

Introduction

Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue, with an extended half-life of approximately 1 week, in development for the treatment of type 2 diabetes (T2D).[1,2] The efficacy and safety of semaglutide has been evaluated in the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) clinical trial programme, including five global trials (SUSTAIN 1–5), two Japanese trials and one preapproval cardiovascular (CV) outcomes trial (SUSTAIN 6), and covers the continuum of T2D care. Semaglutide treatment led to significant and sustained improvements in HbA_{1c} and body weight versus placebo and active comparators across the SUSTAIN programme.[3-8] In SUSTAIN 6, semaglutide demonstrated a significant 26% risk reduction for the primary composite CV outcome versus placebo at 2 years.[8] Microvascular complications were evaluated as a secondary endpoint; a significantly lower risk of new or worsening nephropathy was reported with semaglutide versus placebo (hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.46–0.88; p=0.005). However, semaglutide was associated with a higher rate of diabetic retinopathy complications (DRC) versus placebo (HR, 1.76; 95% CI, 1.11–2.78; p=0.02).[8]

Risk factors for the development and progression of diabetic retinopathy (DR) include poor glycaemic control, long duration of diabetes and poorly controlled blood pressure.[9] The beneficial effect of long-term, stringent glycaemic control on the prevention or delay in onset or progression of DR in patients with type 1 and type 2 diabetes is established.[10-12] However, large and rapid improvements in glycaemic control may be associated with a transient worsening of DR, which in the long term can be counter-balanced by reduction in DR with improved glycaemia.[11,13] Risk factors for DR are well-recognised and should be monitored and managed in accordance with existing guidelines.[14]

This article presents how DR was evaluated, and the results obtained, across the full clinical development programme for semaglutide. Additionally, it presents new analyses that provide further insights into the DRC findings from SUSTAIN 6.

Materials and methods

The SUSTAIN 1–5 and Japanese trials assessed the efficacy and safety of subcutaneous, once-weekly semaglutide (0.5; 1.0 mg) versus placebo or active comparators in adult populations with T2D, ranging from treatment-naïve patients to those treated with insulin (**Supplementary Table 1**).[3-8] In the SUSTAIN 1–5 and Japanese trials, known proliferative retinopathy or maculopathy requiring acute treatment – according to the opinion of the investigator – were exclusion criteria, and the upper limit of HbA_{1c} was 10 or 10.5%.

SUSTAIN 6 was a 2-year CV outcomes trial, designed to assess the CV safety of once-weekly semaglutide (0.5; 1.0 mg) versus volume-matched placebo, as an add-on to standard of care.[8] The primary comparison was pooled semaglutide versus pooled placebo. Secondary microvascular outcomes included new or worsening nephropathy and DRC, both based on event adjudication committee (EAC)-confirmed events. The trial enrolled 3297 patients who, in contrast to the SUSTAIN 1–5 and Japanese trials, represented a population with advanced T2D and high CV risk.[8] Importantly, there were no inclusion/exclusion criteria related to DR, and no upper limit for HbA_{1c}.

Assessment of diabetic retinopathy across the SUSTAIN clinical trial programme

Data collection on DR (**Supplementary Table 2**) included medical history, adverse event (AE) reporting, EAC-confirmed DRC (SUSTAIN 6 only) and fundoscopy or fundus photography.

Medical history

In the SUSTAIN 1–5 and Japanese trials, history of DR was collected as part of a patient's medical history. In SUSTAIN 6, investigators completed a diabetes complications form at baseline, describing the patient's DR status by answering the following questions: does the subject have DR? (Yes/No/Unknown); if yes, what type of DR? (Non-proliferative/Proliferative/Unknown); has the patient had any of the following: macular oedema, treatment with either laser therapy/intravitreal agents, or surgery e.g. vitrectomy?

Fundoscopy/fundus photography

Fundoscopy/fundus photography was performed in all SUSTAIN trials at baseline – unless undertaken within 90 days prior to randomisation. In SUSTAIN 6, fundoscopy/fundus photography was also performed at Week 56 and 104 (planned end of treatment), or following premature discontinuation of treatment; and in the Japanese trials they were also performed at the planned end of treatment. Fundoscopy/fundus photography could be performed by the investigator, local ophthalmologist or optometrist according to local practice. However, no record of who performed the examinations or the type of assessment performed was kept. Furthermore, dilation of the pupil during these assessments was not mandatory, and thus not recorded, and fundus photographs were not centrally graded. Findings were categorised, as per the protocol, by the investigator as 'normal', 'abnormal, not clinically significant', or 'abnormal, clinically significant'. Fundoscopic data from SUSTAIN 1–5 and the Japanese trials are not presented.

Adverse event reporting

DR AEs were collected as part of the standard safety reporting of AEs in all SUSTAIN clinical trials.

EAC-confirmed diabetic retinopathy complications (SUSTAIN 6)

Time to first event of DRC was a secondary endpoint measured in SUSTAIN 6 only. The endpoint was dichotomous (Yes/No) and an event of DRC was defined as the time from randomisation to first occurrence of one or more of the following:

1. need for retinal photocoagulation
2. need for treatment with intravitreal agents
3. vitreous haemorrhage
4. onset of diabetes-related blindness, defined as a Snellen visual acuity of 20/200 [6/60] or less, or a visual field of 20 degrees or less, in the better eye with the best correction possible at the time of the event.

Criteria were not mutually exclusive; simultaneous fulfilment of more than one of the criteria was considered a single event for the DRC endpoint.

Adjudication of DRC was performed by an external EAC (two independent ophthalmologists) who were masked to treatment.

