Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) rationale and design

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Cardiovascular disease (CVD) is a major cause of morbidity and mortality. Although it has been widely appreciated that obesity is a major risk factor for CVD, treatments that produce effective, durable weight loss and the impact of weight reduction in reducing cardiovascular risk have been elusive. Instead, progress in CVD risk reduction has been achieved through medications indicated for controlling lipids, hyperglycemia, blood pressure, heart failure, inflammation, and/or thrombosis. Obesity has been implicated as promoting all these issues, suggesting that sustained, effective weight loss may have independent cardiovascular benefit. GLP-1 receptor agonists (RAs) reduce weight, improve glycemia, decrease cardiovascular events in those with diabetes, and may have additional cardioprotective effects. The GLP-1 RA semaglutide is in phase 3 studies as a medication for obesity treatment at a dose of 2.4 mg subcutaneously (s.c.) once weekly. Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT) is a randomized, double-blind, parallel-group trial testing if semaglutide 2.4 mg subcutaneously once weekly is superior to placebo when added to standard of care for preventing major adverse cardiovascular events in patients with established CVD and overweight or obesity but without diabetes. SELECT is the first cardiovascular outcomes trial to evaluate superiority in major adverse cardiovascular events reduction for an antiobesity medication in such a population. As such, SELECT has the potential for advancing new approaches to CVD risk reduction while targeting obesity. (Am Heart J 2020;229:61-9.)

Today, clinicians around the world are treating increased numbers of patients with obesity and cardiovascular disease (CVD) because of the worldwide epidemic of obesity[1-3] and its relationship to CVD.[3-5] Although great progress has been made in high-income countries in improvements in cardiovascular morbidity and mortality,[6] this may be stagnating,[7] and the leading cause of death globally remains CVD.[8]

Obesity is a crucial contributor to CVD,[3-5] but little progress has been made on effective and durable interventions to reduce body weight and specifically target the increased cardiovascular risk associated with obesity. Treatment approaches are changing, however, with renewed interest in using medications for weight management based on improved understanding of food intake and energy balance regulation.[9] In the absence of established, effective therapies known to decrease cardiovascular risk, a gap exists for cardiologists and other clinicians in addressing excess adiposity as a cause of adverse cardiovascular outcomes.

Glucagon-like peptide-1 (GLP-1) is a gut hormone released in response to food intake that acts as a satiety signal, stimulates insulin release, inhibits glucagon secretion, and regulates gastric emptying.[10,11] In addition, GLP-1 has other effects that are potentially beneficial from a cardiovascular risk perspective, including natriuresis, diuresis, blood pressure reduction, and

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improvements in inflammation.[12] In line with this, GLP-1 receptor agonists (GLP-1 RAs) have demonstrated reduction in risk of atherosclerotic cardiovascular events in several cardiovascular outcomes trials (CVOTs) in patients with type 2 diabetes.[13]

In the field of antiobesity medications, GLP-1 RAs are the latest class of drugs to be approved for the treatment of obesity.[12,14,15] Semaglutide is a second-generation GLP-1 RA[14] that is in phase 3 clinical trials as an antiobesity medication at a dose of 2.4 mg once weekly.[16]

This article describes the design of the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) study, focusing on its rationale and potential importance. SELECT will be the first clinical trial designed to explore the superiority of a long-acting, weekly GLP-1 RA (semaglutide 2.4 mg) versus placebo for reduction of cardiovascular events in patients with established CVD and overweight or obesity but *without* established type 2 diabetes. Both semaglutide and placebo are given with lifestyle recommendations focused on cardiovascular risk reduction.

We provide a brief description of the methods and specific statistical considerations for this trial along with a comprehensive discussion.

