Oral Semaglutide versus Empagliflozin in Patients with Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial

Running title: Oral Semaglutide versus Empagliflozin

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ABSTRACT

OBJECTIVE

Efficacy and safety of the GLP-1 analog, oral semaglutide, and the SGLT-2 inhibitor, empagliflozin, were compared in patients with type 2 diabetes uncontrolled on metformin.

RESEARCH DESIGN AND METHODS

Patients were randomized to once-daily open-label treatment with oral semaglutide 14 mg (n = 412) or empagliflozin 25 mg (n = 410) in a 52-week trial. Key endpoints were change from baseline to week 26 in HbA_{1c} (primary) and body weight (confirmatory secondary). Two estimands addressed efficacy-related questions: treatment policy (regardless of trial product discontinuation or rescue medication) and trial product (on trial product without rescue medication) in all randomized patients.

RESULTS

Four-hundred patients (97.1%) in the oral semaglutide group and 387 (94.4%) in the empagliflozin group completed the trial. Oral semaglutide provided superior reductions in HbA_{1c} versus empagliflozin at week 26 (treatment policy: –1.3% vs. –0.9% [–14 vs. –9 mmol/mol]; estimated treatment difference [ETD]: –0.4%, 95% CI –0.6, –0.3 [–5 mmol/mol, 95% CI –6, –3]; P< 0.0001). The treatment difference in HbA_{1c} significantly favored oral semaglutide at week 26 for the trial product estimand (–1.4% vs. –0.9% [–15 vs. –9 mmol/mol]; ETD: –0.5%, 95% CI –0.7, –0.4 [–6 mmol/mol, 95% CI –7, –5]; P< 0.0001), and at week 52 for both estimands (P< 0.0001). Superior weight loss was not confirmed at week 26 (treatment policy), but oral semaglutide was significantly better than empagliflozin at week 52 (trial product: −4.7 vs. −3.8 kg; P = 0.0114). Gastrointestinal adverse events were more common with oral semaglutide.

CONCLUSIONS

Oral semaglutide was superior to empagliflozin in reducing HbA_{1c} but not body weight at 26 weeks in patients with type 2 diabetes uncontrolled on metformin. At week 52, HbA_{1c} and body weight (trial product estimand) were significantly reduced versus empagliflozin. Oral semaglutide was well tolerated within the established safety profile of GLP-1 receptor agonists.

Trial registration: Clinicaltrials.gov NCT02863328.

Keywords: randomized clinical trial, empagliflozin, GLP-1 receptor agonist, oral semaglutide, phase 3, sodium-glucose co-transporter-2 inhibitor, type 2 diabetes.

Many patients with type 2 diabetes fail to achieve or maintain adequate blood glucose control when treated with metformin monotherapy. Injectable glucagon-like peptide-1 receptor agonists (GLP-1RAs) and oral sodium-glucose transport protein 2 (SGLT-2) inhibitors are recommended as second-line therapy because of their ability to lower glucose without increasing hypoglycemia risk, weight loss effect and associated cardiovascular benefits (1,2).

Semaglutide is a human GLP-1 analog currently available as a once-weekly injection associated with reduced glycated hemoglobin (HbA_{1c}), weight loss and fewer cardiovascular events in type 2 diabetes (3-9). Oral semaglutide is co-formulated in a tablet with the absorption enhancer sodium *N*-(8-[2-hydroxylbenzoyl] amino) caprylate (SNAC), which facilitates semaglutide absorption across the gastric mucosa (10). Oral semaglutide has demonstrated significantly greater reductions in HbA_{1c} and body weight compared with placebo in patients with type 2 diabetes uncontrolled with diet and exercise or oral anti-diabetic medication, including in patients with moderate renal impairment (11-14). Significantly greater reductions in HbA_{1c} and body weight have also been shown with oral semaglutide, given either as 7 or 14 mg/day or flexibly dosed, when compared with sitagliptin in patients uncontrolled with oral anti-diabetic drugs (15,16). Oral semaglutide also resulted in a non-inferior reduction in HbA_{1c} and superior weight loss versus liraglutide in patients on metformin with or without a SGLT-2 inhibitor (13). Cardiovascular safety has been confirmed, with an indication of benefit, by a non-significant 21% risk reduction in major adverse cardiovascular events versus placebo (17).

Empagliflozin is a widely used oral SGLT-2 inhibitor shown to improve glycemic control and body weight (18-22) and associated with a reduced risk of cardiovascular and all-cause mortality in patients at high cardiovascular risk (23). The present phase 3a trial, PIONEER 2, is the first direct comparison of oral semaglutide with a SGLT-2 inhibitor, empagliflozin, in type 2 diabetes uncontrolled on metformin monotherapy.

RESEARCH DESIGN AND METHODS

Trial Design

This randomized, open-label, multinational 52-week trial was conducted at 108 sites in 12 countries (Argentina, Brazil, Croatia, Greece, Hungary, Italy, Poland, Russia, Serbia, Spain, Thailand, USA). Patients were randomized (1:1) to once-daily oral semaglutide 14 mg or empagliflozin 25 mg for 52 weeks using an interactive web response system, with a further 5 weeks' follow-up (Fig. S1). An open-label trial design was used because manufacture of placebo tablets resembling empagliflozin was not feasible within a reasonable timeframe. Oral semaglutide was initiated at 3 mg once-daily, escalated to 7 mg at week 4, and 14 mg after week 8. Since food impairs absorption of oral semaglutide, patients were instructed to administer oral semaglutide in the morning in a fasted state with up to 120 mL of water at least 30 minutes before breakfast and any other oral medication. Empagliflozin was initiated at 10 mg once-daily in the morning, and escalated to 25 mg at week 8.