Further information was requested from the sites by Novo Nordisk after the trial completion regarding the EAC-confirmed blindness cases.

Statistical analysis

The SUSTAIN 1–5 and Japanese trials

Descriptive summaries of DR AEs were completed for the SUSTAIN 1–5 and Japanese trials.

SUSTAIN 6

Post hoc subgroup analyses were conducted for time to first EAC-confirmed DRC using unstratified Cox proportional hazards models, with an interaction between treatment (semaglutide, placebo) and subgroup variable (**Supplementary Materials 2**) as fixed factors.

The impact of insulin use during the trial on the risk of DRC was explored in an unstratified Cox proportional hazards model with an interaction between treatment (semaglutide, placebo) and insulin use during the trial as time-varying covariate (**Supplementary Materials 2**). This analysis was done by baseline DR (Yes, No, Unknown/missing).

A *post hoc* mediation analysis was conducted to evaluate the role that intermediate factors (mediators) play in describing the total effect on DRC using an unstratified Cox proportional hazards model that, in addition to treatment (semaglutide, placebo) as a fixed factor, included the following: change in HbA_{1c} at Week 16 (nadir) as a covariate, and baseline variables, HbA_{1c}, DR (Yes/No/Unknown), and duration of diabetes. This analysis was also expanded to include other baseline variables (**Supplementary Materials 2**). A similar *post hoc* mediation analysis was conducted including change in systolic blood pressure (mmHg) at Week 16 as a covariate, in substitute for HbA_{1c} (**Supplementary Materials 2**).

Results

Baseline characteristics

The baseline characteristics of patients in SUSTAIN 1–5 and Japanese trials versus SUSTAIN 6 are described in **Table 1**. The proportion of patients with DR at baseline in the SUSTAIN 1–5 and Japanese trials was 3.7–14.5%. In SUSTAIN 6, 29.4% of the trial population had known, pre-existing DR at baseline (semaglutide, 30.9%; placebo, 27.8%), and there were similar numbers of patients with proliferative DR at baseline in both treatment groups (semaglutide, 6.3%; placebo, 6.0%) (**Supplementary Table 3**).

Diabetic retinopathy adverse events

DR AEs reported in the SUSTAIN 1–5 and Japanese trials were balanced across treatments, all events were mild or moderate and there were no serious AEs (**Table 2**). In SUSTAIN 6, a greater proportion of AEs were reported in semaglutide- versus

placebo-treated patients. The majority of AEs were mild or moderate; few were reported as SAEs (**Table 2**).

Diabetic retinopathy complications in SUSTAIN 6

More patients treated with semaglutide (50 [3.0%]) versus placebo (29 [1.8%]) experienced EAC-confirmed DRC;[8] more adjudicated events were confirmed with semaglutide versus placebo for all four components of the DRC endpoint (**Supplementary Table 3**). Although 79 patients had DRC, there were 98 events in total as some patients had more than one event (**Supplementary Materials 1; Supplementary Table 4**).

Baseline characteristics of patients with diabetic retinopathy complications

Versus the overall trial population, patients with EAC-confirmed DRC were characterised by pre-existing DR, a longer mean diabetes duration, higher mean HbA_{1c} levels at baseline and greater proportions of patients receiving insulin treatment at trial entry (**Supplementary Table 3**).

A greater proportion of patients with DRC had pre-existing DR at baseline versus the overall trial population (66 [83.5%] versus 969 [29.4%], respectively; 23 [29.1%] versus 202 [6.1%] with proliferative DR, and 14 [17.7%] versus 112 [3.4%] of these had received laser therapy or treatment with intravitreal agents prior to enrolment, respectively). The proportions of patients were similar in each treatment arm (42 [84.0%] and 24 [82.8%] for semaglutide and placebo, respectively; **Supplementary Table 3**; **Figure 1A**). For semaglutide-treated patients with no known pre-existing DR at baseline the risk of DRC was low and there was no statistically significant difference versus placebo (**Supplementary Table 3**; **Figure 1B**); the number [proportion] of patients with no pre-existing DR at baseline who developed an event was 5 [10.0%] for semaglutide and 4 [13.8%] for placebo. Overall, a higher risk for DRC with semaglutide versus placebo was seen in patients with proliferative and non-proliferative DR at baseline (**Supplementary Figure 1**). There was no evidence of a dose-dependent effect

on DRC with semaglutide: 25 patients in each dose group had an event (**Supplementary Figure 2**).

In patients with pre-existing DR at baseline, the risk of DRC was further increased in patients treated with insulin prior to the event (**Figure 1C** and **D**). No increase in risk was associated with prior insulin use in patients without known pre-existing DR at baseline.

Glycaemic control

Semaglutide-treated patients experienced significant and sustained reductions in HbA_{1c} from baseline versus placebo in the overall trial population (**Figure 2A** and **2B**).[8] The reduction in HbA_{1c} with semaglutide versus placebo in patients with DRC was 1.9% and 2.5% at Week 16 with semaglutide 0.5 and 1.0 mg, respectively, versus 0.9% and 1.3% with placebo 0.5 and 1.0 mg (**Figure 2C**) and reductions in HbA_{1c} were greater versus the overall trial population until the end of the trial (Week 104, **Figure 2D**). A similar pattern for the incidence rate of DRC with semaglutide or placebo was seen in patients with pre-existing DR, when stratified according to change in HbA_{1c} by Week 16. The incidence rate of confirmed events was highest in patients with HbA_{1c} reductions greater than 1.5% with semaglutide or placebo (**Figure 3**). In patients without pre-existing DR, the incidence rate of DRC was low and similar between treatment groups, regardless of the magnitude of HbA_{1c} reduction (**Figure 3A**).

