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Study design and baseline profile for adults with type 2 diabetes in the once-weekly subcutaneous SEmaglutide randomized PRAgmatic (SEPRA) trial

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ABSTRACT

Introduction Once-weekly subcutaneous semaglutide, a glucagon-like peptide-1 analog, is approved in the USA as an adjunct to diet and exercise for adults with inadequately controlled type 2 diabetes (T2D) to improve glycemic control and reduce the risk of major adverse cardiovascular events in people with T2D and established cardiovascular disease. The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) phase III clinical trial program demonstrated the efficacy and safety of once-weekly subcutaneous semaglutide; however, determining its effectiveness in a real-world setting could support decision-making by clinicians, payers and policy makers in routine clinical practice.

Research design and methods SEmaglutide PRAgmatic (SEPRA) is an ongoing open-label, randomized, pragmatic clinical trial designed to compare the effects of once-weekly subcutaneous semaglutide versus standard of care in US health-insured adults with T2D and physician-determined inadequate glycemic control. The primary end point is the proportion of participants achieving glycated hemoglobin (HbA1c) <7.0% at year 1; other key outcomes include glycemic control, weight loss, healthcare utilization, and patient-reported outcomes. Individual-level data will be collected from routine clinical practice and health insurance claims. The last patient last visit is expected by June 2023.

Results Between July 2018 and March 2021, 1278 participants were enrolled from 138 study sites across the USA. At baseline, 54% were male with mean±SD age 57.4±11.1 years and body mass index 35.7±8.0 kg/m^2. Mean diabetes duration was 7.4±6.0 years and mean HbA1c was 8.5±1.6%. At baseline, concomitant antidiabetes medications included metformin, sulfonylureas, sodium-glucose co-transporter-2 inhibitors, and dipeptidyl peptidase-4 inhibitors. The majority of participants had hypertension and dyslipidemia. The trial design was self-assessed using the PRagmatic Explanatory Continuum Indicator Summary-2 tool by the study steering group and was scored 4–5 in all domains suggesting a highly pragmatic study.

Conclusions SEPRA, a highly pragmatic ongoing study, will provide data on the effects of once-weekly subcutaneous semaglutide in a real-world setting when used during routine management of T2D.

Trial registration number NCT03596450.
Trial registration number

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The efficacy and safety of once-weekly subcutaneous semaglutide has been demonstrated by data from the phase III Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) randomized clinical trial program.

⇒ Once-weekly subcutaneous semaglutide was superior to both placebo and active comparators for reductions in glycated hemoglobin and body weight in a broad range of patient groups with inadequately controlled type 2 diabetes.

WHAT THIS STUDY ADDS

⇒ SEPRA will evaluate the effectiveness of once-weekly subcutaneous semaglutide versus other commercially available antidiabetes medications in a real-world setting when added to current oral antidiabetic therapy for individuals with inadequate glycemic control.

⇒ The data generated from the study will complement the findings of the SUSTAIN program.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Data from SEPRA may provide evidence to support decision-making by clinicians, payers, and policy makers in routine clinical practice.

⇒ The strategies used to mitigate the operational challenges encountered due to the pragmatic nature of the study may inform the design of future pragmatic clinical trials in diabetes and other chronic diseases.

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a well-established treatment for people with type 2 diabetes (T2D).[1 2] GLP-1RAs help individuals achieve glycemic control by increasing insulin and suppressing glucagon in a glucose-dependent manner, while also supporting weight loss by reducing appetite.[3 4] Selected GLP-1RAs may also provide cardiovascular (CV) benefit in people with T2D.[5 6]

Semaglutide is a GLP-1RA approved in the USA for once-weekly subcutaneous use (as an adjunct to diet and exercise) in adults with inadequately controlled T2D to improve glycemic control, and to reduce the risk of major adverse CV events in adults with T2D and established CV disease.[7–9] The efficacy and safety of once-weekly subcutaneous semaglutide was demonstrated by the phase III Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) randomized clinical trial program.[8–14] In the SUSTAIN 1–7 clinical trials, once-weekly subcutaneous semaglutide was reported to be superior to both placebo and active comparators for reductions in glycated hemoglobin (HbA1c) and body weight in multiple patient groups with inadequately controlled T2D. A significant reduction in CV risk has also been reported for once-weekly subcutaneous semaglutide versus placebo (both as an adjunct to standard of care) in people with T2D and a high risk of CV events during SUSTAIN 6, a CV outcomes trial.[9] A once-daily oral formulation of semaglutide (7 mg and 14 mg maintenance doses) is also available[15] and has been evaluated in the Peptide InnOvatioN for Early diabEtes tReatment phase III clinical trial program.[16–23] However, the present study focuses on once-weekly subcutaneous semaglutide only.