Additional anti-diabetic medication was available for patients with persistent or unacceptable hyperglycemia on trial product and for patients who prematurely discontinued trial product and remained in the trial. Additional anti-diabetic medication was defined as that initiated (or intensification of existing anti-diabetic background medication by a dose increase of >20%) during the planned treatment period (i.e. from randomization to the planned end-of-treatment visit) either as add-on to trial product or initiated after premature discontinuation of trial product. The subset of additional anti-diabetic medication (or intensification of existing anti-diabetic background medication) used as add-on to trial product is defined as rescue medication. Short-term use (≤21 days) of anti-diabetic medication (e.g. in connection with intercurrent illness) was not considered as additional anti-diabetic medication (including rescue medication).

Rescue criteria were fasting plasma glucose >260 mg/dL (14.4 mmol/L) from week 8–13, >240 mg/dL (13.3 mmol/L) from week 14–25, and >200 mg/dL (11.1 mmol/L) (or HbA_{1c} >8.5% [69.4 mmol/mol]) from week 26 onwards). Rescue medication was prescribed at the investigator´s discretion (excluding GLP-1RAs, DPP-4 inhibitors, and amylin analogs in the oral semaglutide arm, and SGLT-2 inhibitors in the empagliflozin arm). Patients who prematurely discontinued trial product remained in the trial and could receive any other anti-diabetic medications at the investigator's discretion (excluding GLP-1RAs in the oral semaglutide arm before completion of the follow-up visit 5 weeks after the last date on trial product).

Two different questions related to the efficacy objectives were addressed through the definition of two estimands ('treatment policy' and 'trial product'). Both estimands were defined based on interactions with regulatory agencies. The treatment policy estimand evaluates the treatment effect for all randomized patients, regardless of trial product discontinuation or use of rescue medication. This estimand reflects the intention-to-treat principle, as defined in International Council on Harmonisation (ICH) E9 (24). The estimand reflects the effect of initiating treatment with oral semaglutide compared to initiating treatment with empagliflozin, both potentially followed by either discontinuation of trial product and/or addition of or switch to another glucose-lowering drug.

The trial product estimand evaluates the treatment effect for all randomized patients under the assumption that all patients remained on trial product for the entire planned duration of the trial and did not use rescue medication. This estimand aims at reflecting the effect of oral semaglutide compared to empagliflozin without the confounding effect of rescue medication. The statistical analysis that was applied to estimate this estimand is similar to how many phase 3a diabetes trials have been evaluated, and results from such analyses are currently included in many product labels (prescribing information, US and summary of product

characteristics [SmPC], European Union) for glucose-lowering drugs (e.g., Ozempic® SmPC).

Trial product discontinuation and initiation of rescue medication are accounted for by the treatment policy strategy for the treatment policy estimand, and by the hypothetical strategy for the trial product estimand as defined in draft ICH E9 (R1) (25). Further details on the use of estimands in this trial are provided in Appendix 2 of the Supplement with further background provided by Aroda et al (26).

The trial protocol was approved by all relevant Institutional Review Board/Independent Ethics Committees, and the trial was conducted in accordance with ICH Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent prior to any trial-related activity. The sponsor (Novo Nordisk) designed the trial and participated in the trial conduct, data collection, and data analysis. Medical writing and editorial support were funded by the sponsor. All authors had full access to the trial data, participated in the drafting or critical revision of the manuscript, approved the final submitted version, and vouch for the accuracy and completeness of the data and adherence to the protocol.

Patients

Eligible patients were adults with type 2 diabetes and HbA_{1c} 7.0–10.5% (53–91 mmol/mol) receiving a stable dose of metformin (≥ 1500 mg or maximum tolerated). Key exclusion criteria (see Table S1 for full list) were: any medication for diabetes or obesity within the previous 90 days, other than metformin or short-term (≤ 14 days) insulin; renal impairment with estimated glomerular filtration rate less than 60 mL/min/1.73 m^2; proliferative retinopathy or maculopathy requiring acute treatment verified by fundus photography or dilated fundoscopy; and history of pancreatitis.

Trial Endpoints

Primary endpoint was change in HbA_{1c} from baseline to week 26. Confirmatory secondary endpoint was change in body weight (kg) from baseline to week 26.

Secondary endpoints included changes from baseline to week 52 in HbA_{1c} and body weight (kg), and changes from baseline to weeks 26 and 52 in fasting plasma glucose, self-measured blood glucose profile (7-point profile and mean postprandial increment over all meals), fasting C-peptide, fasting insulin, fasting pro-insulin, fasting glucagon, HOMA-IR, HOMA-B, C-reactive protein, body weight (%), BMI, waist circumference, and fasting lipid profile. Other secondary endpoints were the proportion of patients achieving: $HbA_{1c} < 7\%$ (53 mmol/mol) or $\leq 6.5\%$ (48 mmol/mol); weight loss of $\geq 5\%$ or $\geq 10\%$; composite endpoint of $HbA_{1c} < 7\%$ (53 mmol/mol) without severe or symptomatic hypoglycemia (blood glucose < 56 mg/dL [< 3.1 mmol/l]) and no weight gain; composite endpoint of an absolute reduction in HbA_{1c} of $\geq 1.0\%$-points (10.9 mmol/mol) and body weight loss of $\geq 3\%$ (weeks 26 and 52); and changes from baseline to weeks 26 and 52 in the patient-reported outcomes, SF-36v2® Health Survey (acute version) (27) and Control of Eating Questionnaire (CoEQ) (28). Further endpoints are listed in Appendix 2 of the Supplement, and the protocol is also included as part of the supplementary material.

Safety endpoints included the number of treatment-emergent adverse events, incidence of American Diabetes Association (ADA)-classified (29) severe or confirmed symptomatic hypoglycemic episodes (blood glucose < 56 mg/dL [< 3.1 mmol/l]), and changes from baseline in heart rate, blood pressure, and other clinical and laboratory assessments. An independent external event adjudication committee (EAC) performed masked validation of predefined adverse events, including deaths, selected cardiovascular events, acute pancreatitis, malignant neoplasms, acute kidney injury, and lactic acidosis.