A *post hoc* mediation analysis showed that when controlling for HbA_{1c} reduction at Week 16, for semaglutide versus placebo, the HR for DRC is reduced to 1.22 (95% CI, 0.71-2.09; p=0.48; **Figure 2E**). Therefore, the majority of the treatment effect could be attributed to the reduction in HbA_{1c} at Week 16. Expansion of the mediation analysis to include other baseline variables did not change the mediator analysis results (**Supplementary Materials 3**).

Blood pressure control

Additional *post hoc* analyses were performed to assess the role of blood pressure control in the DRC finding; however, there was no indication of an effect (**Supplementary Materials 3**).

Onset of diabetes-related blindness in SUSTAIN 6

In total, six patients had EAC-confirmed events of diabetes-related blindness: five with semaglutide; one with placebo (**Supplementary Table 5**). All five semaglutide-treated patients had pre-existing proliferative DR and advanced eye complications (e.g. cataract), and all had received treatment with laser therapy and/or intravitreal agents prior to entering the trial. The placebo-treated patient with diabetes-related blindness had no known pre-existing DR.

Further information was available for three of the five semaglutide-treated patients post event, none of which continued to satisfy the criteria for diabetes-related blindness (two patients 18 months post event, and one subject, 21 days post event).

Fundoscopy/fundus photographs in SUSTAIN 6

Supplementary Table 6 shows fundoscopy/fundus photograph assessments at baseline and end of treatment. After 2 years, the proportion of patients in each category were similar between treatment arms.

Discussion

The SUSTAIN clinical trial programme was designed to evaluate the efficacy and safety of semaglutide across the continuum in patients with T2D; the trials were not specifically designed to investigate DR. Although there was no increase in DR AEs in the SUSTAIN 1–5 or Japanese trials with semaglutide versus comparators, there was a significant 76% increase in the risk of DRC with semaglutide versus placebo in SUSTAIN 6.[8]

The increased risk of DRC in SUSTAIN 6 was identified using a dichotomous secondary endpoint, thus only allowing for the identification of pre-determined events, and the trial

design does not provide a sensitive assessment of progression of retinal changes over time. Furthermore, clinical interpretation of the DRC results is challenging for several reasons: the endpoint is a mixture of treatments and diagnoses; it does not take into account pre-existing eye disease; and there was no routine assessment of visual acuity. Lastly, as the severity of DR was not formally assessed at baseline nor graded during the trial, any potential changes in DR severity cannot be determined from the data collected in SUSTAIN 6.

Semaglutide treatment in SUSTAIN 6 led to more pronounced reductions in HbA_{1c} versus placebo;[8] the difference occurred despite investigators being masked to treatment assignment and encouraged throughout the trial to actively treat hyperglycaemia by adding antihyperglycaemic agents as per local guidelines. A *post hoc* mediation analysis suggests that the increase in DRC seen with semaglutide versus placebo may be associated with the large and rapid decline in HbA_{1c} during the first 16 weeks of treatment. Furthermore, the majority of patients with DRC events were treated with insulin prior to, or at the time of, the event. While no data are available to support an interaction with insulin, use of insulin therapy appears to identify those patients at highest risk of DRC, and includes those with known risk factors for DR, including longer duration of diabetes and high baseline HbA_{1c}. The combination of pre-existing DR and insulin use may be important, therefore, for identifying the patients at the highest risk of developing DRC. Importantly, there was no increase in risk of DRC with semaglutide versus placebo in patients without pre-existing DR, regardless of whether they were receiving insulin treatment.

Rapid and marked reductions in HbA_{1c}, as a result of improved glycaemic control initiated during pregnancy, bariatric surgery or intensified insulin treatment, have previously been associated with transitory worsening of DR;[11,12,15-19] this has also been reported in patients with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT),[12] and in newly diagnosed patients with T2D in the UK Prospective Diabetes Study (UKPDS 33).[11] It is important to note that the DCCT excluded patients with proliferative

retinopathy, and used a more sensitive assessment method with graded retinal imaging to chart the progression of DR.[12] Although the characteristics of patients in the DCCT are different from those in SUSTAIN 6, the increased risk of DRC may be a manifestation of an 'early worsening' phenomenon due to the large and rapid reduction in HbA_{1c}. Consequently, patient profiling and risk assessment before intensification of treatment may help identify patients whose eyes require close monitoring.

Other agents causing abrupt glycaemic improvement (e.g. insulin) have warnings in their prescribing information about the potential association with temporary worsening of DR.[20] In the insulin glargine clinical development programme, more frequent DR progression was reported with insulin glargine versus neutral protamine Hagedorn (NPH) in patients with T2D.[21] However, a subsequent 5-year DR trial, employing 7-field Early Treatment Diabetic Retinopathy Study (ETDRS) fundus photo assessment, showed no detrimental effect with insulin glargine versus NPH on the long-term progression of DR.[22]

As a CV outcomes trial, SUSTAIN 6 was, by design, different from other SUSTAIN trials, and indeed from other phase 3 development programmes. These differences relate to the inclusion of patients with pre-existing advanced DR requiring acute treatment in SUSTAIN 6. Additionally, patients were older, had a higher baseline HbA_{1c}, a longer duration of diabetes, and a higher proportion had pre-existing DR versus those included in the other SUSTAIN trials. All of these factors increased the overall risk of DR in the SUSTAIN 6 population.

