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Safety profile of semaglutide versus placebo in the SELECT study: a randomized controlled trial

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Abstract

Objective: The objective of this study was to assess safety of once-weekly subcutaneous semaglutide 2.4 mg versus placebo, beyond reduction in major adverse cardiovascular events, in patients with established cardiovascular disease and overweight or obesity.

Methods: Safety data focused on serious adverse events (SAEs), all adverse events (AEs) leading to permanent treatment discontinuation irrespective of seriousness, and prespecified AEs of special interest irrespective of seriousness. Tests of treatment differences were determined by two-sided *p* values.

Results: The proportion of patients with SAEs was lower with semaglutide versus placebo (33.4% vs. 36.4%; $p < 0.001$), primarily driven by cardiac disorders (11.5% vs. 13.5%; $p < 0.001$). The proportion of patients with AEs leading to discontinuation was higher with semaglutide versus placebo (16.6% vs. 8.2%; $p < 0.001$), a difference driven by gastrointestinal disorders (10.0% vs. 2.0%); however, proportions due to SAEs leading to discontinuation were similar (3.6% vs. 4.1%). Suicide/self-injury SAEs were low and balanced between groups (0.11% in both groups). Gallbladder-related disorders were more frequent with semaglutide versus placebo (2.8% vs. 2.3%; $p = 0.04$), mainly driven by cholelithiasis (1.4% vs. 1.1%), whereas proportions of cholecystitis were similar between groups (0.6% vs. 0.6%).

Conclusions: The long-term safety profile observed in the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) study is consistent with previously reported semaglutide studies. No new safety concerns were identified for once-weekly semaglutide 2.4 mg.

INTRODUCTION

The availability of once-weekly subcutaneous semaglutide 2.4 mg, a glucagon-like peptide-1 (GLP-1) analog, represents a paradigm shift in the management of obesity, a chronic, progressive, and relapsing disease [1]. Newer-generation nutrient-stimulated, hormone-based therapeutics are more effective for weight loss than previously approved medications [2], provide weight-dependent and other pleotropic cardiometabolic effects [3], and are delivered as convenient weekly formulations [4]. The phase 3 Semaglutide Treatment Effect in People with Obesity (STEP) program evaluated the efficacy, safety, and tolerability of once-weekly subcutaneous semaglutide 2.4 mg versus placebo for weight management in people with obesity or overweight [5].

Once-weekly semaglutide 2.4 mg was approved for chronic weight management by the US Food and Drug Administration (FDA) in 2021 and by the European Medicines Agency (EMA) in 2022. In addition to improvements in body weight and cardiometabolic risk factors, a dedicated cardiovascular (CV) outcomes trial (CVOT) was conducted to evaluate CV safety, as requested by the FDA [6, 7] and EMA [8] for antiobesity medications (AOMs). In the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) study [6, 7], once-weekly subcutaneous semaglutide 2.4 mg reduced major adverse CV events (MACE) by 20% (95% confidence interval [CI]: 0.72–0.90; $p < 0.001$) versus placebo in 17,604 patients with overweight and obesity and preexisting CV disease (CVD) without diabetes [8]. The FDA recently approved a label expansion including this indication.

The effects of semaglutide on weight loss and cardiometabolic risk in a high-risk population must be weighed against its safety profile. The safety profile is evaluated based on prospectively collected clinical trial data and continuous post-marketing reporting. As the longest and largest placebo-controlled study to date systematically evaluating semaglutide, SELECT significantly builds on data from the STEP studies, providing a unique opportunity to explore known and new safety signals. This analysis provides a detailed assessment of the safety data collected in SELECT (including all adverse events [AEs] leading to permanent treatment discontinuation) to support clinicians and policy makers in assessing the risk–benefit and potential coverage of semaglutide for relevant patients.

METHODS

Study design and patients

We report prespecified safety analyses of the randomized, double-blind, placebo-controlled, event-driven phase 3 SELECT study (ClinicalTrials.gov NCT03574597) [6–9]. Similar to the STEP phase 3a studies, patients with tolerability issues could stay on their maximum tolerated dose throughout the study. Further information on dosage in the SELECT study can be found in the online Supporting Information Methods. Randomization occurred from October 2018 through March 2021, with the last patient's last visit on June 29, 2023. The SELECT protocol was approved by the institutional review board and ethics committee at each participating center. Patients provided written informed consent before commencement of any study-specific activity.

Outcomes

The primary objective was to demonstrate superiority of once-weekly subcutaneous semaglutide 2.4 mg versus placebo, in addition to standard of care, in reducing the incidence of MACE [8].

Targeted collection of safety data focused on the following three areas: all investigator-reported serious AEs (SAEs); AEs leading to treatment discontinuation irrespective of seriousness; and prespecified AEs of special interest irrespective of seriousness. Prespecified AEs of special interest were collected by additional data on specified forms or were sent to a blinded, independent Events Adjudication Committee (EAC; Table S1). Definitions of AEs and SAEs can be found in the online Supporting Information Methods. Additionally, due to the COVID-19 pandemic during the SELECT study, COVID-19 AEs irrespective of seriousness were included as targeted data and collected on AE forms for sensitivity analyses related to COVID-19 infection. Nonserious AEs not fulfilling any of the listed criteria were not systematically collected.

AEs were hierarchically categorized based on the prespecified Medical Dictionary for Regulatory Activities (MedDRA) system by system organ class (SOC), high-level group term (HLGT), high-level term, and preferred term (PT) [10]. Safety focus areas were evaluated based on predefined MedDRA searches and allowed for inclusion of all relevant reports if not already covered by the hierarchical architecture of the MedDRA system.

Statistical analyses

Statistical analyses and summary statistics are presented for the in-trial period and based on the intention-to-treat principle, which included all randomized patients irrespective of adherence to semaglutide or placebo or changes to background medications. Patients with events (numbers and proportions), numbers of events, and event rates (reported as rates per 100 patient-years of observation [PYO]) according to treatment group were presented, and the proportions of patients experiencing events were analyzed using Fisher exact test for test of no difference and presented with two-sided p values. Summaries of AEs are categorized by severity, relationship to treatment, and outcome.