The current American Diabetes Association standard of care guidelines recommend adopting a patient-centered approach in the treatment of T2D.[24–26] Pharmacotherapy should be initiated at diagnosis and tailored to the individual, accounting for comorbidities such as atherosclerotic CV disease, efficacy, impact on weight, cost and access, and individual preferences.[24] First-line therapy generally includes metformin together with comprehensive lifestyle changes.[24] In individuals with T2D with or at high risk of CV disease, GLP-1RAs or sodium-glucose co-transporter 2 (SGLT-2) inhibitors with proven CV benefit are recommended independently of background therapy (including metformin) and current or target HbA1c, to reduce the risk of CV events and mortality.[24] GLP-1RAs may also be used as part of treatment intensification, if appropriate for the clinical needs of the individual (eg, where it is beneficial to provide additional HbA1c control, to avoid hypoglycemia, or to minimize weight gain or promote weight loss).[24]

To inform decision-making by clinicians, payers, and policy makers in routine clinical practice, the ongoing SEmaglutide PRAgmatic (SEPRA) clinical trial is a comparative effectiveness study of treatment intensification of current antidiabetic therapy with either once-weekly subcutaneous semaglutide or any other medication indicated for diabetes treatment at the discretion of the treating provider, hereafter termed 'standard of care'. Eligible participants were diagnosed with T2D and treated with two oral antidiabetes medications, but required additional medication as determined by the provider in a variety of practice settings in the USA. Pragmatic clinical trials are used to generate evidence on the effectiveness of an intervention in routine clinical practice, while explanatory clinical trials are conducted in an idealized setting to provide the optimum scenario for a treatment to show a beneficial effect.[27]

Here, we describe the design of the SEPRA trial and present the baseline data collected from participants enrolled, including participant demographics and clinical characteristics, as well as comorbidities and concomitant oral antidiabetes medications. We also present the findings of the PRagmatic Explanatory Continuum Indicator Summary-2 (PRECIS-2) analysis and discuss how we overcame recruitment challenges encountered due to the pragmatic nature of the study.

METHODS

Trial design

SEPRA (NCT03596450) is an ongoing, randomized, open-label, phase IV pragmatic clinical trial that was designed to compare the effects of once-weekly subcutaneous semaglutide versus standard of care when added to up to two oral antidiabetes medications, as treatment intensification among adults with T2D during routine clinical practice in the USA (figure 1).

Participants were recruited from 138 physician sites across the USA between July 2018 and March 2021. The last patient last visit is expected by June 2023.

Measurement of pragmatic elements

The pragmatism of the SEPRA study design, prior to any protocol amendments, was qualitatively assessed using the PRECIS-2 tool by the study steering group at a workshop held in November 2018. The study steering group included 11 members from HealthCore, Novo Nordisk and independent expert advisors who were involved in protocol development. The PRECIS-2 tool has nine domains including eligibility, recruitment, setting, organization, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis.[27]

Each member of the steering group independently assessed the study design prior to the workshop using the PRECIS-2 criteria and the independent assessments were subsequently collated and shared with the group for discussion. Participants were given the opportunity to provide their rationale and a consensus rating was reached for the nine domains during the discussion. The methods are described below as per the PRECIS-2 domains.

Eligibility domain

In the initial protocol, the inclusion and exclusion criteria were minimally restrictive to allow recruitment of a broad population of participants with a focus on the need for T2D treatment intensification and no prior use of semaglutide, as shown in box 1. During the recruitment period, enrollment rates were lower than projected, and the eligibility criteria were subsequently amended to expand the population recruited from each site (box 1; figure 2). The first key amendment in March 2019 allowed for enrollment of participants on up to two oral