Methods

Overall study design and treatment

SELECT (www.clinicaltrials.gov, NCT03574597) is a randomized, double-blind, parallel-group, placebo-controlled trial comparing semaglutide with placebo as an adjunct to standard of care for prevention of major adverse cardiovascular events (MACE) in patients with established CVD and overweight or obesity. The trial is sponsored entirely by Novo Nordisk. The trial protocol was approved by the institutional review board and ethics committee at each participating center. All patients have provided written informed consent before any trial-related activity

An overview of the main design elements of SELECT is provided in Figure 1. Patients are randomized 1:1 to receive once-weekly subcutaneous (sc) semaglutide 2.4 mg or placebo. Patients start on a once-weekly dose of 0.24 mg with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7, and 2.4 mg/wk) until the target dose of 2.4 mg is reached after 16 weeks. The protocol is flexible to mitigate potential adverse effects and allows for elongated escalation and treatment pauses, if needed. Ongoing support from a Global Exert Panel, consisting of local experts with expertise in CVOTs and GLP-1RA use, is in place for the investigators, and there is strong focus on educating and supporting the investigators throughout the trial. Because the main adverse effects are gastrointestinal (nausea, vomiting, diarrhea, constipation), provider and patient materials on handling these have been developed and circulated. Overall, a strong focus to optimize exposure to trial product is included in trial conduct. During the SELECT trial, there is a focus on treatment of cardiovascular risk factors to ensure adherence to standard of care for participants according to international guidelines. A standard-of-care document that is updated periodically is provided as guidance for investigators.

To secure retention and compliance and to optimize treatment, the patient is in contact with the investigator every 13th week throughout the trial. Site visits occur more frequently during the first months of the trial to support the patient during the dose-escalation period. During trial conduct, there are detailed monitoring and capture of treatment pauses, missed visits, and potential loss to follow-up. An array of mitigating actions is in place to ensure a high retention rate and ongoing support to investigators and patients participating in SELECT.