RESULTS

The study included 17,604 patients (8803 received semaglutide, and 8801 received placebo) with mean (SD) age of 61.6 (8.9) years (range 45–93 years). Patients were mostly male (72.3%), White (84.0% vs. 8.2% Asian and 3.8% Black), and not Hispanic or Latino (88.7% vs. 10.3% Latino). Mean (SD) body mass index (BMI) was 33.3 (5.0) kg/m^2. Current smokers, never smokers, and previous smokers accounted for 16.8%, 34.8%, and 48.5% of the study population, respectively. Mean (SD) treatment exposure was 34.2 (13.7) months, and follow-up was 39.8 (9.4) months. A total of 97.1% of the semaglutide group and 96.8% of the placebo group completed the study. Similar proportions of patients completed drug treatment (73.3% of those treated with semaglutide vs. 76.4% of those treated with placebo) [8]. Additional analyses of baseline characteristics have been published [6, 8, 9].

Study Importance

What is already known about this subject?

- The phase 3 Semaglutide Treatment Effect in People with Obesity (STEP) program demonstrated that, overall, semaglutide 2.4 mg was well tolerated by patients with overweight or obesity, and its safety profile was consistent with the glucagon-like peptide-1 receptor agonist class, with no unexpected findings. However, the longest treatment duration in these trials was 104 weeks, and, overall, a healthy population was included; therefore, the side effect profile was not completely explored.

What does this study add?

- The safety of semaglutide 2.4 mg was confirmed for the first time in the longest treatment period of any studies to date in a geographically and racially diverse population ($n = 17{,}604$) with overweight or obesity with established cardiovascular disease (CVD) and without diabetes.
- In particular, there was no difference between groups in reporting of serious psychiatric disorders, including suicide and self-injury, acute pancreatitis, or malignant neoplasms, including primary location in the pancreas, thyroid gland, and breast (female individuals only). More adverse events (AEs) of gallbladder-related disorders were reported with semaglutide compared with placebo, mainly driven by cholelithiasis, whereas cholecystitis AEs were balanced between groups.

How might the results change the direction of research or the focus of clinical practice?

- Findings from the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) study confirm the overall safety profile of semaglutide treatment in people with overweight or obesity and established CVD without diabetes.

SAEs

The proportion of patients with SAEs was lower in the semaglutide versus placebo groups (33.4% vs. 36.4%; $p < 0.001$), a difference primarily driven by cardiac disorders (11.5% vs. 13.5%; $p < 0.001$), infections and infestations (7.1% vs. 8.4%; $p < 0.001$), nervous system disorders (5.0% vs. 5.6%; $p = 0.08$), and surgical and medical procedures (4.9% vs. 6.2%; $p < 0.001$), as previously reported [8]. When MACE were excluded, serious cardiac disorders were reported in 8.8% of patients treated with semaglutide and 10.3% of patients treated with placebo; nervous system disorders were reported in 3.4% of patients treated with semaglutide and 3.8% of

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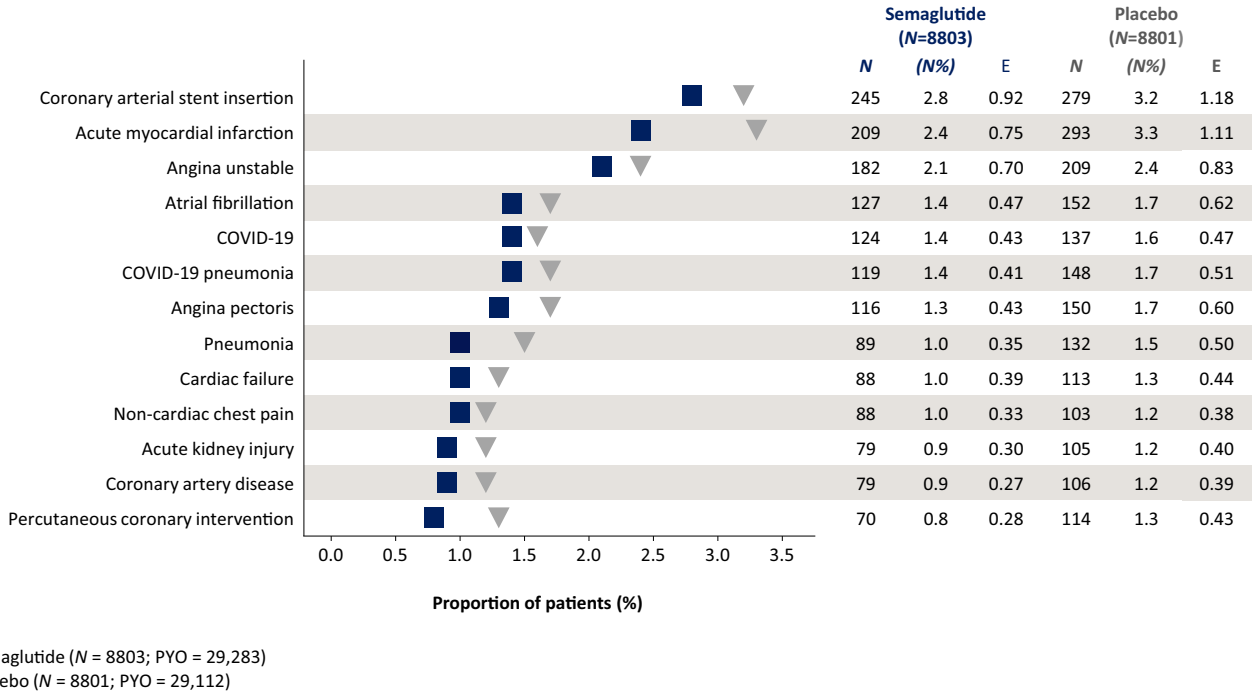

FIGURE 1 SAEs by PT reported in ≥1% of patients in any treatment arm. Plot shows the proportion of patients with ≥1 SAE at the PT level, sorted in descending order of frequency in the semaglutide group. E, events per 100 patient-years; *N*, number of patients; *N%*, percentage of patients in full analysis set; PT, preferred term; PYO, patient-years of observation; SAE, serious adverse event. [Color figure can be viewed at wileyonlinelibrary.com]

patients treated with placebo (Table S2). SAEs were infrequently related to trial product, deemed (by investigators) as probable (0.5% vs. 0.4%) and possible (2.4% vs. 2.1%) for semaglutide and placebo, respectively.