Limited data are available regarding DR with GLP-1 receptor agonists (GLP-1 RAs). In the LEADER trial, the CV outcomes trial of liraglutide, the HR for the DRC endpoint disfavoured liraglutide, although the difference was not significant (HR, 1.15; 95% CI, 0.87–1.52; p=0.33).[23] With exenatide, a retrospective analysis of patients receiving treatment twice daily for longer than 6 months showed that DR had progressed in 30% of patients and progression of DR was associated with greater reductions in HbA_{1c}; there was no comparator.[24] In the same group of patients, DR had improved or remained

stable after follow-up, suggesting that early worsening did not progress.[25] With albiglutide, a higher incidence of on-therapy DR AEs was reported versus placebo (3.6% versus 1.7%), but not with comparators.[26] Importantly, only one of these studies applied robust methods for assessing DR prospectively;[25] whereas the majority of the DR findings relating to GLP-1 RAs were based on standard AE reporting and not retinal imaging. The patient populations and the inclusion/exclusion criteria differ across the clinical development programmes, making clinical interpretation difficult.

Although the DRC data in SUSTAIN 6 are consistent with an early worsening phenomenon secondary to glycaemic improvement in patients with pre-existing DR, it is important to consider alternative aetiologies. Animal toxicology studies with semaglutide and liraglutide in non-diabetic animals have shown no evidence for a direct GLP-1 RA effect on the retina, and semaglutide data have shown no treatment-related changes (including DR) in the eyes of any of the species studied.[27]

The increased risk of DRC with semaglutide versus placebo in patients with poor glycaemic control and pre-existing DR in SUSTAIN 6 must be viewed in the wider context of the overall benefits with semaglutide treatment, including reduction in HbA_{1c}, body weight, and CV risk reduction.[8]

The beneficial effect of intensive glycaemic control on microvascular outcomes in the long term is well described, and optimisation of glycaemic control remains the cornerstone of diabetes management and the prevention of microvascular diseases such as DR progression and renal impairment. Improved glycaemic control had a beneficial effect on DR in both the DCCT and the UKPDS in the long term, and the magnitude of benefit on the risk of DR continued to increase over time, and was more pronounced in patients with DR at baseline.[11,12]

Although fundoscopic assessments were collected in SUSTAIN 6, there are significant limitations to the granularity of these data and it is necessary to interpret them with caution. However, they do provide reassurance that the retinal changes observed with

semaglutide appear to be similar to those seen with placebo at the end of treatment. Furthermore, EAC-confirmed 'onset of diabetes-related blindness' was not annulled if blindness resolved, spontaneously or as a result of treatment, as occurred in the three patients for whom further information was available, out of the five semaglutide-treated patients. In this context, it is important to note that there are further limitations associated with the collection of the DRC data: the definition of onset of diabetes-related blindness did not exclude other sight-threatening conditions and visual acuity was only recorded once at the time of the event. Regarding vitreous haemorrhage, no data are available on duration or severity.

In conclusion, an increase in DRC was observed in SUSTAIN 6 in high-risk patients, and the data are consistent with the phenomenon of early worsening of pre-existing DR, secondary to an initial, rapid improvement in glycaemic control. This conclusion is supported by a *post hoc* mediation analysis, which suggests that the DRC finding in SUSTAIN 6 is seen in patients with pre-existing DR and primarily attributable to the magnitude and rapidity of reduction in HbA_{1c} during the first 16 weeks of the trial. Additionally, there was no evidence for an increase in DR AE reporting in the SUSTAIN 1–5 or Japanese trials with semaglutide versus comparators. While further clinical evidence is required to understand fully the impact of semaglutide in general and on the progression of DR, it should be noted that physicians are alerted to the risk of worsening DR associated with intensified treatment in the prescribing information for insulins; similar recommendations may be appropriate when initiating other efficacious treatments, such as semaglutide.

Acknowledgements

We thank all the participants, investigators and trial-site staff who were involved in the conduct of the trial.

We also thank Eirik Quamme Bergan, MD, Mikkel Agersnap, MD, PhD, and Oluf Hansen, MSc (all from Novo Nordisk), for their review and input into the manuscript. Madeleine

Nowak, MSci (AXON Communications), provided medical writing and editorial assistance and received compensation from Novo Nordisk.

Author contributions

TV: data collection and review, writing the manuscript; **SB:** data collection and review, writing the manuscript; **LAL:** data collection and review, writing the manuscript; **IL:** data collection and review, writing the manuscript; **DM:** data review, writing the manuscript **RS:** data review, writing the manuscript; **IC:** data collection and review, writing the manuscript; **NW:** data collection and review, writing the manuscript. **ML:** data review, writing the manuscript.

Conflicts of interest

TV declares personal fees from Amgen, Boehringer Ingelheim, Eli Lilly, AstraZeneca, Merck Sharp & Dohme, Sanofi, Novo Nordisk and Bristol-Myers Squibb, and grants (to her institution) from Eli Lilly, and Novo Nordisk. **SB** has received grants (to his institution) and personal fees from Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Sanofi, Merck Sharp & Dohme, Janssen, and Cellnovo. **LAL** has received grants (to his institution) and personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi, personal fees from Servier and grants (to his institution) from GlaxoSmithKline. **IL** has received grants (to her institution) and/or other fees from Novartis, GI dynamics, Pfizer, Merck, and Novo Nordisk; personal fees from AstraZeneca, Sanofi, and Lilly, and non-financial (editorial) support from AstraZeneca, Sanofi, Lilly, Novo Nordisk and Boehringer Ingelheim. **DM** has had received grants (to his institution) from Novo Nordisk and Takeda and reports support from Janssen, Servier and Novartis; **RS** reports grants (to his institution) and personal fees from Novo Nordisk and OM Pharma, personal fees from Bayer, and non-financial support from Sanofi. **IC** and **NW** are full-time employees of Novo Nordisk. **ML** reports personal fees from Novo Nordisk.