Statistical Analysis

The primary endpoint of change from baseline to week 26 in HbA_{1c} was tested for both non-inferiority and superiority of oral semaglutide versus empagliflozin, with a sample size calculation to ensure a power of at least 90% for testing superiority. The confirmatory secondary endpoint of change from baseline to week 26 in body weight was tested for superiority of oral semaglutide versus empagliflozin. The confirmation of efficacy of oral semaglutide on change in HbA_{1c} and body weight from baseline to week 26 was based on a weighted Bonferroni closed testing strategy (30) to control the overall type 1 error for the hypotheses evaluated by the treatment policy estimand (Fig. S2). Because of the potential for type I errors due to multiple comparisons, findings for analyses of additional secondary endpoints should be interpreted as exploratory.

The treatment policy estimand was estimated by a pattern mixture model using multiple imputation to handle missing week 26 data for both confirmatory endpoints. Data collected at week 26, irrespective of premature discontinuation of trial product or initiation of rescue medication, were included in the statistical analysis. Imputation was done within groups defined by trial product and treatment status at week 26. Both the imputation and the analysis were based on analysis of covariance models. The results were combined by use of Rubin's rule (31) Prior to testing for non-inferiority, a value of 0.4% (the non-inferiority margin) was added to imputed values at week 26 for the oral semaglutide treatment arm only (32).

The trial product estimand was estimated by a mixed model for repeated measurements that used data collected prior to premature trial product discontinuation or initiation of rescue medication from all randomized patients.

Further details on the statistical analyses can be found in the Fig. S2 in the Supplement. All analyses were performed using SAS Version 9.4M2.

RESULTS

Patients

A total of 1,122 patients were screened, with 822 randomized to oral semaglutide 14 mg once-daily (*n* = 412) or empagliflozin 25 mg once-daily (*n* = 410). Four-hundred patients (97.1%) in the oral semaglutide group and 387 (94.4%) in the empagliflozin group completed the trial (Fig. S3). Baseline characteristics were well balanced between treatment groups (Table 1). Patients, of whom half (49.5%) were female, had a mean age of 58 years, baseline HbA_{1c} of 8.1% (65 mmol/mol), fasting plasma glucose of 173 mg/dL (9.6 mmol/L), average duration of diabetes of 7.4 years, and mean body weight of 91.6 kg.

Use of additional anti-diabetic medication and rescue medication are shown in Table S2. Through to week 26, 17 (4.1%) patients initiated additional anti-diabetic medication in the oral semaglutide group, in 8 (1.9%) of whom it was rescue medication. In the empagliflozin group, 13 (3.2%) patients initiated additional anti-diabetic medication through to week 26, with this being rescue medication in 5 (1.2%) patients. Through to week 52, 52 (12.7%) patients initiated additional anti-diabetic medication in the oral semaglutide group, in 31 (7.5%) of whom it was rescue medication while, in the empagliflozin group, 56 (13.7%) patients initiated additional anti-diabetic medication, with this being rescue medication in 44 (10.7%) patients. Sulfonylureas were the most commonly used additional anti-diabetic and rescue medication. Disposition of patients throughout the trial is shown in Fig S4.

Glycemic Control

Oral semaglutide 14 mg provided a superior reduction in HbA_{1c} compared with empagliflozin 25 mg at week 26 when evaluated by the treatment policy estimand (regardless of rescue medication or trial product discontinuation) (–1.3%-points vs. –0.9%-points [–14 vs. –9 mmol/mol]; estimated treatment difference [ETD]: –0.4%-points, 95% CI: –0.6, –0.3 [–5

mmol/mol, 95% CI –6, –3]; $P < 0.0001$ for non-inferiority and superiority) (Fig. 1). Results from sensitivity analyses supported the results of the confirmatory analysis (Fig. S5). When evaluated by the trial product estimand (on trial product and without the use of rescue medication), the reduction in HbA_{1c} was significantly greater with oral semaglutide at week 26 (–1.4%-points vs. –0.9%-points [–15 vs. –9 mmol/mol]; ETD: –0.5%-points, 95% CI –0.7, –0.4 [–6 mmol/mol, 95% CI –7, –5]; $P < 0.0001$) (Fig. 1). Significantly greater reductions in HbA_{1c} with oral semaglutide compared to empagliflozin were also observed at week 52 (both estimands, Fig. 1). More patients achieved the predefined HbA_{1c} targets with oral semaglutide than empagliflozin, and the odds of doing so were significantly greater at weeks 26 and 52 (both estimands, all $P < 0.0001$) (Fig. 1; Table 2).

Fasting plasma glucose was reduced with both treatments, with no significant difference between groups (Table 2; Fig. S6). Oral semaglutide resulted in significantly greater reductions in mean 7-point self-measured blood glucose profiles compared with empagliflozin at both week 26 and 52 (Table 2; Fig. S6), and significantly reduced mean post-prandial increments, averaged for all meals (excluding the treatment policy estimand evaluation at week 26) (Table 2).