Of the 10 most reported SAEs by PT, 6 were related to cardiac disorders, which were less frequent in the semaglutide versus placebo groups (Figure 1). Differences in infections were largely driven by COVID-19 pneumonia (1.4% vs. 1.7%) and unspecified pneumonia (1.0% vs. 1.5%) for semaglutide versus placebo. The imbalance in nervous system disorders was primarily driven by reporting within the HLGT central nervous system vascular disorders (2.9% vs. 3.5%), e.g., transient ischemic attack (0.4% vs. 0.7%), cerebrovascular accident (0.4% vs. 0.6%), and cerebral infarction (0.2% vs. 0.3%). There were no differences in the proportions of patients reporting malignant or benign neoplasms (4.6% vs. 4.6%).

SAEs from gastrointestinal disorders were balanced between the semaglutide and placebo groups (3.9% vs. 3.7%). The most common events were inguinal hernia (0.4% vs. 0.3%), diarrhea (0.3% vs. 0.2%), gastrointestinal hemorrhage (0.3% vs. 0.2%), and vomiting (0.2% vs. 0.1%). Terms within the HLGT gastrointestinal stenosis and obstruction occurred in 29 (0.3%) patients in each treatment group. Corresponding cases of specific reports about ileus were observed in three versus two patients, respectively.

EAC-confirmed deaths were 375 (4.3%) in the semaglutide group versus 458 (5.2%) in the placebo group (hazard ratio [HR], 0.81; 95% CI: 0.71–0.93). The most frequent EAC-confirmed cause of death was CV death, occurring in 146 patients treated with semaglutide (1.7% with 0.50 events per 100 PYO) versus 172 patients treated with placebo (2.0% with 0.59 events per 100 PYO), in whom sudden cardiac death followed by stroke and heart failure was the most frequently reported. Non-CV, nonrenal deaths occurred in 152 patients treated with semaglutide (1.7% with 0.52 events per 100 PYO) versus 196 patients treated with placebo (2.2% with 0.67 events per 100 PYO), mostly driven by infection (0.7% vs. 1.0%) and malignancy (0.6% vs. 0.7%). Of the total 149 deaths due to infection, 72% were reported as related to COVID-19 (69% vs. 75% for patients treated with semaglutide and patients treated with placebo, respectively). Finally, the EAC concluded the cause of death as undetermined in 77 (0.9%) versus 90 (1.0%) patients treated with semaglutide versus placebo.

There were fewer SAEs in the semaglutide versus placebo groups in both sexes, i.e., 34.2% versus 37.9% for male individuals and 31.3% versus 32.5% for female individuals, respectively. The proportions of SAEs based on baseline BMI categories appeared comparable across categories and were lower for patients treated with semaglutide versus those treated with placebo (Figure 2). The occurrence of SAEs increased with advancing age (Figure 3) in both treatment groups. For age cohorts <55 years, ≥55 to <65 years, ≥65 to <75 years, and ≥75 years, the proportions of SAEs for the semaglutide and placebo groups were 26.9% versus 29.0%, 30.2% versus 33.4%, 38.7% versus 42.3%, and 47.9% versus 51.0%, respectively; corresponding fatality occurred in 2.4% versus 2.4%, 3.1% versus 4.3%, 5.4% versus 7.2%, and 10.2% versus 11.0%, respectively.

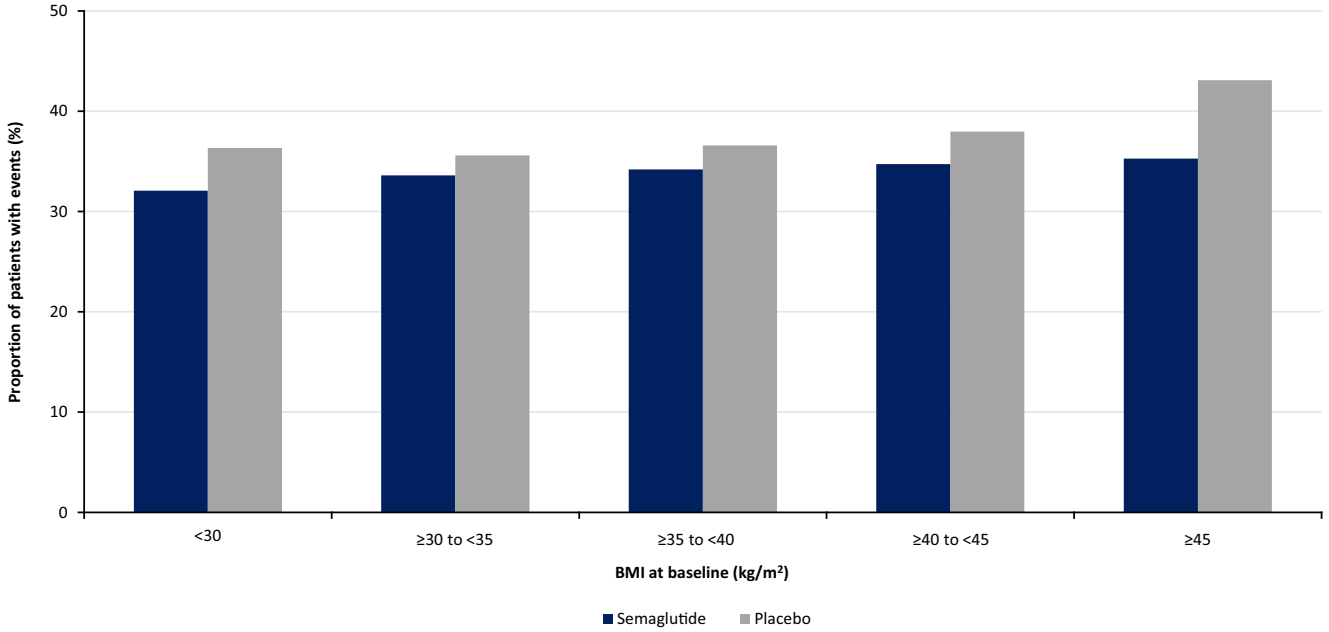

FIGURE 2 SAEs by baseline BMI. Data from the full analysis set in the trial period. SAE, serious adverse event. [Color figure can be viewed at wileyonlinelibrary.com]