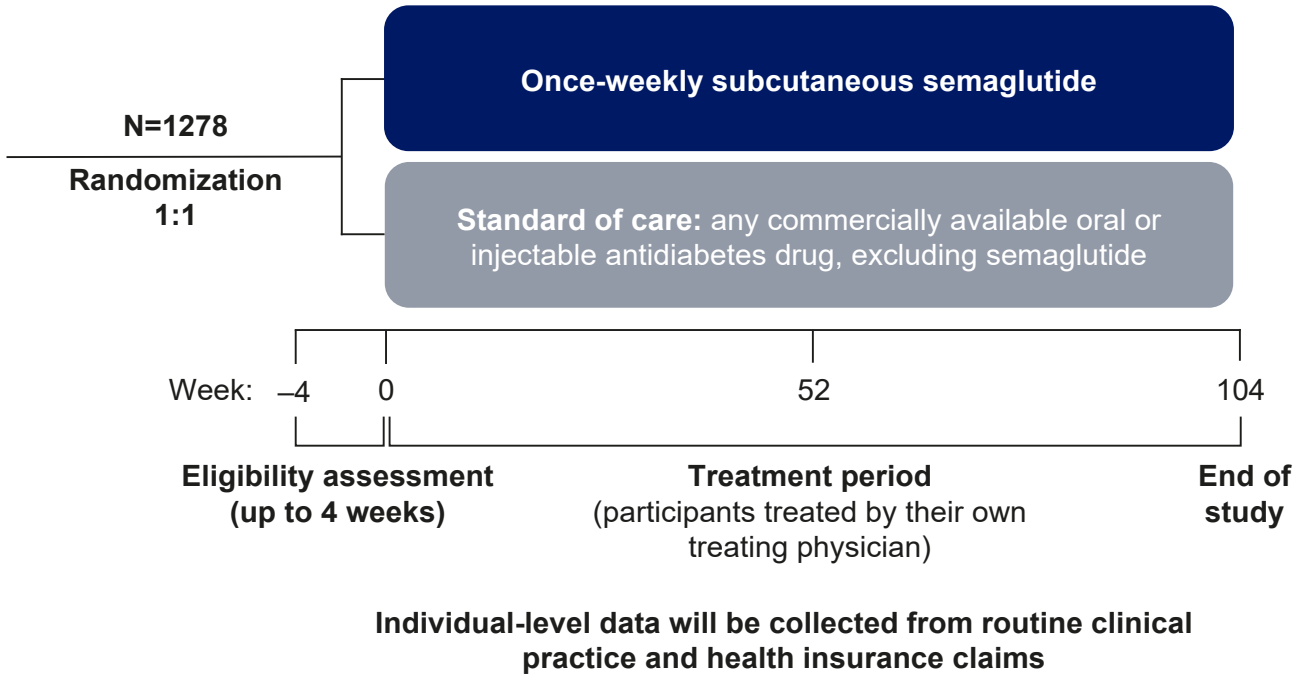

Figure 1 Study design of the SEmaglutide randomized PRAgmatic trial.

antidiabetes medications rather than metformin alone and the second key amendment in August 2019 allowed the enrollment of participants with any health plan with pharmacy benefits. The eligibility criteria were further amended in December 2019 to specify the exclusion of participants receiving oral semaglutide. If patients are not started on study medication this is considered a protocol violation, but the participant will be included in the analysis dataset.

Box 1 Study inclusion and exclusion criteria

Original eligibility criteria (March 2018)
- ⇒ Adult participants (≥18 years) with type 2 diabetes (T2D) treated with metformin monotherapy.
- ⇒ Requirement for further treatment intensification for glycemic control with an additional antidiabetes medication (treating study physician determined) as per the Food and Drug Administration-approved subcutaneous semaglutide label.[7]
- ⇒ Current member of an Anthem-affiliated commercial health plan with pharmacy benefits.
- ⇒ Recorded glycated hemoglobin value within the last 90 days prior to randomization.
- ⇒ No previous randomization in the study.
- ⇒ No treatment with any medication indicated for diabetes other than metformin in the 30 days before eligibility assessment.
- ⇒ No contraindications to semaglutide (as according to the Food and Drug Administration-approved label).
- ⇒ For women, not being pregnant, breast feeding or intending to become pregnant.
- ⇒ No participation in another clinical trial.

Amended eligibility criteria (March 2019)
- ⇒ Adult participants (≥18 years) with T2D treated with one or two oral antidiabetes medications.

Amended eligibility criteria (August 2019)
- ⇒ Current member of any health plan with pharmacy benefits.

Amended eligibility criteria (December 2019)
- ⇒ Adult participants (≥18 years) with T2D treated with one or two oral antidiabetes medications, excluding oral semaglutide.