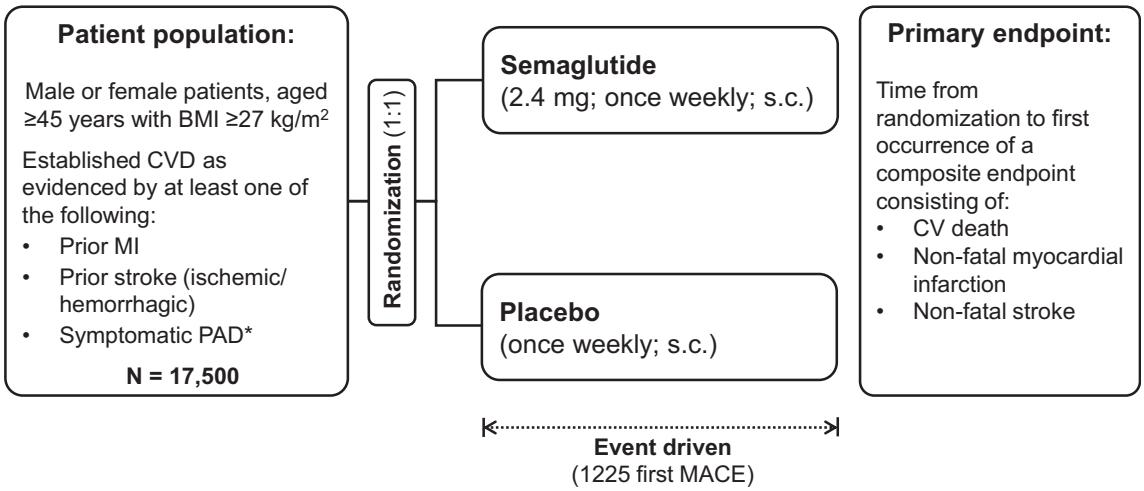
Population

Approximately 17,500 volunteers will be enrolled in the study from >750 sites from around the world, including sites across 6 continents (Africa, Asia, Oceania, Europe, and North and South America). The first patient was randomized November 2018, and although event driven, the trial is expected to last 5 years. Eligible patients are aged ≥45 years with a body mass index (BMI) of ≥27 kg/m^2 and established CVD. Established CVD includes 1 or more of the following: prior myocardial infarction (MI), prior ischemic or hemorrhagic stroke, symptomatic peripheral arterial disease (PAD) in the form of intermittent claudication with ankle-brachial index <0.85 at rest, prior peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease. Patients with hemoglobin A1c (HbA1c) ≥48 mmol/mol (6.5%); with a history of type 1 or type 2 diabetes; or who had suffered MI, stroke, hospitalization for unstable angina pectoris, or a transient ischemic attack within 60 days of screening are excluded. Please see Table I for the complete eligibility criteria. Patients who develop diabetes during the study remain in the study and receive concomitant medication (excluding other GLP-1 RAs) for diabetes at the discretion of the investigator.

The eligibility criteria have been designed to select a broad population with atherosclerotic cardiovascular disease by allowing entry into the trial with manifestation of atherosclerosis in at least 1 of the 3 major vascular territories: brain, heart, and peripheral arteries.

The specific rationale for including patients with PAD in SELECT was based on the observation in FOURIER[17] and other trials where the cardiovascular event rate in participants with PAD alone was similar or greater than in participants with stroke alone or MI alone, which aligns with the evidence for PAD as coexisting with coronary artery disease. The rationale for excluding patients with diabetes is that although semaglutide has demonstrated

Figure 1



SELECT: trial design, population, and primary end point. The figure provides a snapshot of key components of SELECT trial design.**Symptomatic PAD* defined as intermittent claudication with ankle-brachial index <0.85 (at rest) **OR** peripheral arterial revascularization procedure **OR** amputation due to atherosclerotic disease.

reduction in cardiovascular events in patients with type 2 diabetes in SUSTAIN 6,[18] the SELECT study seeks to evaluate CVD risk reduction out of the context of glycemic control or patients with established diabetes and the potential cardiovascular risk associated with that diagnosis. By excluding patients with diabetes, any cardiovascular benefit seen in SELECT will likely be less dependent on improved glycemic control as the mechanism by which semaglutide reduces cardiovascular risk. In this regard, SELECT moves more proximally in terms of intervening in the continuum of cardiovascular risk reduction that has shifted from patients with established CVD to those with diabetes but no CVD to the unanswered question of event reduction in those with obesity but no diabetes at the time of screening.

Objectives and end points

The primary objective is to demonstrate superiority of semaglutide 2.4 mg sc versus placebo when given as an adjunct to standard-of-care cardiovascular risk reduction with respect to reducing the incidence of *MACE*, defined as time from randomization to first occurrence of a composite end point comprising cardiovascular death, nonfatal MI, or nonfatal stroke. Confirmatory secondary end points are time from randomization to cardiovascular death and time from randomization to all-cause death. Additional secondary objectives are to compare the effect of semaglutide 2.4 mg sc once weekly versus placebo on a broad range of secondary cardiometabolic outcomes that are being measured, including cardiovascular risk factors, glucose metabolism, body weight, and renal function. See Supplementary Table SI for key end points.

There is selective safety reporting in SELECT; hence, in all sites, serious adverse events (SAEs), and adverse events (AEs), regardless of seriousness, leading to discontinuation of trial product and events with additional data collection are reportable by the investigators. For most European countries, all AEs, regardless of seriousness will also be reported. These investigator-reported events and the outcome of adjudication are reviewed in an ongoing fashion by the Data Monitoring Committee (DMC), which is an independent, external committee composed of members whose expertise covers relevant specialties including statistics. The DMC is established to review and evaluate accumulated data from the trial at predefined time points as well as ad hoc. This is done to protect the safety of the subjects and to evaluate the benefit-risk balance. The DMC will have access to unblinded data and will provide recommendations on trial continuation, modification, or termination.