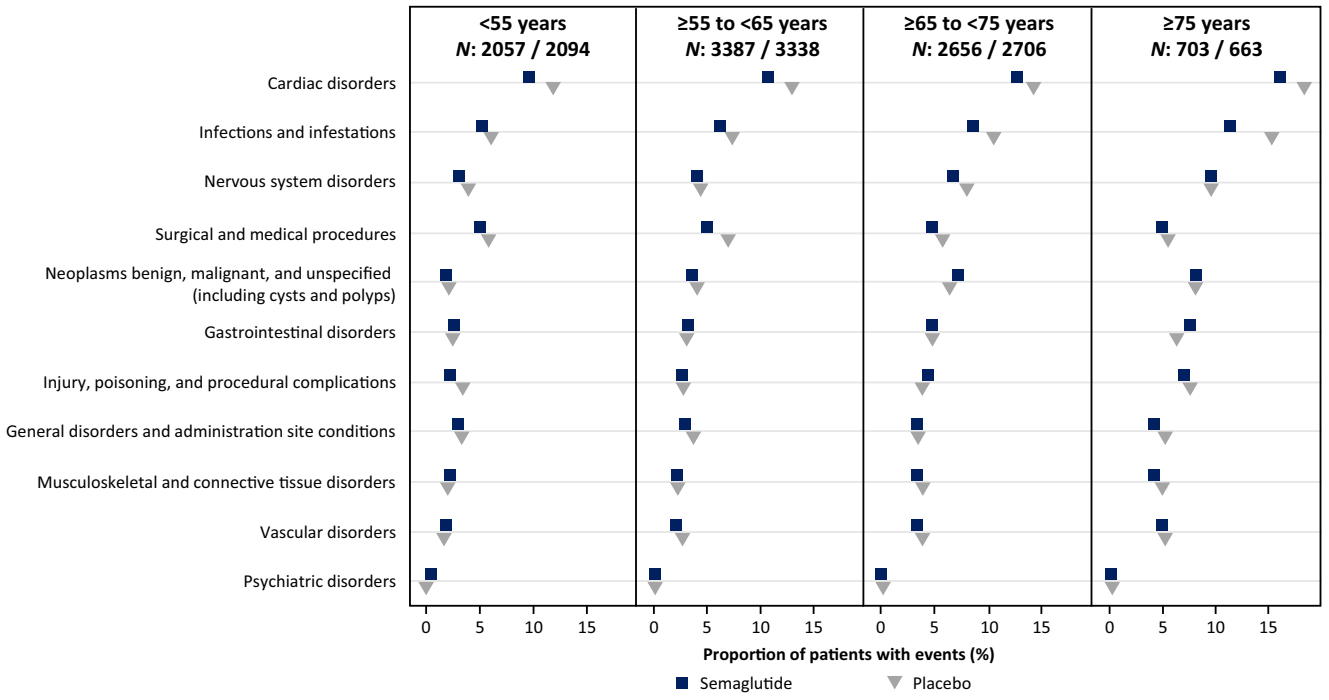

FIGURE 3 SAEs by age cohort by SOC. Plot shows SAEs by SOC by absolute count, in which absolute count >1 in the total population (up to 15 in the case of a tie). SAEs by SOC are sorted in descending order by overall frequency in the semaglutide group. SAE, serious adverse event; SOC, system organ class. [Color figure can be viewed at wileyonlinelibrary.com]

AEs leading to permanent discontinuation of trial product

The proportion of patients with AEs leading to permanent treatment discontinuation was higher in the semaglutide versus placebo groups (16.6% vs. 8.2%; $p < 0.001$); however, the proportions of patients with discontinuation of study drug due to SAEs were similar (3.6% vs. 4.1%). The imbalance of AEs was largely driven by gastrointestinal disorders (10.0% vs. 2.0%; $p < 0.001$), shown as PT in Table 1 and Figure 4, which also provide events per 100 PYO (rates), as well as AEs probably or possibly related to trial product assessed by the investigator [8] and primarily occurring during the first 16-week dose-escalation phase

TABLE 1 AEs leading to permanent product discontinuation by PT reported in ≥0.5% of patients in any treatment arm, irrespective of seriousness.

	Semaglutide (n = 8803)			Placebo (n = 8801)		
	Patients, n (%)	Events per 100 patient-years (rates)	Probably or possibly related to trial product, n (%)[a]	Patients, n (%)	Events per 100 patient-years (rates)	Probably or possibly related to trial product, n (%)[a]
Nausea	378 (4.3)	1.3	367 (4.2)	35 (0.4)	0.1	32 (0.4)
Diarrhea	207 (2.4)	0.7	197 (2.2)	32 (0.4)	0.1	27 (0.3)
Vomiting	126 (1.4)	0.4	122 (1.4)	6 (0.1)	0.0	5 (<0.1)
Decreased appetite	93 (1.1)	0.3	91 (1.0)	9 (0.1)	0.0	9 (0.1)
Constipation	81 (0.9)	0.3	76 (0.9)	15 (0.2)	0.1	13 (0.1)
Dyspepsia	77 (0.9)	0.3	75 (0.9)	9 (0.1)	0.0	8 (<0.1)
Abdominal pain	44 (0.5)	0.2	40 (0.5)	13 (0.2)	0.0	11 (0.1)

Note: Data are sorted in descending order by PT based on the proportion of patients with ≥1 event in the semaglutide group. Up to 3 AEs could be reported as leading to trial product discontinuation.
Abbreviations: AE, adverse event; PT, preferred term.
[a]Number and proportion of patients with events in which the investigator assessed the relationship to trial product as either probable or possible.