Body Weight

Superiority of body weight reduction at week 26 with oral semaglutide over empagliflozin was not confirmed (treatment policy estimand: −3.8 vs. −3.7 kg; ETD −0.1, 95% CI −0.7, 0.5; $P = 0.7593$). Results from sensitivity analyses supported the results of the confirmatory analysis (Fig. S5). There was no difference between treatments using the trial product estimand: −4.2 versus −3.8 kg; ETD −0.4, 95% CI −1.0, 0.1; $P = 0.1358$ (Fig. 1). A significantly greater reduction in body weight was achieved with oral semaglutide versus empagliflozin at week 52 when evaluated by the trial product estimand (−4.7 vs. −3.8 kg;

ETD −0.9, 95% CI −1.6, −0.2; *P* = 0.0114), but not the treatment policy estimand (−3.8 vs. −3.6 kg; ETD −0.2, 95% CI −0.9, 0.5; *P* = 0.6231). Proportions of patients achieving ≥ 5% or ≥ 10% weight loss are shown in Fig. 1 and Table 2, respectively. Reductions in waist circumference were significantly greater with oral semaglutide than empagliflozin at week 26 (both estimands) and at week 52 (trial product estimand, Table 2).

Other Outcomes

More patients achieved the two composite endpoints (HbA_{1c} < 7% [53 mmol/mol] without severe or symptomatic hypoglycemia and no weight gain, and an absolute reduction in HbA_{1c} of ≥ 1.0%-points [10.9 mmol/mol] and body weight loss of ≥ 3%) with oral semaglutide versus empagliflozin, and the odds of doing so were significantly greater at both weeks 26 and 52 (Table 2). Reduction in C-reactive protein was significantly greater with oral semaglutide versus empagliflozin (Table 2). Other secondary endpoints are presented in Tables 2 and S3.

For the CoEQ, the domains ‘craving control’ (weeks 26 and 52) and ‘craving for savory’ (week 52) were significantly improved in favor of oral semaglutide versus empagliflozin (treatment policy estimand). Both domains were significantly in favor of oral semaglutide at both weeks 26 and 52 for the trial product estimand. Patient-reported outcomes are summarized in Fig. S7.

Safety

The overall number of adverse events and proportion of patients reporting adverse events were similar with oral semaglutide and empagliflozin, and most events were mild-to-moderate severity (Table 3). Fewer patients experienced serious adverse events in the oral semaglutide group. There was one death in the empagliflozin group (undetermined cause). The most frequent adverse event with oral semaglutide was nausea, which was non-serious,

usually mild-to-moderate severity, transient, and did not exceed a prevalence of 10% at any time (Table 3, Fig. S8). Female and male genital mycotic infections of mild-to-moderate severity occurred more frequently with empagliflozin compared to oral semaglutide (8.5% and 6.7% vs. 2.0% and 0%, respectively) (Table S4).

Adverse events resulting in trial product discontinuation were more frequent with oral semaglutide than empagliflozin (10.7% vs. 4.4%), and were primarily related to gastrointestinal symptoms (8.0% vs. 0.7%, Table 3). In both groups, premature discontinuations mainly occurred in the first 16 weeks of treatment.

Incidence of severe or confirmed symptomatic hypoglycemic episodes (< 56 mg/dL [< 3.1 mmol/L]) was low and similar in both groups (Table 3). Diabetic retinopathy-related adverse events were reported in 14 patients (3.4%) in the oral semaglutide group and in 5 (1.2%) in the empagliflozin group (in-trial period; Table S5). All such events were identified by routine eye examination as part of the trial protocol, and were non-serious, of mild or moderate severity, and did not require treatment. EAC-confirmed malignant neoplasms were identified in seven patients (1.7%) in the oral semaglutide group and two patients (0.5%) in the empagliflozin group (in-trial period). There was no clustering of malignancies in any particular organ or system (Table S6). Cardiovascular events occurred at a similar rate in both groups (EAC-confirmed; oral semaglutide, *n* = 5 [1.2%]; empagliflozin, *n* = 6 [1.5%]; Table S6). Other EAC-confirmed events and safety assessments are reported in Tables S6 and S7.

CONCLUSIONS

Oral semaglutide is the first oral GLP-1RA to be investigated for the treatment of type 2 diabetes. In PIONEER 2, oral semaglutide was superior to empagliflozin, with meaningful reductions in HbA_{1c} at 26 weeks in patients with type 2 diabetes uncontrolled on metformin monotherapy. Furthermore, the difference between treatments remained significant at 52

weeks. Attainment of ADA-recommended HbA_{1c} targets at 26 and 52 weeks was also significantly greater with oral semaglutide. Reductions in fasting plasma glucose were similar in both groups, suggesting differences in glycemic control may be mostly driven by the greater reduction in postprandial glucose with oral semaglutide.

Reductions in body weight occurred with both treatments but superiority of oral semaglutide versus empagliflozin could not be confirmed at week 26. However, weight loss in the empagliflozin group stabilized around week 26, whereas in the oral semaglutide group weight loss continued until around week 38 and was significantly greater at 52 weeks based on the trial product estimand. This significantly greater weight loss at 52 weeks with oral semaglutide based on the trial product estimand reflects the treatment effect without the confounding influence of rescue medication and treatment discontinuations. Patients discontinuing oral semaglutide could not be switched to additional anti-diabetic medication with a comparable weight-reducing effect, while patients on empagliflozin could be switched to GLP-1RAs.

The safety profile of oral semaglutide was consistent with previous trials (11-16). More patients prematurely discontinued treatment because of adverse events with oral semaglutide than empagliflozin, mainly due to gastrointestinal symptoms associated with dose escalation. The proportion of adverse events leading to discontinuation of oral semaglutide (10.7%) was similar to previous observations with injectable GLP-1RAs (6–11%) (4,33,34).