References

1. Kapitza C, Nosek L, Jensen L, Hartvig H, Jensen CB, Flint A. Semaglutide, a once-weekly human GLP-1 analog, does not reduce the bioavailability of the combined oral contraceptive, ethinylestradiol/levonorgestrel. *Journal of Clinical Pharmacology.* 2015;55(5):497-504.
2. Marbury TC, Flint A, Jacobsen JB, Derving Karsbol J, Lasseter K. Pharmacokinetics and tolerability of a single dose of semaglutide, a human glucagon-like peptide-1 analog, in subjects with and without renal impairment. *Clinical Pharmacokinetics.* 2017: doi: 10.1007/s40262-017-0528-2.
3. Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *The Lancet Diabetes & Endocrinology.* 2017;5(4):251-260.
4. Ahren B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *The Lancet Diabetes & Endocrinology.* 2017;5(5):341-354.
5. Ahmann A, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide vs. exenatide ER in subjects with type 2 diabetes (SUSTAIN 3). American Diabetes Association, 76th Annual Scientific Sessions; 2016.
6. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *The Lancet Diabetes & Endocrinology.* 2017;5(5):355-366.
7. Rodbard HW, Lingvay I, Reed J, et al. Efficacy and safety of semaglutide once-weekly vs placebo as add-on to basal insulin alone or in combination with metformin in subjects with type 2 diabetes (SUSTAIN 5). European Association for the Study of Diabetes, 52nd Annual Meeting; 2016.
8. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *The New England Journal of Medicine.* 2016;375(19):1834-1844.
9. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care.* 2012;35(3):556-564.
10. ACCORDION Eye Study Group, ACCORDION Study Group. Persistent effects of intensive glycemic control on retinopathy in type 2 diabetes in the action to control cardiovascular risk in diabetes (ACCORD) follow-on study. *Diabetes Care.* 2016;39(7):1089-1100.
11. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet.* 1998;352(9131):837-853.
12. Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *The New England Journal of Medicine.* 1993;329(14):977-986.
13. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Archives of Ophthalmology.* 1998;116(7):874-886.
14. American Diabetes Association. Standards of Medical Care in Diabetes-2016 Abridged for Primary Care Providers. *Clinical diabetes: a publication of the American Diabetes Association* 2016;34(1):3.
15. American Diabetes Association. Management of diabetes in pregnancy. *Diabetes Care* 2015;38 Suppl:S77-79.
16. Gorman DM, le Roux CW, Docherty NG. The effect of bariatric surgery on diabetic retinopathy: good, bad, or both? *Diabetes & Metabolism Journal.* 2016;40(5):354-364.
17. Kroc Collaborative Study Group. Blood glucose control and the evolution of diabetic retinopathy and albuminuria. A preliminary multicenter trial. *The New England Journal of Medicine.* 1984;311(6):365-72.

18. Lauritzen T, Frost-Larsen K, Larsen HW, Deckert T. Two-year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neuropathy. *Diabetes.* 1985;**34 Suppl 3**:74-79.
19. Dahl-Jørgensen K. Near-normoglycemia and late diabetic complications. The Oslo Study. *Acta Endocrinologica Supplementum.* 1987;284:1-38.
20. Sanofi-Aventis. Lantus® (insulin glargine), EU Summary of Product Characteristics. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000284/WC500036082.pdf Accessed May 2017.
21. Davis MD, Beck RW, Home PD, Sandow J, Ferris FL. Early retinopathy progression in four randomized trials comparing insulin glargine and NPH [corrected] insulin. *Experimental and Clinical Endocrinology & Diabetes.* 2007;115(4):240-243.
22. Rosenstock J, Fonseca V, McGill JB, et al. Similar progression of diabetic retinopathy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: a long-term, randomised, open-label study. *Diabetologia.* 2009;52(9):1778-1788.
23. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *The New England Journal of Medicine.* 2016;375(4):311-322.
24. Varadhan L, Humphreys T, Hariman C, Walker AB, Varughese GI. GLP-1 agonist treatment: implications for diabetic retinopathy screening. *Diabetes Research and Clinical Practice.* 2011;94(3): e68-71.
25. Varadhan L, Humphreys T, Walker AB, Varughese GI. The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. *Diabetes Research and Clinical Practice.* 2014;103(3):e37-39.
26. US Food & Drug Administration Medical Reviews. Albiglutide. www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125431Orig1s000MedR.pdf Last accessed May 2017.
27. Novo Nordisk. Data on file. 2017.

Figure legends

Figure 1: Kaplan—Meier plots showing time to first EAC-confirmed diabetic retinopathy complication in SUSTAIN 6 by: baseline diabetic retinopathy status, Yes (A), No (B); in patients with diabetic retinopathy at baseline with insulin use prior to event, Yes (C), No (D)

CI, confidence interval; DR, diabetic retinopathy; EAC, event adjudication committee; HR, hazard ratio. The proportion of patients with events with 'Unknown' status of DR at baseline was 3 for semaglutide and 1 for placebo (HR, 2.73; 95% CI, 0.28–26.26); the proportion of patients with events with 'Unknown' status of DR at baseline with insulin use 'Yes' was 1 for semaglutide and 1 for placebo (HR, 1.29; 95% CI, 0.07–22.15). The incidence rate per 100 patient-years for DR complications with semaglutide versus placebo by baseline DR status was 4.16 and 2.63 (with DR); 0.24 and 0.18 (without DR); and 1.33 and 0.49 (unknown/missing), respectively.