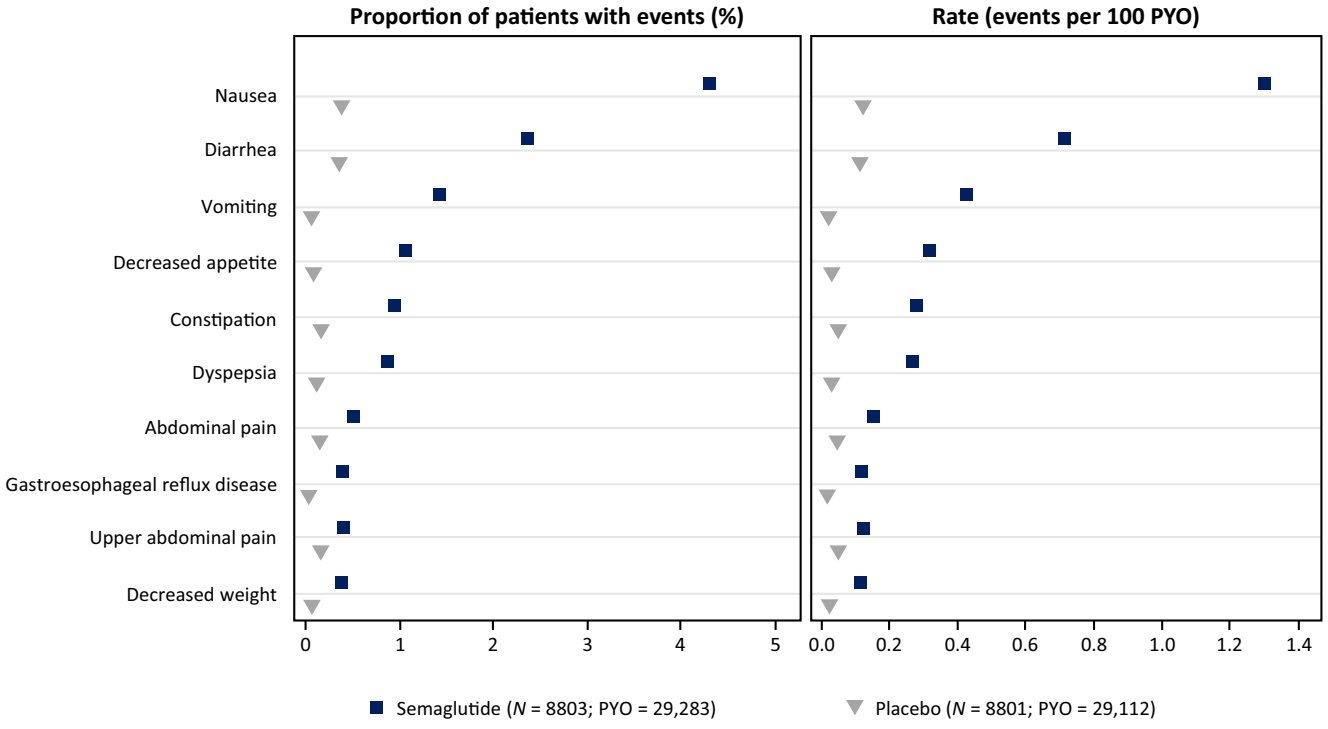

FIGURE 4 Most frequent AEs leading to permanent trial product discontinuation by PT irrespective of seriousness. Plot shows 10 most frequent AEs by absolute count, in which absolute count >1 in the total population. Trial product discontinuation was defined as either withdrawal of drug or interruption of treatment due to AEs. AEs are sorted in descending order by frequency in the semaglutide group. AE, adverse event; PT, preferred term; PYO, patient-years of observation. [Color figure can be viewed at wileyonlinelibrary.com]

(Figure 5). The two most common non-gastrointestinal causes occurring more often for the semaglutide group compared with the placebo group were decreased appetite (1.1% vs. 0.1%) and decreased weight (0.4% vs. 0.1%). Permanent discontinuation was similar for male (16.5% vs. 8.1%) and female individuals (16.8% vs. 8.3%) in the semaglutide and placebo groups, respectively.

Prespecified AEs of special interest

Gallbladder-related disorders were more frequent in patients treated with semaglutide versus placebo (246 [2.8%] patients, 1.02 events per 100 PYO vs. 203 [2.3%] patients, 0.85 events per 100 PYO; $p = 0.04$) [8]. These were mainly driven by cholelithiasis (1.4%

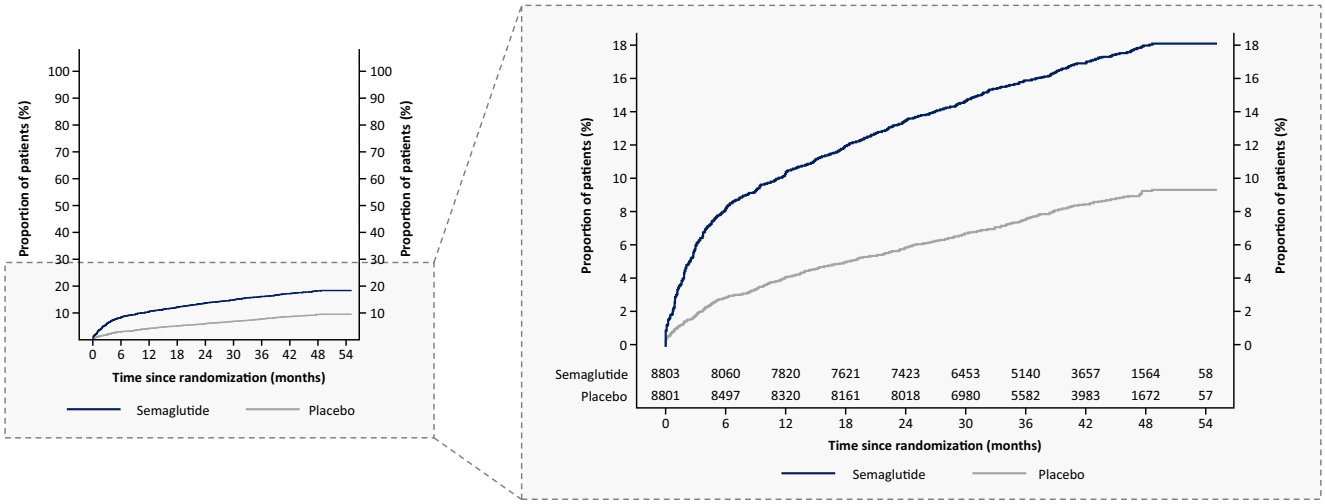

FIGURE 5 AEs leading to permanent trial product discontinuation irrespective of seriousness. Data are from the in-trial period. Cumulative incidence estimates were based on the time from randomization to first AE leading to permanent trial discontinuation, with all-cause death as a competing risk. Patients without events of interest were censored at the end of their in-trial period. AE, adverse event. [Color figure can be viewed at wileyonlinelibrary.com]