Setting and recruitment domain

Potential physician sites, including both primary care practitioners and endocrinologists, were selected by querying the HealthCore Integrated Research Database (HIRD) to identify eligible individuals (ie, those with Anthem-affiliated commercial health plans with pharmacy benefits) and subsequently mapping back to healthcare providers. The HIRD is a large administrative healthcare database containing longitudinally integrated medical and pharmacy claims data from commercially insured individuals across the USA (from January 1, 2006 to present). Following recruitment challenges, the protocol was updated in August 2019 to allow participation of sites with prior research experience with semaglutide.

Eligible individuals were invited to participate in the study when they presented to their physician during routine clinical care and through proactive identification from within the study site patient population. The assessment that an individual had inadequate glycemic control on up to two oral antidiabetes medications was made by the treating study physician prior to, and independently of, study enrollment and prior to signing informed consent. On determining a need for treatment intensification, the physician assessed suitability according to the current eligibility criteria and the approved label for once-weekly subcutaneous semaglutide.

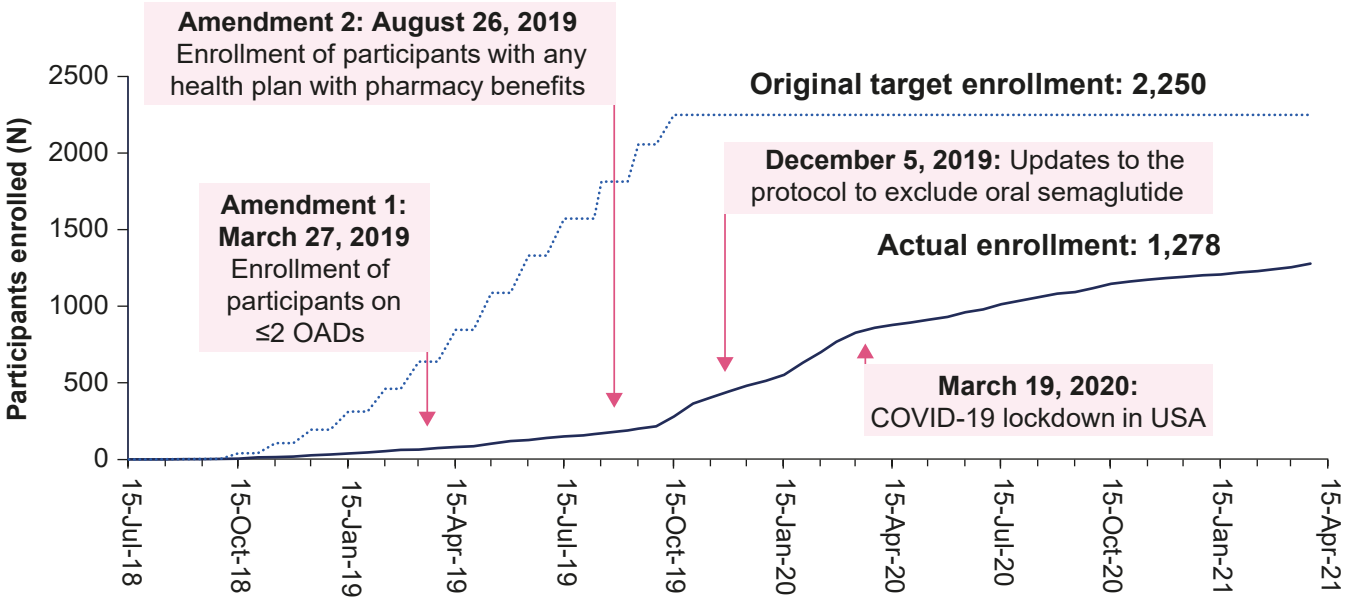

Figure 2 Projected and actual recruitment rate. Amendment 1 included enrollment of participants on ≤2 oral antidiabetes medications; amendment 2 included enrollment of participants with any health plan with pharmacy benefits. OADs, oral antidiabetes medications.