Statistical considerations

SELECT is an event-driven trial, and with the planned 17,500 patients enrolled, the trial will have 90% power (using a 1-sided type I error rate of 0.025) to detect a rate reduction of 17% (hazard ratio of 0.83) in the primary end point based on events observed in 1,225 patients. This hazard ratio is based upon a conservative assessment of the point estimate for the hazard ratio observed in the previous SUSTAIN 6 trial with semaglutide[18] (0.74; 95% CI 0.58-0.95) for a similar definition of MACE. Additional

Table I. SELECT: eligibility criteria

Eligibility criteria
Inclusion
• Informed consent obtained before any trial-related activities*
• Male or female aged ≥45 y at the time of signing informed consent
• Body mass index ≥27 kg/m^2
• Established CVD as evidenced by at least 1 of the following: prior myocardial infarction and/or prior stroke (ischemic or hemorrhagic stroke) and/or symptomatic peripheral arterial disease, as evidenced by intermittent claudication with ankle-brachial index <0.85 (at rest), peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease
Exclusion
CV related
• Any of the following: myocardial infarction, stroke, hospitalization for unstable angina pectoris, or transient ischemic attack within the past 60 d prior to the day of screening
• Planned coronary, carotid, or peripheral artery revascularization known on the day of screening
• Presently classified New York Heart Association Class IV heart failure
Glycemia related
• HbA1c ≥48 mmol/mol (6.5%) as measured by the central laboratory at screening
• History of type 1 or type 2 diabetes (history of gestational diabetes is allowed)
• Treatment with glucose-lowering agent(s) within 90 d before screening
• Treatment with any GLP-1 RA within 90 d before screening
General safety
• History or presence of chronic pancreatitis
• Presence of acute pancreatitis within the past 180 d prior to the day of screening
• Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
• End-stage renal disease or chronic or intermittent hemodialysis or peritoneal dialysis
• Presence or history of malignant neoplasms within the past 5 y prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in situ are allowed.
• Severe psychiatric disorder which in the investigator's opinion could compromise compliance with the protocol
• Known or suspected hypersensitivity to trial product(s) or related products
• Previous participation in this trial. Participation is defined as randomization.
• Receipt of any investigational medicinal product within 30 d before screening
• Female who is pregnant, is breast-feeding, or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method
• Any disorder, unwillingness, or inability which, in the investigator's opinion, might jeopardize the patient's safety or compliance with the protocol

*Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.

assumptions include an annual event rate in the placebo arm of 2.2%, 1% annual loss to follow-up or withdrawal, an enrolment duration of 28 months, and a total study duration of approximately 59 months. The assumed event rate is based on CVOTs in patients without type 2 diabetes (FOURIER,[17] SCOUT,[19] and IRIS[20]) and CVOTs with liraglutide and semaglutide in patients with type 2 diabetes (SUSTAIN 6[18] and LEADER[24]) and adjusted to the inclusion and exclusion criteria of the SELECT trial. The trial uses a group sequential design, and interim testing for superiority will be performed by an independent DMC. To ensure type I error rate control in relation to the interim testing, the Lan-DeMets α spending function approximating the O'Brien-Fleming stopping boundaries is used.[21]

The impact of the randomized treatment on the primary end point will be evaluated by an intention-to-treat estimand, that is, evaluating the effect of the randomized treatment irrespective of adherence to treatment and changes to background medication. The treatment effect will be expressed as a hazard ratio with corresponding 95% CI and will be estimated using a Cox proportional hazards model with indicator variable for treatment group (ie, semaglutide 2.4 mg or placebo) as the only covariate. Patients who either withdraw or are lost to follow-up during the trial will be censored at the time of withdrawal or time of last contact, respectively.