The use of subcutaneous semaglutide has previously been associated with a higher rate of diabetic retinopathy-related complications compared with placebo, consistent with the phenomenon of early worsening of pre-existing diabetic retinopathy secondary to an initial, rapid improvement in glycaemic control (6,35). The possible effect of subcutaneous semaglutide on diabetic eye disease is being further investigated in the ongoing FOCUS trial

(NCT03811561) (36). In the current trial, diabetic retinopathy-related adverse events were more frequent with oral semaglutide compared with empagliflozin, although occurrence was low in both groups (3.4% versus 1.2%). All events were non-serious, most were mild in severity, and none required treatment or led to trial product discontinuation. All were discovered during routine end-of-treatment eye examination and were diagnosed as non-proliferative diabetic retinopathy. In a longer-term 78-week, double-blind trial, no imbalance in the occurrence of diabetic-retinopathy related events were observed between oral semaglutide 3, 7 and 14 mg and sitagliptin (6.7%, 6.0%, 5.6% and 7.7%, respectively) (15). Occurrence of diabetic retinopathy-related events was also similar with oral semaglutide and placebo (7.1% versus 6.3%) in a double-blind trial assessing cardiovascular outcomes in patients at high cardiovascular risk (17).

This trial provides a comparison of two increasingly used drug classes that are commonly added to metformin when glycemic control is not achieved. The principal limitation of the trial was the open-label design.

In conclusion, the oral GLP-1 analog oral semaglutide was superior to the SGLT-2 inhibitor empagliflozin for reduction in HbA_{1c}, but not body weight, at 26 weeks in patients with type 2 diabetes uncontrolled with metformin. Reductions in HbA_{1c} were significantly greater with oral semaglutide at 52 weeks. Assessed by the trial product estimand, oral semaglutide provided significant reductions in body weight at 52 weeks. Oral semaglutide was well tolerated, with a safety profile consistent with that of GLP-1RAs.

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Author Contributions

H.W.R. and E.M. were signatory investigators on the study, had full access to all of the data in the trial and take responsibility for the integrity of the data and the accuracy of the data analysis. S.O.L. and M.B.T. were involved in the concept and design of the study. A.L.S. was responsible for the statistical analysis. All authors were responsible for the acquisition, analysis, or interpretation of data, and drafting of or critical revision of the manuscript for important intellectual content. H.W.R. and E.M. are the guarantors of this work and had full access to all the data in the study and takes responsibility for the content and accuracy of this publication.

Additional Contributions

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Conflicts of Interest

H.W.R. reports consulting, advisory boards, clinical research, lecturing for AstraZeneca, Boehringer-Ingelheim, Janssen, Lilly, Merck, Novo Nordisk, Sanofi, and Regeneron. J.R. reports scientific advisory boards, honoraria or consulting fees from Eli Lilly, Novo Nordisk, Sanofi, Janssen, Boehringer Ingelheim, and Intarcia; grants/research support from Merck, Pfizer, Sanofi, Novo Nordisk, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, AstraZeneca, Janssen, Genentech, Boehringer Ingelheim, Intarcia, and Lexicon. L.H.C.

reports clinical research for Novo Nordisk, Janssen, Lilly, and Sanofi; lecturing for Sanofi, and Boehringer-Ingelheim. C.D. reports consulting, advisory boards, clinical research, lecturing for AstraZeneca, Boehringer-Ingelheim, Janssen, Lilly, Novo Nordisk, Merck, Sanofi, Takeda, and MSD. J.G. has received speaker's or consulting honoraria from Novo Nordisk, Eli Lilly, Servier, Merck Sharp & Dohme, Bioton (Poland), Merck (Darmstadt), Sanofi, Polpharma (Poland), Polfa Tarchomin (Poland), Astra, and Boehringer Ingelheim. I.L. reports consulting, advisory board, and/or research grants from Novo Nordisk, AstraZeneca, Boehringer-Ingelheim, Sanofi, Lilly, Intarcia, Mannkind, Valeritas, Novartis, Mylan, Merck, and Pfizer. E.M. reports scientific advisory board, consulting, lecturing and/or research grants from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Grupo Ferrer Internacional SA, Intarcia Therapeutics, Inc., Menarini, Janssen Pharmaceuticals, Laboratoires Servier, Merck Sharp & Dohme, Novo Nordisk, and Novartis. S.Ø.L., A.L.S., and M.B.T. are employees of Novo Nordisk A/S; A.L.S. and M.B.T. have shares in Novo Nordisk A/S.

Meeting Presentation

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Role of the Funders/Sponsors

Novo Nordisk (the sponsor) designed the trial, monitored sites, and collected and analyzed the data. Editorial support was funded by the sponsor and provided by independent medical writers under the guidance of the authors.

Data-sharing statement

Data will be shared with bona fide researchers submitting a research proposal approved by the independent review board. Access request proposals can be found at novonordisk-trials.com. Data will be made available after research completion, approval of the product and product use in the European Union and USA. Individual participant data will be shared in data sets in a de-identified/anonymised format using a specialized SAS data platform.

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TABLES

Table 1—Baseline Characteristics and Demographics

	Oral semaglutide 14 mg (*N* = 411)	Empagliflozin 25 mg (*N* = 410)	Total (*N* = 821)
Age (years), mean (SD)	57 (10)	58 (10)	58 (10)
Female, *n* (%)	205 (49.9)	201 (49.0)	406 (49.5)
Race, *n* (%)			
White	355 (86.4)	353 (86.1)	708 (86.2)
Black or African American	26 (6.3)	33 (8.0)	59 (7.2)
Asian	28 (6.8)	21 (5.1)	49 (6.0)
Other	2 (0.5)	3 (0.7)	5 (0.6)
Ethnicity, *n* (%)			
Hispanic or Latino	91 (22.1)	108 (26.3)	199 (24.2)
Duration of diabetes (years), mean (SD)	7.2 (5.8)	7.7 (6.3)	7.4 (6.1)
Body weight (kg), mean (SD)	91.9 (20.5)	91.3 (20.1)	91.6 (20.3)
BMI (kg/m^2), mean (SD)	32.9 (6.3)	32.8 (5.9)	32.8 (6.1)

HbA_{1c} (%, mmol/mol), mean (SD)	8.1 (0.9), 65 (10)	8.1 (0.9), 65 (10)	8.1 (0.9), 65 (10)
Fasting plasma glucose (mmol/L, mg/dL), mean (SD)	9.5 (2.3), 171.5 (41.8)	9.7 (2.5), 174.0 (45.2)	9.6 (2.4), 172.8 (43.5)
Estimated glomerular filtration rate* (mL/min/1.73 m^2), mean (SD)	96 (15)	95 (15)	95 (15)

* Glomerular filtration rate was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. SD, standard deviation.