Organization (randomization and trial regimen) domain

This is an open-label study in which randomization was included to reduce selection bias and ensure comparable patient populations in the two treatment groups. There is a 4-week screening period during which time the treating physician can confirm the need for antidiabetic therapy intensification and ensure the participant meets eligibility criteria. Participants are then randomized in a 1:1 ratio with permuted blocks of size four using centralized allocation via the study electronic data capture system to be prescribed either once-weekly subcutaneous semaglutide or standard of care, both as add-on to up to two oral antidiabetes medications, on enrollment to the study (online supplemental figure 1). Standard of care is defined as a single mixed comparator arm that follows routine clinical practice most closely (as patient and doctor preferences/prescribing determined the mix of treatments in this arm), and thus renders higher generalizability to settings where a similar mix of usual care treatments is used. Furthermore, in a trial with a long duration (in this case 2 years), standard of care may change during the conduct of the trial, for example, due to changes in reimbursement or if a new medication becomes available on the market. In this situation, changes in usual care in newly recruited patients, or switches to a new usual care regimen in enrolled patients, may be appropriate to continuously reflect routine clinical practice. Otherwise, generalizability may decrease.

Standard of care includes addition of any commercially available oral or injectable antidiabetes medications, other than semaglutide, prescribed at the discretion of the physician for antidiabetic treatment intensification following randomization. Commercially available GLP-1RAs, except semaglutide, could be prescribed. The study drug in the standard of care group was defined as the drug class of the first antidiabetes oral or injectable medication prescribed for treatment intensification following randomization. In the event that a fixed-dose combination product was prescribed, the treating study physician (ie, the participant's own physician enrolled in the study) chose one to be the study drug. Participants were not permitted to switch to semaglutide at any point during the study period.

Participants are prescribed once-weekly subcutaneous semaglutide or another standard of care medication based on the randomization allocation by the treating physician via routine prescribing methods at the time of the randomization visit. Postrandomization diabetes care is managed by their own treating physician, who adjusts treatment according to their own clinical judgment.

Flexibility (delivery and adherence) domains

Each treating study physician is responsible for making treatment decisions according to their clinical judgment and knowledge of their patient. Participants randomized to the once-weekly subcutaneous semaglutide group are being prescribed subcutaneous semaglutide in a prefilled pen injector, with semaglutide initiated according to approved labeling. Add-on, discontinuation, or dose modification of oral antidiabetes medications, including subcutaneous semaglutide, during the study are at the discretion of the treating study physician.

In both treatment groups, prescriptions for randomized study drug are being handled and dispensed by a pharmacy of the participant's choice per routine care, in line with their preference and health plan benefits. All participants are responsible for paying an equalized (ie, the same amount for once-weekly subcutaneous semaglutide arm and alternative antidiabetes medications in the standard of care arm) out-of-pocket maximum cost

of US$20/month. This is to minimize the impact of any differential out-of-pocket costs between the treatment groups influenced by variations in individual health plan design and benefits. The participants' out-of-pocket cost will be up to the specified maximum for the randomized study drug and ancillary needles (if required to administer the study drug), and the sponsor will reimburse additional costs above this maximum related to randomized study drug. Payment is processed at the pharmacy.

Follow-up domain

Treating study physicians or site personnel are collecting patient characteristics and study data at each visit, either directly from the patient or from the patient's medical records, and entering them into the electronic case report form.

Participants will be followed up for 2 years after randomization, regardless of changes in antidiabetes medication over the course of the study, unless informed consent is withdrawn. Medical and pharmacy claims data will be extracted from the HIRD and other administrative claims databases for the 2-year study period, as well as up to 12 months prior to randomization, where available. These data are not anticipated to be available for all patients.

Outcome domain (study end points and assessments)

The primary end point is the proportion of participants who achieve HbA1c <7.0% (53 mmol/mol) at year 1. Confirmatory secondary end points and other supportive end points, including patient-reported outcomes (PROs) and clinician-reported outcomes, are listed in online supplemental table 1 and appendix 1.

Diabetes treatment satisfaction, generic health-related quality of life, work productivity, and patient and clinician global assessments will be assessed throughout the study. The tools employed include the Diabetes Treatment Satisfaction Questionnaire; Short Form 12-Item version 2 (V.2) Health Survey; Work Productivity and Activity Impairment: General Health questionnaire; the Patient Global Impression of Disease Severity and Patient Global Impression of Change scales; and the Clinician Global Impression of Disease Severity and Clinician Global Impression of Change scales, described in online supplemental appendix 1.[28–33] Paper-based PROs will be completed by each patient, either in person or mailed to the study site, and reviewed for completeness by site study personnel before responses are entered into the electronic case report form.

Serious adverse events, adverse events leading to study drug discontinuation, and pregnancies will be collected and coded using the Medical Dictionary for Regulatory Activities and descriptively summarized by System Organ Class and Preferred Term.