vs. 1.1%), whereas cholecystitis events (grouped PT: cholecystitis, acute cholecystitis, and infective cholecystitis) were balanced (0.56% vs. 0.59%). There were no group differences in seriousness, severity, relationship to trial product, outcome, or action taken for gallbladder-related disorders. SAEs for gallbladder-related disorders categorized by <5%, 5% to <15%, and ≥15% weight loss were 2.8%, 2.7%, and 3.0% for semaglutide and 2.2%, 2.5%, and 3.4% for placebo, respectively. Among the 13.6% of patients with a history of gallbladder disease at screening, the proportion with gallbladder-related disorders was 3.1% in the semaglutide group versus 2.9% for the placebo group (reporting for the PT cholelithiasis; semaglutide 0.9% vs. placebo 1.2%). The corresponding proportion of patients with reported gallbladder-related disorders but without a history of gallbladder disease was 2.7% for semaglutide versus 2.2% for placebo (reporting for the PT cholelithiasis; semaglutide 1.5% vs. placebo 1.1%).

Acute pancreatitis occurred similarly between groups (17 patients [0.2%] treated with semaglutide vs. 24 [0.3%] treated with placebo) [8]. In both treatment groups, most confirmed events were categorized by the EAC as acute, mild-to-moderate-severity pancreatitis. No patients with a history of pancreatitis at screening ($n = 69$) had an acute pancreatitis event confirmed by the EAC.

Similar proportions of patients in both groups reported malignant neoplasms. No group differences were observed in seriousness, severity, relationship, and action taken for trial product, as well as outcome of the events. Fatal malignant neoplasms were reported at similar frequencies and rates in the semaglutide group (59 patients, 0.7%, 0.22 events per 100 PYO) and the placebo group (60 patients, 0.7%, 0.22 events per 100 PYO). The most frequently reported primary location of malignant neoplasms in both groups was skin (1.1% vs. 1.2%) and male reproductive system (1.3% vs. 1.2%) in the semaglutide and placebo groups, respectively (Figure S1). Malignant neoplasms with primary location in the breast (female individuals only) were reported at similar frequencies with semaglutide (0.7%) and placebo (0.8%). Malignant neoplasms with primary location in the pancreas were reported in eight (<0.1%) patients treated with semaglutide versus eleven (0.1%) patients treated with placebo. Malignant neoplasms with primary location in the thyroid gland were reported in six (<0.1%) patients treated with semaglutide versus eight (<0.1%) patients treated with placebo. All reported events of medullary thyroid cancer ($n = 3$), identified based on baseline calcitonin assessments, occurred in the placebo group.

The occurrence of acute kidney failure was balanced between the semaglutide and placebo groups (1.9% vs. 2.3%; $p = 0.13$), of which 1.0% and 1.3% of cases were classified as serious and led to six (0.1%) deaths in each group. The most frequently reported AE was acute kidney injury (1.4% vs. 1.7% for the semaglutide and placebo groups, respectively).

Because the study was conducted during the COVID-19 pandemic, nearly one-quarter of patients in the semaglutide group (24.0%) and the placebo group (24.4%) ($p = 0.46$) had COVID-19–related AEs, reported as serious in 2.6% versus 3.2% and resulting in death in 43 (0.5%) and 65 (0.7%) patients, respectively. COVID-19 pneumonia was reported in 1.6% versus 1.8% of patients for the two groups, respectively.

Additional safety focus areas

The proportions of patients reporting psychiatric disorders as SAEs were similar in the semaglutide and placebo groups: 75 events in 59 (0.7%) patients (0.26 events per 100 PYO) versus 59 events in 49 (0.6%) patients (0.20 events per 100 PYO), respectively (Table S3) [8]. Focusing in on the SAEs identified by the predefined MedDRA search for suicide/self-injury, few events were reported, with no imbalance between treatment groups (12 events in 10 [0.1%]

patients) and 0.04 events per 100 PYO in both treatment groups. All 12 events in the semaglutide group were judged by the investigator as unlikely to be related to trial product. Suicide as EAC-confirmed cause of death occurred in five patients in the semaglutide group and in three patients in the placebo group. Approximately one-half of the patients with SAEs including suicide/self-injury had either depression and/or anxiety in their medical history.

The numbers of events and corresponding proportions of patients with hypoglycemia SAEs were low and similar between treatment groups (three events in three patients corresponding to 0.03% in the semaglutide group and one event in one patient corresponding to 0.01% in the placebo group). The proportions of patients with hepatic disorder SAEs were low and similar in the semaglutide and placebo groups (0.4% vs. 0.4%). Most events in both treatment groups were judged by the investigator as unlikely related to trial product. The numbers and proportions of patients who experienced elevated liver function tests during the study are included in Table S4. Serious allergic reactions were reported for similar proportions of patients in each treatment group (0.3% vs. 0.3%).

Overall, when evaluating fractures on the HLGT level (1.5% in the semaglutide group vs. 1.7% in the placebo group) and SOC level (3.5% in the semaglutide group vs. 3.6% in the placebo group), no imbalance was identified. When evaluating the "female" and "elderly >75 years" subgroups, increased numerical imbalances were seen for hip (0.3% vs. 0% in female individuals and 1.3% vs. 0.15% in patients aged ≥75 years in the semaglutide and placebo groups, respectively) and pelvic (0.3% vs. 0.04% in female individuals and 0.4% vs. 0 in patients aged ≥75 years in the semaglutide and placebo groups, respectively) fractures. However, the numbers of patients were low, and, when subgroups were assessed on HLGT and SOC levels, no clear imbalances were found. Further details on serious fracture events are included in Table S5.