Table 2—Selected Secondary Endpoints (Treatment Policy Estimand and Trial Product Estimand)[a]

	Treatment policy estimand				Trial product estimand			
	Week 26		Week 52		Week 26		Week 52	
	Oral semaglutide 14 mg	Empagliflozin 25 mg	Oral semaglutide 14 mg	Empagliflozin 25 mg	Oral semaglutide 14 mg	Empagliflozin 25 mg	Oral semaglutide 14 mg	Empagliflozin 25 mg
Patients, *n*	411	410	411	410	411	410	411	410
$HbA_{1c} \leq 6.5\%$ (48 mmol/mol)								
Patients reaching endpoint, *n* (%)	186 (47.4)	68 (17.2)	182 (47.4)	83 (21.7)	181 (52.2)	68 (18.0)	164 (54.1)	74 (23.4)
Estimated OR (95% CI) oral semaglutide	4.62 (3.28, 6.52); $P < 0.0001$		3.36 (2.43, 4.66); $P < 0.0001$		5.61 (3.93, 8.01); $P < 0.0001$		4.32 (3.05, 6.13); $P < 0.0001$	

vs. empagliflozin; *P* value								
Body weight reduction ≥ 10%								
Patients reaching endpoint, *n* (%)	49 (12.5)	27 (6.8)	58 (15.0)	30 (7.8)	49 (14.1)	27 (7.1)	56 (18.2)	28 (8.7)
Estimated OR (95% CI) oral semaglutide vs. empagliflozin; *P* value	1.98 (1.21, 3.25); *P* = 0.0066		2.05 (1.28, 3.28); *P* = 0.0028		2.18 (1.33, 3.57); *P* = 0.0021		2.51 (1.57, 4.01); *P* < 0.0001	
HbA_{1c} < 7% (53 mmol/mol) without hypoglycemia† and no weight gain								

Patients reaching endpoint, *n* (%)	237 (60.5)	141 (35.7)	214 (55.7)	149 (39.0)	222 (64.0)	139 (36.8)	191 (63.0)	139 (44.0)
Estimated OR (95% CI) oral semaglutide vs. empagliflozin; *P* value	2.88 (2.12, 3.91); $P < 0.0001$		2.03 (1.50, 2.74); $P < 0.0001$		3.31 (2.40, 4.56); $P < 0.0001$		2.39 (1.74, 3.30); $P < 0.0001$	
HbA_{1c} reduction ≥ 1% (10.9 mmol/mol) and body weight loss ≥ 3%								
Patients reaching endpoint, *n* (%)	177 (45.2)	111 (28.1)	164 (42.7)	101 (26.4)	172 (49.6)	110 (29.1)	148 (48.8)	91 (28.8)
Estimated OR (95% CI) oral semaglutide vs.	2.10 (1.55, 2.85); $P < 0.0001$		2.10 (1.54, 2.87); $P < 0.0001$		2.41 (1.77, 3.29); $P < 0.0001$		2.33 (1.69, 3.21); $P < 0.0001$	

empagliflozin; *P* value								
Waist circumference (cm)								
Estimated mean	104.8	105.5	105.1	105.7	104.5	105.6	104.4	105.6
Estimated mean change from baseline	–3.7	–3.0	–3.5	–2.9	–4.1	–3.0	–4.2	–2.9
Estimated treatment difference (95% CI) oral semaglutide vs.	–0.7 (–1.4, –0.0); *P* = 0.0400		–0.6 (–1.4, 0.2); *P* = 0.1488		–1.1 (–1.8, –0.4); *P* = 0.0033		–1.3 (–2.1, –0.4); *P* = 0.0030	

empagliflozin; *P* value								
Fasting plasma glucose, mmol/L (mg/dL)								
Estimated mean	7.59 (136.8)	7.57 (136.5)	7.58 (136.6)	7.50 (135.1)	7.39 (133.2)	7.60 (137.0)	7.48 (134.7)	7.58 (136.7)
Estimated mean change from baseline	–1.99 (–35.9)	–2.01 (–36.3)	–2.01 (–36.2)	–2.09 (–37.6)	–2.19 (–39.5)	–1.99 (–35.8)	–2.11 (–38.1)	–2.00 (–36.1)
Estimated treatment difference (95% CI) oral semaglutide vs.	0.02 (–0.24, 0.28), 0.4 (–4.3, 5.0);*P* = 0.8812		0.08 [–0.20, 0.36], 1.4 (–3.6, 6.4); *P* = 0.5759		-0.21 [–0.44, 0.03], –3.7 (–8.0, 0.5); *P* = 0.0874		–0.11 [–0.37, 0.15], –2.0 (–6.6, 2.6): *P* = 0.4016	

empagliflozin; *P* value								
Mean 7-point SMBG, mmol/L (mg/dL)								
Estimated mean	8.0 (143.7)	8.3 (148.8)	7.9 (142.4)	8.2 (147.4)	7.7 (138.8)	8.3 (148.7)	7.7 (138.5)	8.2 (147.1)
Estimated mean change from baseline	–2.2 (–39.8)	–1.9 (–34.7)	–2.3 (–41.1)	–2.0 (–36.1)	–2.4 (–44.0)	–1.9 (–34.0)	–2.5 (–44.3)	–2.0 (–35.7)
Estimated treatment difference (95% CI) oral semaglutide vs. empagliflozin; *P* value	–0.3 (–0.5, –0.0), –5.0 (–9.5, –0.6); *P* = 0.0267		–0.3 (–0.5, –0.0), –5.1 (–9.7, –0.4); *P* = 0.0328		-0.6 (–0.8, –0.3), –10.0 (–13.8, –6.1); *P* < 0.0001		–0.5 (–0.7, –0.2), –8.7 (–12.9, –4.4); *P* < 0.0001	