The confirmatory secondary end points will be analyzed similarly to the primary end point. If superiority of semaglutide 2.4 mg over placebo for reducing the primary end point event rate is established, the treatment effects in the confirmatory secondary end points will be tested subsequently in the following hierarchical order: (1) cardiovascular death and (2) all-cause death. Statistical significance is required before testing the next hypothesis in this hierarchical testing procedure. The nominal statistical significance level for testing the confirmatory secondary end points will be adjusted to account for the group sequential design. Additionally, the nonfatal components of the primary end point will be analyzed and reported together with the secondary cardiometabolic outcomes.

Discussion

GLP-1 is an appealing target for developing novel strategies for cardiovascular risk reduction in persons with obesity. This gut hormone is released in response to food intake and controls glucose metabolism and energy homeostasis. GLP-1 acts centrally as a satiety signal, slows gastric emptying, stimulates insulin production in a glucose-dependent manner, and inhibits glucagon secretion. GLP-1 has diverse effects, including on the cardiovascular system, which may be either dependent or independent of the expression of the GLP-1 receptor in a given cell type or organ (Figure 2).[12] GLP-1's physiologic effects on organs and cells have been reported to improve blood pressure, body weight, inflammation, thrombosis, glycemia, and postprandial lipids while also promoting natriuresis and diuresis.[12] In

Figure 2

Implications of GLP-1 physiology with regard to cardiovascular disease.[18,23-30] The targets for GLP-1 that may impact the risk of developing cardiovascular disease, and the effects of GLP-1 action in specific tissues and cell types with implications for cardiovascular disease are shown. Adapted and reprinted from *Cell Metabolism*, 24, DJ Drucker, The Cardiovascular Biology of Glucagon-Like Peptide-1, 15-30, Copyright (2016), with permission from Elsevier.[12]

a mouse model of atherosclerosis, GLP-1 RAs were found to reverse and stabilize atherosclerotic plaques, an effect proposed to be mediated by anti-inflammatory mechanisms.[22] Because the cardioprotective effect of GLP-1 has been primarily demonstrated in patients with diabetes, it is of great interest to assess whether GLP-1 RAs designed for pharmacologic effects in obesity would have similar effects in a population with high cardiovascular risk but without diabetes, a prospect facilitated by the lack of hypoglycemia seen with these agents.

The GLP-1 RAs harness the beneficial physiologic effects of GLP-1 by enhancing GLP-1 receptor signaling well above physiologic levels; hence, these agents lead to glucose lowering with a low risk of hypoglycemia and produce weight loss. Several agents in this class have been approved to date for the treatment of type 2 diabetes: exenatide, lixisenatide, liraglutide, dulaglutide, albiglutide, exenatide extended release, and semaglutide.[31] Furthermore, liraglutide is also approved for the medical treatment of obesity, and semaglutide is currently under investigation for that indication.[16]

All GLP-1 RAs have demonstrated no increased cardiovascular risk during their development programs, whereas several of these agents demonstrated statistically significant reduction in MACE in populations with type 2 diabetes and high cardiovascular risk.[13] Selected information on these different studies is shown in Table II. The table highlights that, with the exception of 1 study that was largely a primary prevention subpopulation, all were dedicated predominantly to secondary prevention. In general, most of the studies have shown some beneficial effect.

The GLP-1 RAs used in these studies exerted beneficial effects on the classical cardiovascular risk factors as they reduce blood pressure, promote weight loss, and reduce lipid levels in addition to lowering glucose levels. Although the design of these studies typically included a placebo arm with a goal of glycemic equipoise based on following local guidelines for glycemic control, this was not always achieved. Thus, it could be asked whether the

Table II. Summary of key cardiovascular outcomes trials of GLP-1 receptor agonists[13]