DISCUSSION

Medication prescription is based on the risk–benefit ratio for a patient. In addition to showing CV benefit, the SELECT study prospectively evaluates the safety of semaglutide in a large, diverse, global patient cohort over nearly 4 years of follow-up. Safety findings from the SELECT study are consistent with previous semaglutide studies; no unexpected safety concerns were identified. In particular, no increased rates of acute pancreatitis, malignant neoplasms, acute kidney failure, or suicidal ideation and behavior were seen in semaglutide-treated patients versus placebo. This is reassuring based on previous safety concerns over the use of GLP-1 receptor agonists (GLP-1RAs). SAE proportions were generally comparable across baseline BMI categories and lower in patients treated with semaglutide versus those treated with placebo. Because eligibility criteria for the SELECT study excluded key safety concerns, e.g., history or presence of chronic pancreatitis, presence or history of malignant neoplasms within the past 5 years prior to screening, and severe psychiatric disorders, generalization of the results to these patient populations needs to be interpreted with caution. As expected, the proportions of all SAEs increased with age for both treatment groups; however, the proportion of SAEs was lower in patients treated with semaglutide versus those treated with placebo in each age subgroup, highlighting the safety of semaglutide even in the highest age groups. Consistent with previous GLP-1RA studies, gastrointestinal events were the main AE leading to permanent treatment discontinuation.

It is relevant to compare the SELECT study safety results with those of other semaglutide studies when assessing the risk–benefit profile. The STEP studies evaluated the efficacy and safety of once-weekly semaglutide 2.4 mg versus placebo in addition to lifestyle interventions for weight loss in adults with overweight or obesity with or without diabetes [5, 11]. Because the SELECT study excluded patients with diabetes, a comparison with the non-diabetes STEP studies (STEP 1, 3, 4, 5, and 8) is warranted. These studies enrolled predominantly female patients (74%–81%) with a younger mean age (46–47 years), higher mean BMI (38 kg/m^2), and shorter treatment duration (68–204 weeks). In the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN 6) CVOT, patients with type 2 diabetes and established CVD, chronic kidney disease, or both were randomized to once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo [12]. This study population was more comparable with the SELECT study but had diabetes, had a shorter duration of treatment (104 weeks), and used a lower maintenance dose of semaglutide (up to 1.0 mg).

SAEs in the non-diabetes STEP studies were less frequent than in the SELECT study and ranged from 7.7% to 9.8% for semaglutide versus 2.9% to 11.8% for placebo, reflecting shorter study durations and younger, healthier populations. In contrast, the proportions of SAEs in the SUSTAIN 6 CVOT were 35% (43.5 events per 100 PYO) and 33.6% (36.7 events per 100 PYO) for semaglutide 0.5 mg and 1.0 mg, respectively, versus 39.9% (44.8 events per 100 PYO) and 36.1% (41.1 events per 100 PYO) for placebo. Although the proportions of patients with events in the SELECT study were similar to SUSTAIN 6, the event rates in the SELECT study are lower both in the patients treated with semaglutide (22.6 events per 100 PYO) and those treated with placebo (25.8 events per 100 PYO), despite the higher semaglutide dose in SELECT (2.4 mg vs. 0.5 and 1.0 mg).

The SELECT study was conducted during the COVID-19 pandemic; nearly one-quarter of patients had reported COVID-19–related AEs. Accordingly, the second most common SAE in the SELECT study was infections and infestations (7.1% of patients in the semaglutide group vs. 8.4% of patients in the placebo group), largely driven by COVID-19 pneumonia (1.4% vs. 1.7%) and pneumonia from other infectious agents (1.0% vs. 1.5%). The proportion of patients with fatal outcomes due to COVID-19 was 0.5% versus 0.7% in the semaglutide versus placebo groups, respectively [13]. Obesity is a known risk factor for developing COVID-19 and related hospitalizations, mechanical ventilation, and death [14, 15]. The lower proportions of SAEs and deaths in the semaglutide group versus the placebo group deserve further inquiry and may relate to greater weight loss and anti-inflammatory properties of GLP-1RAs [16].

The proportion of patients with AEs leading to permanent treatment discontinuation was higher in the semaglutide versus placebo groups (16.6% vs. 8.2%). Proportional differences for SUSTAIN 6 were

11.5% and 14.5% for semaglutide 0.5 mg and 1.0 mg, respectively, and 5.7% and 7.6% for the placebo groups [17]. In contrast, the proportions of patients discontinuing trial product were lower in the STEP studies, i.e., 3.2% to 7.0% for semaglutide versus 2.9% to 4.6% for placebo [11]. Caution should be exercised when comparing the proportions across studies, as long studies such as the SELECT study are expected to report higher proportions compared with shorter studies such as SUSTAIN 6 and the STEP studies, just as more patients are likely to experience the event of interest. Event rates take this into account, but the rates were not available for comparison.

Gastrointestinal side effects were the main AEs driving treatment discontinuation in the SELECT study, which is consistent with other studies of GLP-1RAs [18], although the incidence varies among studies. In the SELECT study, permanent treatment discontinuation due to gastrointestinal AEs was 10.0% in the semaglutide group versus 2.0% in the placebo group. This proportion is higher than that observed in the phase 3 STEP studies (0.8%–4.5% for semaglutide compared with 0.7%–1.2% for placebo) [11]. Treatment discontinuation due to gastrointestinal tolerability in SUSTAIN 6 was 5.7% and 9.4% for semaglutide 0.5 mg and 1.0 mg groups, respectively, and 1.2% and 1.0% for the corresponding placebo groups. Permanent treatment discontinuation primarily occurred during the 16-week dose escalation due to gastrointestinal symptoms (nausea, diarrhea, and vomiting). The higher proportion of patients experiencing gastrointestinal AEs leading to discontinuation in the SELECT study compared with STEP is likely due to the longer study duration, limited dietary counseling intended to mitigate side effects, and differences in patient motivation and expectations (given that the SELECT study focused on MACE reduction rather than weight loss). Differences between the SELECT study and SUSTAIN 6 may be due to the higher dose of semaglutide (2.4 mg vs. 0.5 mg and 1.0 mg), longer study duration, and study population (without vs. with diabetes).