Figure 2: HbA_{1c} in SUSTAIN 6: Change in HbA_{1c} over time and from baseline to Week 104 in the overall population (A and B); Change in HbA_{1c} over time and from baseline to Week 104 in subjects with diabetic retinopathy complications (C and D); *Post hoc* mediation analysis of the effect of change in HbA_{1c} (%) at Week 16 for time to first EAC-confirmed diabetic retinopathy complication (E)

*Indicates significance (p-value <0.0001). Overall trial population, n= 3297; patients with DRC, n=79. Values are estimated means (± standard errors) from a mixed model for repeated measurements analysis using 'in-trial' data from patients in the full analysis set. The table summarises the results of a *post hoc* mediation analysis for time to first EAC-confirmed retinopathy complication together with the results of the prespecified analysis. The mediation analysis assesses the effect of change in HbA_{1c} at Week 16 on time to first retinopathy complication. This is analysed by an unstratified Cox proportional hazards model, which in addition to treatment (semaglutide, placebo) as a fixed factor also includes 'change in HbA_{1c} (%-points) at Week 16' as a covariate as well as confounding variables 'HbA_{1c} at baseline', 'retinopathy at baseline' ('Yes', 'No', 'Unknown/missing') and 'baseline duration of diabetes'. Variables were deemed to be confounding if they were significantly associated with both a change in HbA_{1c} at Week 16 and time to first retinopathy complications. This was analysed by use of separate univariate ANCOVAs and Cox proportional hazards models. Other considered confounders were 'gender' and 'body weight' at baseline. Missing values of HbA_{1c} were imputed as predicted values from a mixed model for repeated measurements. 'Proportion eliminated' is calculated as: (total effect of treatment − controlled direct effect of treatment)/(total effect of treatment −1), i.e. the absolute risk reduction from the mediation analysis divided by the total excess risk. Panel A is from *The New England Journal of Medicine*: Marso, S.P., Bain, S.C., Consoli, A. et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes, 375(19): 1834-44. Copyright © (2016) Massachusetts Medical Society. Reprinted with permission.

ANCOVA, analysis of covariance; CI, confidence interval; DRC, diabetic retinopathy complications; EAC, (external) event adjudication committee; HR, hazard ratio.

Figure 3: Incidence of diabetic retinopathy complications in SUSTAIN 6 by baseline diabetic retinopathy and HbA1c reduction: patients without baseline diabetic retinopathy (A); patients with known pre-existing diabetic retinopathy (B)

PYR, patient-years. Values are observed incidence rates per 100 patient years of risk with error bars representing 95% confidence intervals. A patient's risk time is defined as the time from randomisation to first event or censoring.

Figures and tables

Table 1: Baseline characteristics across the SUSTAIN clinical trial programme

Mean (SD)	SUSTAIN 1 N=387	SUSTAIN 2 N=1225	SUSTAIN 3 N=809	SUSTAIN 4 N=1082	SUSTAIN 5 N=396	JP SUSTA MONO N=30
Age, years	53.7 (11.3)	55.1 (10.0)	56.6 (10.7)	56.5 (10.4)	58.8 (10.1)	58.3 (10
HbA_{1c}, %	8.1 (0.9)	8.1 (0.9)	8.3 (1.0)	8.2 (0.9)	8.4 (0.8)	8.1 (0.
T2D duration, years	4.2 (5.5)	6.6 (5.1)	9.2 (6.3)	8.6 (6.3)	13.3 (7.8)	8.0 (6.
Systolic BP, mmHg	128.8 (13.2)	132.6 (14.9)	133.5 (14.5)	132.1 (15.3)	134.8 (16.0)	129.1 (14.8
Medical history of DR, n (%)	15 (3.9)	94 (7.7)	30 (3.7)	50 (4.6)	55 (13.9)	42 (13.