	ELIXA (n = 6068)[23]	LEADER (n = 9340)[24]	SUSTAIN-6 (n = 3297)[18]	EXSCEL (n = 14,752)[26]	HARMONY Outcomes (n = 9463)[25]	REWIND (n = 9901)[27]	PIONEER-6 (n = 3183)[30]
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide
Structural basis	Exendin-4	Human GLP-1	Human GLP-1	Exendin-4	Human GLP-1	Human GLP-1	Human GLP-1
Administration route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Oral
Dose	20 μg/d	1.8 mg/d	0.5 or 1 mg/wk	2 mg/wk	30 or 50 mg/wk	1.5 mg/wk	14 mg/d
Mean age, y (SD)	60 (10)*	64 (7)	65 (7)	62 (9)	64 (9)	66 (7)	66 (7)
Sex, n (%)							
Male	4207 (69)	6003 (64)	2002 (61)	9149 (62)	6569 (69)	5312 (54)	2176 (68)
Female	1861 (31)	3337 (36)	1295 (39)	5603 (38)	2894 (31)	4589 (46)	1007 (32)
Ethnic origin, n (%)							
White	4576 (75)	7238 (77)	2736 (83)	11,175 (76)	6583 (70)	7498 (76)	2300 (72)
Other	1492 (25)	2102 (23)	561 (17)	3577 (24)	2880 (30)	2403 (24)	883 (28)
Mean BMI, kg/m^2 (SD)	30.1 (5.6)*	32.5 (6.3)	32.8 (6.2)	32.7 (6.4)	32.3 (5.9)	32.3 (5.7)*	32.3 (6.5)
Mean diabetes duration, y (SD)	9.2 (8.2)*	12.8 (8.0)*	13.9 (8.1)	12.0 (IQR 7.0-18.0)†	14.1 (8.6)*	10.5 (7.3)*	14.9 (8.5)
Mean HbA1c, % (SD)	7.7 (1.3)*	8.7 (1.6)*	8.7 (1.5)	8.0 (IQR 7.3-8.9)†	8.7 (1.5)	7.3 (1.1)*	8.2 (1.6)
Established CVD, n (%)	6068 (100)	7598 (81)	2382 (72)	10,782 (73)	9463 (100)	3114 (31)	2695 (85)‡
3-component MACE							
Hazard ratio	1.02	0.87	0.74	0.91	0.78	0.88	0.79
(95% CI)	(0.89-1.17)	(0.78-0.97)	(0.58-0.95)	(0.83-1.00)	(0.68-0.90)	(0.79-0.99)	(0.57-1.11)
P value	.81	.01	.016	.061	<.001	.026	.17
All-cause mortality							
Hazard ratio	0.94	0.85	1.05	0.86	0.95	0.90	0.51
(95% CI)	(0.78-1.13)	(0.74-0.97)	(0.74-1.50)	(0.77-0.97)	(0.79-1.16)	(0.80-1.01)	(0.31-0.84)
P value	.50	.02	.79	.016§*	.64	.067	.008

Adapted and reprinted from *The Lancet Diabetes & Endocrinology*, 7, SL Kristensen et al, Cardiovascular, Mortality, and Kidney Outcomes with GLP-1 Receptor Agonists in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Cardiovascular Outcome Trials, 776-785, Copyright (2019), with permission from Elsevier.[13]
Values are for the full population, where available; otherwise, they are from the intervention arm (denoted by *).
† SD unavailable from primary source reference.
‡ Includes CVD or chronic kidney disease.
§ Not regarded statistically significant due to hierarchical statistical testing plan.

benefit was related to glucose control. Results from the study using albiglutide, one of the long-acting GLP-1 RAs, strongly suggest that cardiovascular benefit was independent of glucose control. Although albiglutide had limited effect on glycemic control, this agent demonstrated an unequivocal reduction in cardiovascular events.[25] Moreover, the preponderance of prior evidence from studies that failed to achieve a reduction in cardiovascular events through improved glucose control also argues against GLP-1 RAs achieving cardiovascular benefit solely through glucose control. GLP-1 RAs may exert benefit through control of other nonglycemic risk factors, through a combination of these factors, or even through pleiotropic effects independent of these risk factors.[12] Our understanding of how GLP-1 RAs exert their cardioprotective actions may be further elucidated through SELECT.