In the SELECT study, gallbladder-related disorders were more common in the semaglutide versus placebo groups (2.8% vs. 2.3%). Similar proportions in SUSTAIN 6 were 3.9% and 3.2% for semaglutide 0.5 mg and 1.0 mg, respectively, versus 4.6% and 2.8% for placebo. For the STEP program, event rates ranged from 0.2% to 4.9% for semaglutide versus 0.7% to 3.7% for placebo. Specifically, a higher proportion of cholelithiasis events was seen for semaglutide (1.4%) versus placebo (1.1%) in the SELECT study; however, cholecystitis events were balanced between groups. Increased occurrence of acute gallbladder disease due to cholelithiasis was noted, and cholecystitis is listed as a warning on the semaglutide 2.4 mg US package insert. A systematic review and meta-analysis of 76 randomized clinical trials (60 for diabetes) found a significantly increased risk of gallbladder or biliary disease (risk ratio [RR], 1.37; 95% CI: 1.23–1.52) for all GLP-1RA treatments combined compared with controls, as well as increased risk of cholelithiasis (RR, 1.27; 95% CI: 1.10–1.47) [19]. Treatment variables that increase the risk of gallbladder or biliary diseases include higher dosing, for longer duration, and for weight loss in obesity [20–23].

No clear relationship between percentage weight loss and occurrence of gallbladder disorder SAEs was observed in the SELECT study. Among the 13.6% of patients who had a history of gallbladder disease at screening, the proportion with cholelithiasis and cholecystitis was slightly higher than in those without a history of gallbladder disease; however, it was similar between the semaglutide and placebo groups. This observation is clinically important and should be considered when determining the risk–benefit ratio of prescribing semaglutide to a patient with a history of preexisting gallbladder disease.

Acute pancreatitis occurred similarly between treatment groups. The proportions of patients in SUSTAIN 6 with reported pancreatitis were 0.7% and 0.4% for semaglutide 0.5 mg and 1.0 mg, respectively, versus 0.4% and 1.1% for placebo. The proportions in the STEP program were 0% to 0.2%. The FDA and EMA noted no association between incretin-based drugs prescribed for diabetes and pancreatitis [24]. An additional meta-analysis of seven CVOTs enrolling 56,004 patients with type 2 diabetes found that the risk of acute pancreatitis with GLP-1RA treatment was not significantly different from that in the placebo arm (odds ratio, 1.05; 95% CI: 0.78–1.40; $p = 0.76$) [20]. However, neither report included semaglutide data. Acute pancreatitis is listed as a warning on the semaglutide 2.4 mg US package insert. Patients with a history or presence of chronic pancreatitis or acute pancreatitis within 180 days before screening were excluded from the SELECT study. None of the 69 patients with a medical history of acute pancreatitis >180 days before screening had an acute pancreatitis event confirmed by the EAC.

Psychiatric AEs have been an important safety focus following reports of increased anxiety, depression, and suicide in the Rimonabant for Prevention of Cardiovascular Events (CRESCENDO) CVOT [21, 22], leading to its market removal in Europe. Subsequently, since 2012, the FDA has required all studies of AOMs to include psychiatric disorders as a safety focus area and prospective assessment of suicidal ideation and behavior occurrence [23]. A study of 240,618 patients with overweight or obesity who were prescribed semaglutide or non-GLP-1RA AOMs found that semaglutide was associated with a lower risk of incident (HR, 0.27) and recurrent (HR, 0.44) suicidal ideation versus the non-GLP-1RA group [25]. Recent communications by the FDA and EMA's Pharmacovigilance Risk Assessment Committee also found no association between GLP-1RA use and the occurrence of suicidal thoughts or actions [25–27]. A recent post hoc analysis of the STEP 1, 2, 3, and 5 trials showed that the risk of developing symptoms of depression or suicidal ideation/behavior was similar between semaglutide 2.4 mg and placebo [28]. There was no imbalance in reported events of suicide/self-injury between treatment groups in the SELECT study. Based on the collected data on SAEs, there appears to be no relationship between suicidal ideation or behavior and the use of semaglutide. Patients were excluded from the SELECT study if they had a severe psychiatric disorder that, in the investigator's opinion, could compromise protocol compliance.

CONCLUSION

The SELECT study was the largest and longest randomized clinical study of GLP-1RAs in patients with overweight or obesity and existing

CVD without diabetes. Compared with the placebo group, SAEs were lower in the semaglutide group, largely driven by CV events. Consistent with other GLP-1RA studies, gastrointestinal disorders were the most commonly reported AEs leading to trial product discontinuation, with most occurring during the dose-escalation period. Gallbladder-related disorders were more frequently seen in the semaglutide group, mainly driven by cholelithiasis, although proportions of cholecystitis were similar to those in the placebo group. There were no unexpected safety concerns and no increased risk of acute pancreatitis, malignant neoplasms, or acute kidney failure. There was no difference in proportions of serious psychiatric disorders between groups, including suicide and self-injury. The SELECT study safety results support the use of once-weekly semaglutide 2.4 mg for the secondary prevention of CVD in patients with overweight or obesity without diabetes.O

AUTHOR CONTRIBUTIONS

Study design: Robert F. Kushner, Ildiko Lingvay, and A. Michael Lincoff. Study investigators: Ildiko Lingvay, Alexander Kokkinos, Cintia Cercato, Denes Pall, Chau-Chung Wu, and A. Michael Lincoff. Enrollment of patients: Ildiko Lingvay, Alexander Kokkinos, Cintia Cercato, Denes Pall, and Chau-Chung Wu. Collection and assembly of data: Ildiko Lingvay, Alexander Kokkinos, and Cintia Cercato. Data analysis: Robert F. Kushner, Petra Weimers, Ole Kleist Jeppesen, Klaus Kallenbach, and Nina M. Harder-Lauridsen. Data interpretation: all authors. Manuscript preparation: Robert F. Kushner, Petra Weimers, Ole Kleist Jeppesen, Klaus Kallenbach, and Nina M. Harder-Lauridsen. Manuscript review and revisions: all authors. Final approval of manuscript: all authors.

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CONFLICT OF INTEREST STATEMENT

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CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov identifier NCT03574597.

DATA AVAILABILITY STATEMENT

Data will be shared with bona fide researchers who submit a research proposal approved by the independent review board. Individual patient data will be shared in datasets in a deidentified and anonymized format. Information regarding data access request proposals can be found at the following link: novonordisk-trials.com

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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