Organization and intervention domain (data collection)

Primary data are collected prospectively at study visits and include demographic and clinical data, participant-completed PRO data, and clinician-reported global assessments. Secondary data are collected from administrative claims data from health plans, where available.

Dedicated study visits are taking place at randomization, year 1, and year 2. Any other visits during the study are routine clinical visits, including office visits and other participant contacts. Clinical data are also collected at these routine visits (assessments are described in online supplemental table 2).

Analysis domain (statistical analysis)

Two different scientific questions related to the efficacy objectives will be addressed through the definition of two estimands: 'intention-to-treat (ITT)' and 'if all participants had adhered'. The primary estimand for all end points is the ITT estimand, which evaluates the effectiveness of randomized treatment intervention, irrespective of adherence or changes to other antidiabetes medications. The secondary estimand for all end points, except for the adherence and persistence to treatment objective, is the 'if all participants had adhered' estimand. This estimand evaluates the effect of randomized treatment intervention for all randomized participants if all participants had adhered to randomized treatment, regardless of changes to other antidiabetes medication.

At study initiation, the planned enrollment was 2250 participants to provide 90% power to jointly confirm superiority of the primary end point and the three confirmatory secondary end points. The target sample size was subsequently revised to 1387 participants, which aims to provide 90% power to confirm superiority of the primary end point and 85% power to also confirm superiority of the first confirmatory secondary end point (based on an analysis of the primary estimand for each of the end points).

Demographic and baseline characteristics were summarized using descriptive statistics.

RESULTS

Enrollment

Overall, 138 physician sites were enrolled to the study from across the USA (online supplemental table 3). Of these sites, the majority are primary care clinics (72.5%) and the others are endocrinology care clinics (27.5%), and less than one out of four sites have prior experience with semaglutide research.

Baseline profile of the total study population

From July 2018 through March 2021 (a recruitment period of 33 months), a total of 1312 participants were screened, of whom 1278 were randomized, following which the site initiated the enrollment process.

Participants with high variability across a broad range of demographic and clinical characteristics were enrolled. Of the 1278 participants enrolled, just over half (54.2%) were male and the majority (78.6%) were white. The mean (±SD) age was 57.4±11.1 years and 25.8% (330/1278) were aged 65 years or over. The overall mean (±SD) duration of T2D was 7.4±6.0 years (table 1).

Table 1 Baseline demographic and clinical characteristics of participants

Variables	Overall (n=1278)
Age (years), mean (SD)	57.4 (11.1)
Sex, n (%)*	
Women	585 (45.8)
Men	692 (54.2)
Race, n (%)*	
White	1004 (78.6)
Black or African-American	189 (14.8)
Native Hawaiian or other Pacific Islander	5 (0.4)
American Indian or Alaska Native, Asian	43 (3.4)
Other	36 (2.8)
Hispanic or Latino, n (%)*	114 (8.9)
Weight (pounds), mean (SD)†	228.2 (56.6)
Body mass index (kg/m^2), mean (SD)†	35.7 (8.0)
Systolic blood pressure (mm Hg), mean (SD)‡	131.0 (14.5)
Diastolic blood pressure (mm Hg), mean±SD‡	79.2 (9.1)
Comorbid conditions, n (%)*§	
Hypertension	986 (77.2)
Dyslipidemia	911 (71.3)
Hypothyroidism	204 (16.0)
Diabetic neuropathy	179 (14.0)
Ischemic heart disease	84 (6.6)
Myocardial infarction	30 (2.3)
Diabetic nephropathy	50 (3.9)
Peripheral vascular disease	30 (2.3)
Diabetic retinopathy	25 (2.0)
Heart failure	24 (1.9)
Stroke	19 (1.5)
Concomitant cardiovascular medication use, n (%)¶	
Yes	1081 (84.9)
No	192 (15.1)
Concomitant cardiovascular medication type, (reported in >10% of participants), n (%)¶	
Statins	706 (55.5)
ACE inhibitor	423 (33.2)
Angiotensin receptor blockers	288 (22.6)
Beta-blockers	260 (20.4)
Aspirin	239 (18.8)
Calcium channel blockers	209 (16.4)
Thiazide diuretic	168 (13.2)
Diabetes duration (years), mean (SD)*	7.4 (6.0)
Baseline HbA1c (%), mean (SD)	8.5 (1.6)
Baseline HbA1c category n (%)	
<8.0	582 (45.5)
≥8.0	696 (54.5)
Individualized HbA1c target (%), mean (SD)	6.7 (0.5)
Difference between baseline HbA1c and individualized HbA1c target (%), mean (SD)	−1.8 (1.5)
Participants receiving 1/2/3+ oral antidiabetes medications, n (%)**	
1	805 (63.0)
2	426 (33.3)
3+	18 (1.4)
Concomitant oral antidiabetes medications type, n (%)††	
Metformin	1134 (88.7)
Sulfonylureas	266 (20.8)
SGLT-2 inhibitors	194 (15.2)
DPP-4 inhibitors	139 (10.9)
Thiazolidinediones	34 (2.7)
Other	0 (0.0)