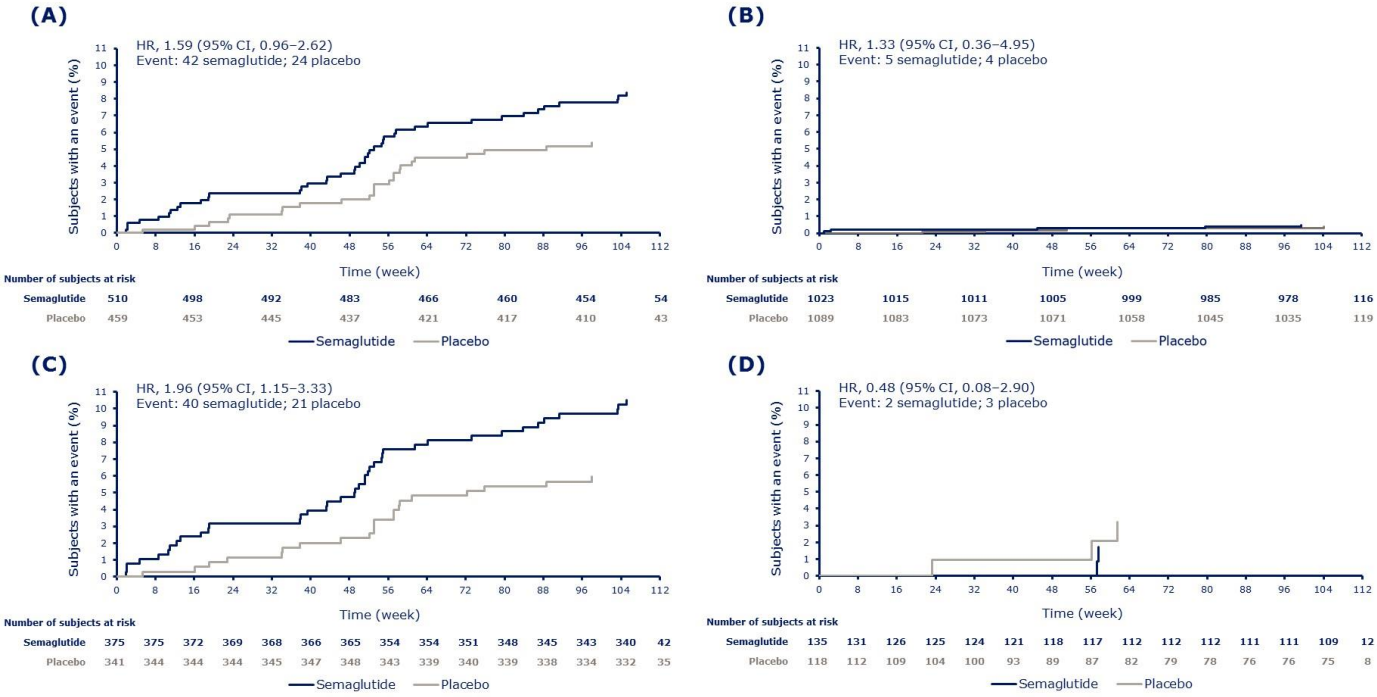
BP, blood pressure; DR, diabetic retinopathy; JP, Japanese; MONO, monotherapy; OAD, oral antidiabetic drug; SD, standard devi

Table 2: Diabetic retinopathy adverse events with their respective investigator-assessed seve
SUSTAIN clinical trial programme

SUSTAIN 1-5 and Japanese SUSTAIN trials									
	Semaglutide 0.5 mg N=1373				Semaglutide 1.0 mg N=1777				
	n	(%)	E	R	n	(%)	E	R	n
All events	32	(2.1)	35	2.6	30	(1.5)	36	1.9	3
Severe	0		0		0		0		(
Moderate	3	(0.2)	4	0.3	3	(0.2)	5	0.3	6
Mild	29	(1.9)	31	2.3	27	(1.3)	31	1.6	2
SAEs	0		0		0		0		(
SUSTAIN 6									
	Semaglutide 0.5 mg N=826				Semaglutide 1.0 mg N=822				
	n	(%)	E	R	n	(%)	E	R	n
All events	74	(9.0)	86	5.0	82	(10.0)	99	5.8	12
Severe	5	(0.6)	6	0.4	5	(0.6)	5	0.3	1
Moderate	27	(3.3)	33	1.9	22	(2.7)	25	1.5	3
Mild	44	(5.3)	47	2.8	57	(6.9)	69	4.1	8
SAEs	6	(0.7)	7	0.4	5	(0.6)	6	0.4	8

Proportions for SUSTAIN 1-5 and Japanese SUSTAIN trials are adjusted proportions. Mild, no or transient symptoms, no interferen
moderate, marked symptoms, moderate interference with the subject's daily activities; severe, considerable interference with the
events; R, events per 100 patient-years of observation; SAE, serious adverse event.

Figure 1: Kaplan—Meier plots showing time to first EAC-confirmed diabetic retinopathy complication in SUSTAIN 6 by: baseline diabetic retinopathy status, Yes (A), No (B); in patients with diabetic retinopathy at baseline with insulin use prior to event, Yes (C), No (D)



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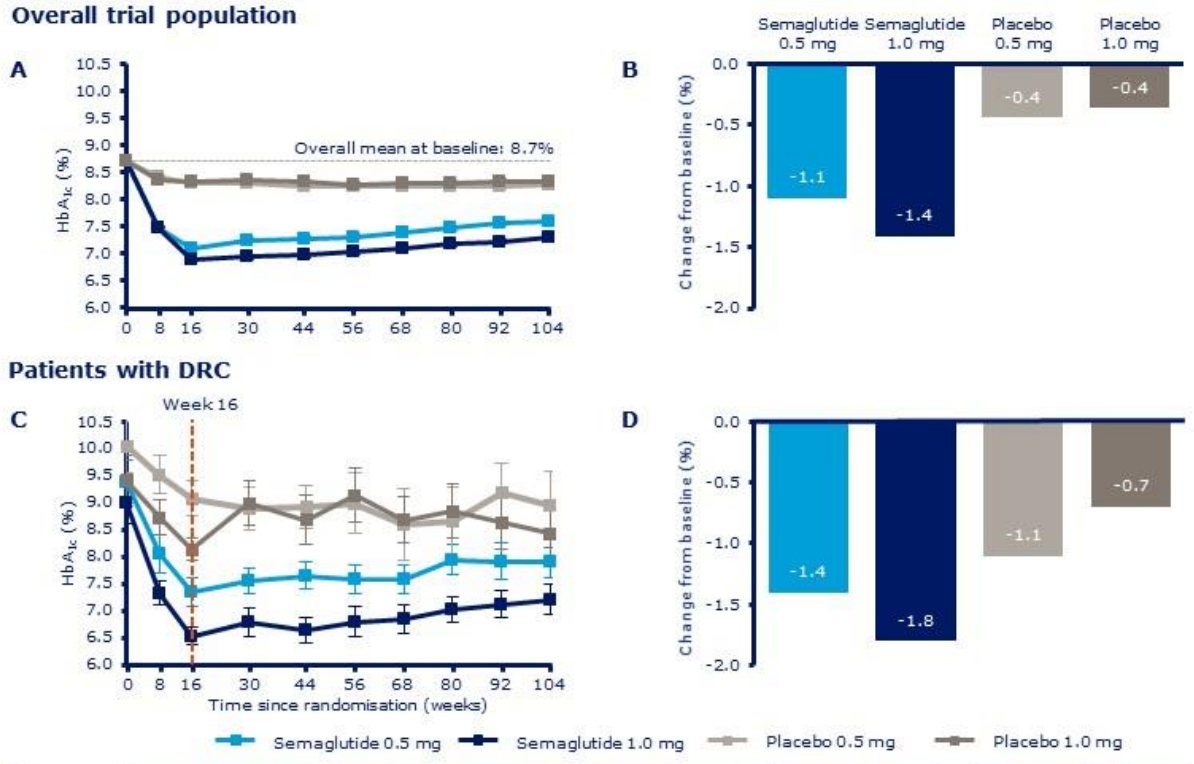