Semaglutide is a long-acting GLP-1 RA with a half-life of approximately 7 days[32] and has been shown to have the most potent effect on glucose lowering and weight loss within the class.[33-35] It is currently approved for the treatment of type 2 diabetes in a weekly s.c. injectable form at a dose of 0.5 and 1 mg, and an oral form at doses of 7 and 14 mg. Semaglutide's cardiovascular effect in patients with type 2 diabetes and high cardiovascular risk has been examined in 2 studies: SUSTAIN 6,[18] which assessed the weekly s.c. formulation, and PIONEER 6,[30] which assessed the daily oral formulation. Both studies were designed to assess cardiovascular safety and therefore had relatively small sample sizes and short duration of follow-up, and neither can be considered definitive, but there were fewer MACE with semaglutide compared with placebo in both studies (hazard ratio 0.74 [95% CI 0.58-0.95], $P = .016$ in SUSTAIN 6 and 0.79 [95% CI 0.57-1.11], $P = .17$ in PIONEER 6). The larger SOUL trial (www.clinicaltrials.gov, NCT03914326) is currently ongoing and will further assess the cardioprotective effect of semaglutide (oral formulation, 14 mg) in patients with type 2 diabetes.

In a dose-ranging phase 2 study, semaglutide demonstrated clinically relevant weight loss in patients with obesity who do not have diabetes, with mean weight reduction ranging from 6.0% to 13.8% from baseline body weight, depending on dose.[16] The phase 3 program is currently ongoing (www.clinicaltrials.gov, NCT03548935, NCT03693430, NCT03811574, NCT04102189, NCT03552757, NCT03548987, NCT03611582). Given the promising weight loss effects of semaglutide and positive preliminary cardiovascular data in patients with type 2 diabetes, this medication is well positioned to be the first GLP-1 RA to be tested as a cardioprotective agent in high-risk individuals with overweight or obesity but without diabetes.

SELECT is poised to provide unique insight into the intersection of obesity, diabetes, and CVD. If the SELECT study has a positive outcome and demonstrates reduced CVD events in persons with obesity and prior CVD but without diabetes, semaglutide 2.4 mg once weekly treatment should inform obesity guidelines and be the standard-of-care treatment approach in this population. Clinicians currently have access to many drugs for risk reduction that work through lipid control, glycemic control, and improvements in inflammation and thrombosis. The next major frontier in CVD management is to target obesity, and the SELECT study could open a new avenue for addressing CVD risk while targeting obesity.