7-point SMBG post-prandial increment. mmol/L (mg/dL)								
Estimated mean	1.5 (27.5)	1.7 (30.0)	1.3 (23.2)	1.7 (30.7)	1.4 (25.1)	1.6 (29.1)	1.2 (22.5)	1.7 (30.2)
Estimated mean change from baseline	–0.5 (–8.7)	–0.3 (–6.2)	–0.7 (–13.0)	–0.3 (–5.5)	–0.6 (–11.4)	–0.4 (–7.3)	–0.8 (–14.0)	–0.3 (–6.3)
Estimated treatment difference (95% CI) oral semaglutide vs. empagliflozin; *P* value	–0.1 (–0.4, 0.1), –2.5 (–6.6, 1.6); *P* = 0.2388		–0.4 (–0.6, –0.2), –7.5 (–11.5, –3.4); *P* = 0.0003		–0.2 (–0.4, –0.0), –4.1 (–7.9, –0.3); *P* = 0.0356		–0.4 (–0.6, –0.2), –7.7 (–11.5, –3.9); *P* < 0.0001	
Fasting C-peptide (nmol/L)								

Estimated mean	0.958	0.798	0.959	0.827	0.964	0.799	0.964	0.805
Estimated ratio to baseline	1.08	0.90	1.09	0.94	1.09	0.91	1.09	0.91
Estimated treatment ratio (95% CI) oral semaglutide vs. empagliflozin; *P* value	1.20 (1.15, 1.25); $P < 0.0001$		1.16 (1.11, 1.22); $P < 0.0001$		1.21 (1.15, 1.26); $P < 0.0001$		1.20 (1.14, 1.26); $P < 0.0001$	
Fasting insulin (pmol/L)								
Estimated mean	88	65	86	66	87	63	83	63
Estimated ratio to baseline	1.06	0.78	1.03	0.79	1.03	0.75	0.99	0.75

Estimated treatment ratio (95% CI) oral semaglutide vs. empagliflozin; *P* value	1.35 (1.26, 1.46); *P* < 0.0001		1.31 (1.21, 1.41); *P* < 0.0001		1.37 (1.29, 1.46); *P* < 0.0001		1.32 (1.23, 1.41); *P* < 0.0001	
Fasting pro-insulin (pmol/L)								
Estimated mean	18.3	17.1	18.7	17.9	17.3	16.8	17.6	17.0
Estimated mean change from baseline	0.72	0.68	0.74	0.71	0.68	0.66	0.69	0.67
Estimated treatment difference (95%	1.07 (0.98, 1.17); *P* = 0.1403		1.05 (0.96, 1.14); *P* = 0.3034		1.03 (0.94, 1.12); *P* = 0.5453		1.04 (0.95, 1.14); *P* = 0.4479	

CI) oral semaglutide vs. empagliflozin; *P* value								
Fasting glucagon (pg/mL)								
Estimated mean	86	95	84	90	85	95	84	89
Estimated ratio to baseline	0.92	1.01	0.89	0.95	0.90	1.01	0.89	0.95
Estimated treatment ratio (95% CI) oral semaglutide vs. empagliflozin; *P* value	0.91 (0.88, 0.94); $P < 0.0001$		0.94 (0.90, 0.97); $P = 0.0008$		0.89 (0.86, 0.92); $P < 0.0001$		0.94 (0.90, 0.97); $P = 0.0011$	

C-reactive protein (mg/L)								
Estimated mean	1.85	2.65	1.81	2.45	1.78	2.68	1.71	2.45
Estimated ratio to baseline	0.69	0.99	0.67	0.91	0.65	0.98	0.63	0.90
Estimated treatment ratio (95% CI) oral semaglutide vs. empagliflozin; *P* value	0.70 (0.62, 0.79); $P < 0.0001$		0.74 (0.65, 0.84); $P < 0.0001$		0.66 (0.58, 0.75); $P < 0.0001$		0.70 (0.61, 0.80); $P < 0.0001$	

[a] Additional endpoints are reported in the Appendix table S4.

† Severe or blood-glucose confirmed (plasma glucose < 3.1 mmol/L [56 mg/dL]) symptomatic hypoglycemic episode. %: proportion of subjects with non-missing information. *P* values are unadjusted two-sided p values for the test of no difference;

Treatment policy estimand: ANCOVA for continuous endpoints and logistic regression for binary endpoints, using data irrespective of discontinuation of trial product or initiation of rescue medication. Missing values were imputed by a pattern mixture model using multiple imputation (MI). Patterns were defined by use of trial product and rescue medication. Trial product estimand: mixed model for repeated measurements for continuous endpoints and logistic regression for binary endpoints. Data collected after discontinuation of trial product or initiation of rescue medication is excluded. For binary endpoints missing values were imputed from subjects randomized to same trial product using sequential MI.

SE, standard error of the mean; OR, odds ratio; SMBG, self-monitored blood glucose.