E

	HR (95% CI) Semaglutide vs placebo	P value Semaglutide vs placebo	Semaglutide (N=1648) n (%)	Placebo (N=1649) n (%)
Prespecified analysis				
Total effect of treatment	1.76 (1.11; 2.78)	0.02	50 (3.0)	29 (1.8)
Post-hoc mediation analysis				
Controlled direct effect of treatment	1.22 (0.71; 2.09)	0.48	50 (3.0)	29 (1.8)
Effect of change in HbA_{1c} (%) at Week 16	1.26 (1.03; 1.57)	0.03		
Proportion eliminated	0.72			

*Indicates significance (p-value <0.0001). Overall trial population, n= 3297; patients with DRC, n=79. Values are estimated means (± standard errors) from a mixed model for repeated measurements analysis using 'in-trial' data from patients in the full analysis set. The table summarises the results of a *post hoc* mediation analysis for time to first EAC-confirmed retinopathy complication together with the results of the prespecified analysis. The mediation analysis assesses the effect of change in HbA_{1c} at Week 16 on time to first retinopathy complication. This is analysed by an unstratified Cox proportional hazards model, which in addition to treatment (semaglutide, placebo) as a fixed factor also includes 'change in HbA_{1c} (%-points) at Week 16' as a covariate as well as confounding variables 'HbA_{1c} at baseline', 'retinopathy at baseline' ('Yes', 'No', 'Unknown/missing') and 'baseline duration of diabetes'. Variables were deemed to be confounding if they were significantly associated with both a change in HbA_{1c} at Week 16 and time to first retinopathy complications. This was analysed by use of separate univariate ANCOVAs and Cox proportional hazards models. Other considered confounders were 'gender' and 'body weight' at baseline. Missing values of HbA_{1c} were imputed as predicted values from a mixed model for repeated measurements. 'Proportion eliminated' is calculated as: (total effect of treatment − controlled direct effect of treatment)/(total effect of treatment −1), i.e. the absolute risk reduction from the mediation analysis divided by the total excess risk. Panel A is from *The New England Journal of Medicine*: Marso, S.P., Bain, S.C., Consoli, A. et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes, 375(19): 1834-44. Copyright © (2016) Massachusetts Medical Society. Reprinted with permission.

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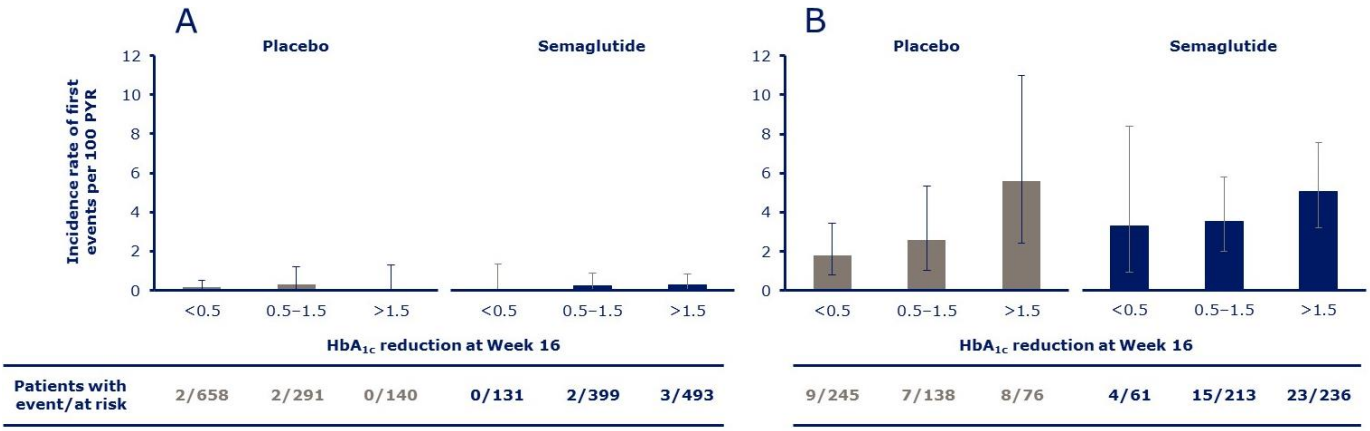

Patients with event/at risk	2/658	2/291	0/140	0/131	2/399	3/493	9/245	7/138	8/76	4/61	15/213	23/236

PYR, patient-years. Values are observed incidence rates per 100 patient years of risk with error bars representing 95% confidence intervals. A patient's risk time is defined as the time from randomisation to first event or censoring.