*Missing data for one participant.
†Missing data for two participants.
‡Missing data for three participants.
§Based on relevant comorbid conditions prespecified in study protocol, participants can contribute to multiple comorbid conditions therefore percentages may exceed 100%.
¶Missing data for five participants.
**Individuals receiving 3+ oral antidiabetes medications are protocol deviations but will be kept in the statistical analysis. 29 participants not included due to reported oral antidiabetic data not meeting definition of baseline (within 4 weeks of randomization) or detailed data missing.
††Defined as any antidiabetes medication being taken within 4 weeks prior to randomization.
DPP-4, dipeptidyl peptidase-4; HbA1c, glycated hemoglobin; SGLT-2, sodium-glucose co-transporter 2.

The overall mean (±SD) body mass index (BMI) was 35.7±8.0 kg/m^2, which was broadly distributed across a range from 17.0 to 100.6 kg/m^2 (figure 3A). At baseline, the mean (±SD) HbA1c was 8.5±1.6% (69.2 mmol/mol). Baseline HbA1c values ranged from 4.9% to 18.5%, showing a wide range of glycemic control with substantial representation of elevated HbA1c levels (figure 3B).

Concomitant medications and comorbidities

Concomitant antidiabetes medications at baseline were metformin (88.7%), sulfonylureas (20.8%), SGLT-2 inhibitors (15.2%), dipeptidyl peptidase-4 inhibitors (10.9%), and thiazolidinediones (2.7%). The majority (85%) of participants were receiving concomitant CV medications at baseline (table 1). The most frequently used (reported in >10% of participants) were statins (55.5%), ACE inhibitors (33.2%), angiotensin receptor blockers (22.6%),