Table 3—On-Treatment Adverse Events

	Oral semaglutide 14 mg (*N* = 410)	Empagliflozin 25 mg (*N* = 409)
	Patients, *n* (%)	
Adverse events	289 (70.5)	283 (69.2)
Serious adverse events	27 (6.6)	37 (9.0)
Adverse event severity:		
Mild	242 (59.0)	240 (58.7)
Moderate	140 (34.1)	118 (28.9)
Severe	24 (5.9)	23 (5.6)
Severe or blood glucose-confirmed symptomatic hypoglycemic episode*†‡	7 (1.7)	8 (2.0)
ADA-classified hypoglycemic episode*	45 (11.0)	39 (9.5)
Severe hypoglycemic episode*†	1 (0.2)	1 (0.2)
Most frequent adverse events ≥ 5% in either group (preferred term):		

Nausea	81 (19.8)	10 (2.4)
Diarrhea	38 (9.3)	13 (3.2)
Vomiting	30 (7.3)	7 (1.7)
Decreased appetite	21 (5.1)	2 (0.5)
Influenza	8 (2.0)	21 (5.1)
Adverse events resulting in premature trial drug discontinuation	44 (10.7)	18 (4.4)
Adverse events resulting in premature trial drug discontinuation (>1% for any system organ class or preferred term):		
Gastrointestinal disorders:	33 (8.0)	3 (0.7)
Nausea	21 (5.1)	2 (0.5)
Vomiting	11 (2.7)	1 (0.2)
Abdominal pain	5 (1.2)	0
Infections and infestations	0	5 (1.2)
Deaths	0	1 (0.2)[§]

Safety endpoints were assessed using the safety analysis set (all patients exposed to ≥ 1 dose of trial product) and evaluated for both the on-treatment period (while on trial product) and

in-trial period (while in trial, regardless of discontinuation of trial product or use of rescue medication).

* Hypoglycemic episodes were reported on a separate form to adverse events.

† An episode that is severe, according to the American Diabetes Association classification (requires assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions) (29).

‡Blood glucose confirmation of symptomatic hypoglycemia was based on a blood glucose value (< 56 mg/dL) with symptoms consistent with hypoglycemia.

§ One patient in the empagliflozin group died due to undetermined reasons after 268 days on trial drug.

FDA, Food and Drug Administration.

FIGURE LEGENDS

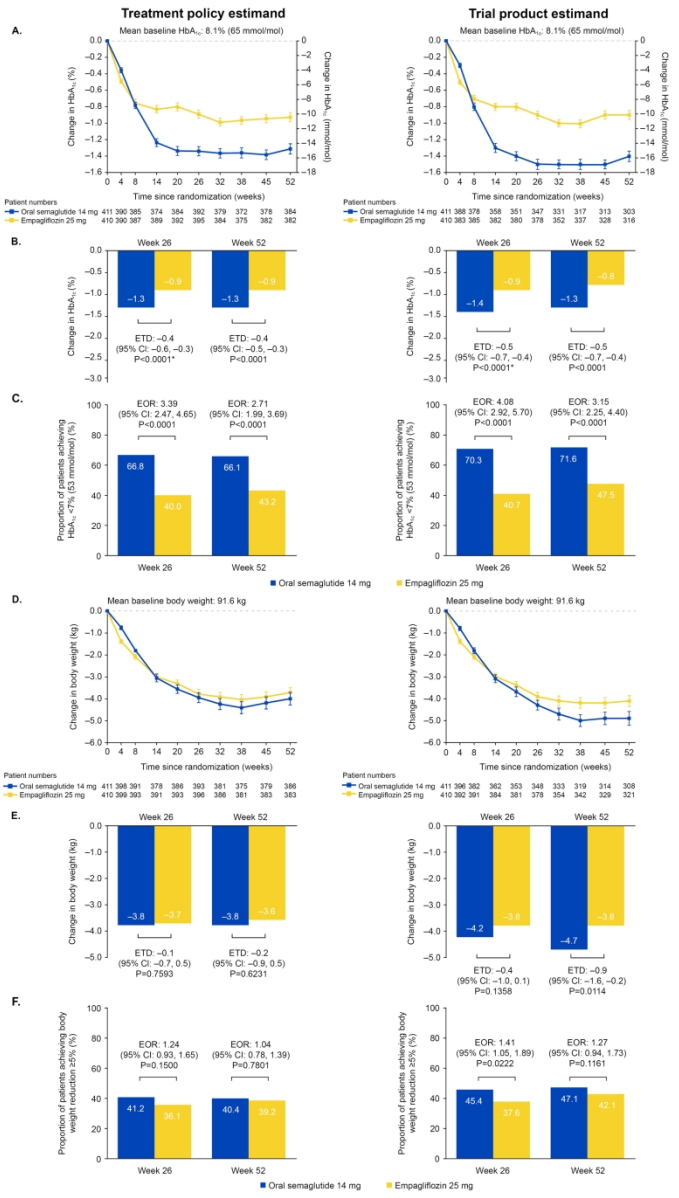
Figure 1—Glycemic control and body weight-related efficacy endpoints

A: Observed absolute change in HbA_{1c} over time; B: Estimated changes from baseline in HbA_{1c} at weeks 26 and 52; C: Observed proportions of patients achieving $HbA_{1c} < 7\%$ (53 mmol/mol) at weeks 26 and 52; D: Observed absolute change in body weight over time; E: Estimated changes from baseline in body weight at weeks 26 and 52; F: Observed proportions of patients achieving body weight reduction ≥ 5% at weeks 26 and 52.

* Superiority confirmed for oral semaglutide versus empagliflozin.

Observed mean change (± the standard error of the mean) from baseline (Panel A/D), estimated mean changes from baseline at week 26 and 52 (Panel B/E), and observed proportions of patients achieving target at weeks 26 and 52 (Panel C/F). *N* values represent the number of patients contributing to the means/proportions. Treatment policy estimand: data irrespective of discontinuation of trial product and initiation of rescue medication were included. Trial product estimand: data collected after discontinuation of trial product or initiation of rescue medication is excluded. *P* values are two-sided and unadjusted.

CI, confidence interval; EOR, estimated odds ratio; ETD, estimated treatment difference.



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