Disclosures

Donna H. Ryan has received personal fees from Novo Nordisk for serving on the SELECT steering committee board and has received personal fees from Amgen, Bausch Health Companies Inc, Boehringer Ingelheim, IFA Celtic, CVK Technologies Private Limited, Eli Lilly and Company, Epitomee Medical Ltd., Gila Therapeutics Inc, Novo Nordisk, Phenomix Sciences LLC, Real Appeal Inc, Redesign Health Inc, Sanofi, and Scientific Intake Limited Co. Ildiko Lingvay has received an institutional grant from Novo Nordisk for conducting this clinical study and for serving on the SELECT steering committee board, and has received grants from Merck & Co, Mylan, Novo Nordisk, and Pfizer and personal fees from AstraZeneca, Duke Clinical Research Institute, Eli Lilly and Company, Janssen Pharmaceuticals Inc, Intacia, Mannkind, Novo Nordisk, Sanofi, TARGETpharma, and Valeritas. John Deanfield has received personal fees from Novo Nordisk for serving on the SELECT and SOUL Steering Committee Boards and has received personal fees from Aegerion Pharmaceuticals Inc, Amgen, Boehringer Ingelheim, Merck & Co, Novo Nordisk, Pfizer, Sanofi Aventis, and Takeda. Jorge Plutzky has received personal fees for consultancy from Novo Nordisk, Janssen Pharmaceuticals Inc, and Vivus during the conduct of this study and has received personal fees for consultancy from Amarin, Amgen, Correvio Pharma Corporation, Eidos Therapeutics, and Janssen Pharmaceuticals Inc and grants from Boehringer Ingelheim outside the submitted work; in addition, Jorge Plutzky has a patent issued for retinaldehyde dehydrogenase inhibition to treat obesity via thermogenesis. Robert F. Kushner has received personal fees from Novo Nordisk for serving on the SELECT steering committee board, grant support from Novo Nordisk for conducting the STEP clinical trials, and personal fees from Novo Nordisk for serving on global and national scientific advisory boards and for participating in educational films. Steven E. Kahn has received personal fees from Novo Nordisk for serving on the SELECT steering committee board and from Boehringer Ingelheim, Eli Lilly and Company, Intarcia Therapeutics, Janssen Pharmaceuticals Inc, Merck & Co, Novo Nordisk, and Pfizer. Steve Marso has received grants, personal fees, and other from Novo Nordisk for serving on the SELECT steering committee board; grants, personal fees, and other for clinical research and physician education from Asahi Group Holdings Ltd; and personal fees and other for physician education from Abbott Vascular Inc, Boehringer-Ingelheim, and Boston Scientific Corporation. Helen M. Colhoun has received honorarium for serving on an advisory panel for Novartis Pharmaceuticals; has served on an advisory panel for Sanofi; has received grants from AstraZeneca, Pfizer, and Regeneron Pharmaceuticals Inc; has received grants and personal fees from Novo Nordisk; and is a shareholder of Hoffmann-La Roche. Scott S. Emerson has received personal fees from Novo Nordisk for serving on the SELECT steering committee board and from Amgen, AstraZeneca, Bayer, Biomarin, Boehringer Ingelheim, Bristol Myers Squibb, Correvio Pharma Corporation, Daiichi Sankyo, Denovo Biopharma, Esteve, GlaxoSmithKline, Intercept Pharmaceuticals Inc, Janssen Pharmaceuticals Inc, Merck & Co, Novartis Pharmaceuticals, Pfizer, Principia Biopharma, Hoffmann-La Roche, and Sanofi. Kirstine Brown-Frandsen is an employee of and holds stock in Novo Nordisk. Marianne O. L. Gronning is an employee of and holds stocks in Novo Nordisk. G. Kees Hovingh is a part-time employee of Novo Nordisk and has received research grants from Netherlands Organization for Scientific Research, Fonds Klinkerpad, and the European Union; institutional research support from Aegerion Pharmaceuticals Inc, Amgen, AstraZeneca, Eli Lilly and Company, Ionis Pharmaceuticals, Kowa Pharmaceuticals, Pfizer, Regeneron Pharmaceuticals Inc, Hoffmann-La Roche, Sanofi and Sanofi Genzyme, and The Medicines company; and personal fees for consultancy or personal fees for attending speakers' bureau from Aegerion Pharmaceuticals Inc, Amgen, Regeneron Pharmaceuticals Inc, and Sanofi. Anders Gaarsdal Holst is an employee of and holds stocks in Novo Nordisk. Henrik Ravn is an employee of and holds stock in Novo Nordisk. A. Michael Lincoff has received personal fees for consultancy from Novo Nordisk during the conduct of this study and has received

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Data sharing statement

Deidentified participant data will be made available for this article on a specialized SAS data platform. Data sets from Novo Nordisk will be available permanently after research completion and approval of product and product use in both the EU and USA. The study protocol and redacted clinical study report will be available according to Novo Nordisk data sharing commitments. Access to data can be made through a request proposal form, and the access criteria can be found online. Data will be shared with bona fide researchers submitting a research proposal requesting access to data. Data use is subject to approval by the Independent Review Board according to the IRB Charter (see novonordisk-trials.com).

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