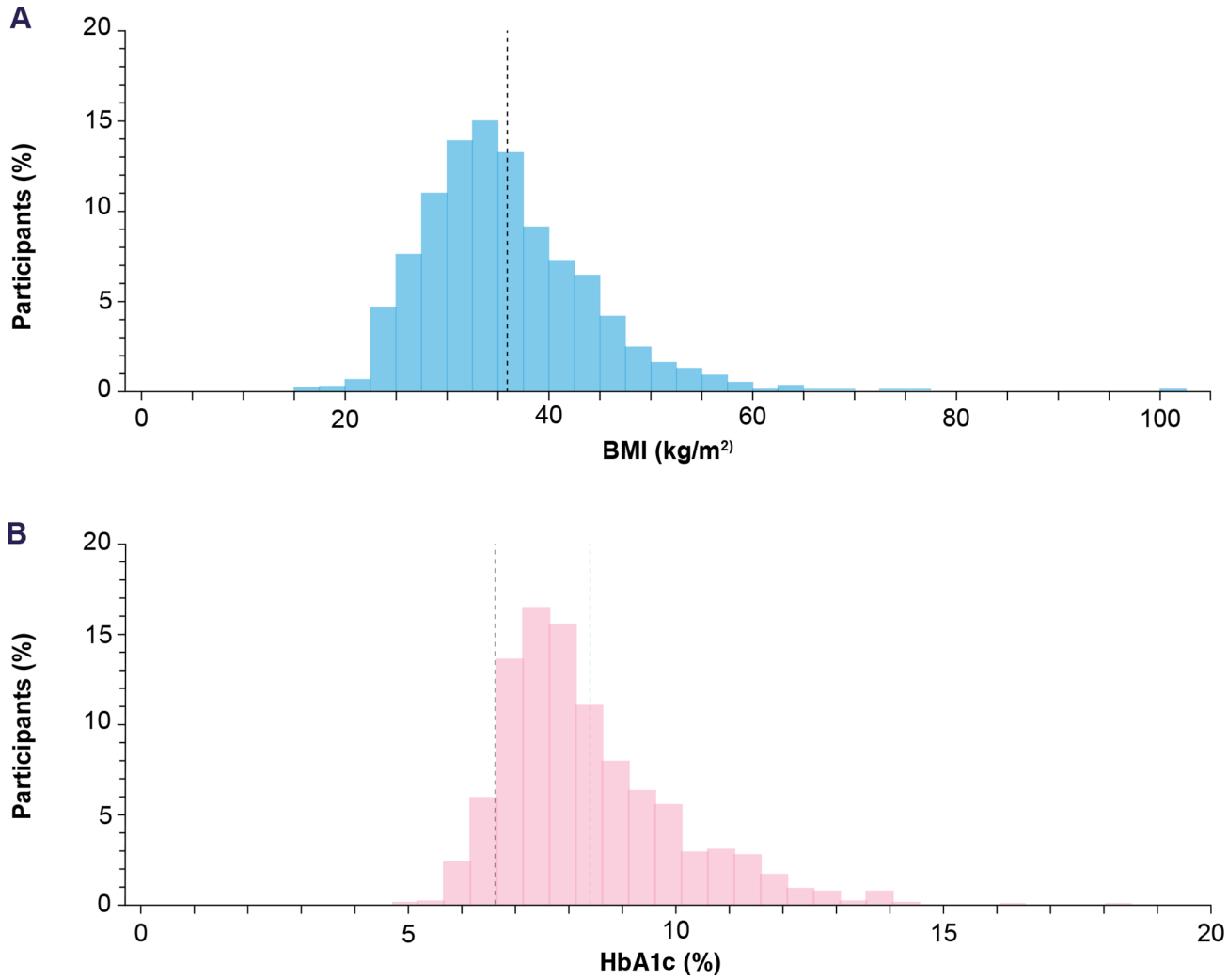

Figure 3 Histogram of mean BMI (range: 17.0–100.6 kg/m^2) (A) and HbA1c (range: 4.9%–18.5%) (B) at baseline. (A) The black dashed line indicates the mean (SD) BMI (35.7±8.0 kg/m^2). (B) The black dashed line indicates the mean (SD) individualized HbA1c target (6.7%±0.5), and the light grey line indicates the mean HbA1c (8.5%±1.6). BMI, body mass index; HbA1c, glycated hemoglobin.

beta-blockers (20.4%), aspirin (18.8%), calcium channel blockers (16.4%), and thiazide diuretics (13.2%). The majority of participants (92.6%) had a comorbid condition, the most common of which were hypertension (77.2%) and dyslipidemia (71.3%) (table 1).

PRECIS-2 assessment

The trial design was retrospectively assessed using the PRECIS-2 tool[27] by the study steering group in December 2018. The allocated scores were plotted in a PRECIS-2 wheel (which is similar to a radar or spider chart) showing that the study was scored 4–5 in all nine domains (1=very explanatory and 5=very pragmatic) (online supplemental figure 1; online supplemental table 4).

Eligibility criteria domain

Eligibility criteria, defined as how strict (explanatory) or open (pragmatic) the eligibility criteria for the trial are, was rated as 4. This was based on the rationale that study participants were enrolled during routine clinical care with limited exclusion criteria, following the decision of treating study physicians to intensify antidiabetes treatment based on their clinical judgment to achieve individualized glycemic targets.

Recruitment domain

Recruitment was rated as 5. Recruitment efforts were limited to reminder calls from HealthCore to the study sites and efforts were made to avoid interrupting the usual flow of standard care as individuals were recruited during their routine care and interactions with the site.

Setting domain

Setting, defined as where the trial is being conducted, was rated as 5. The study was performed within settings in which the study participants received their routine clinical care.

Organization domain

Organization was defined by how much expertise and additional resources the physician requires to execute the trial, including both infrastructure and the knowledge

needed to deliver the intervention. A consensus was reached on a score of 4. Treating study physicians did not need to have large research infrastructure to complete the trial as there were minimal study visits, targeted site data collection, and no requirements for study medication storage/dispensing. The study interventions were all US Food and Drug Administration-approved antidiabetes medications. It was also noted that compliance and persistence could be influenced by participants being aware of participating in a pragmatic clinical trial versus what might be observed in real-world practice.

Flexibility domains

Flexibility (delivery), defined as how the intervention should be delivered, was scored 5. Flexibility (adherence), defined as what measures are in place to ensure participants adhere to the intervention, was scored 5. Treatments are prescribed via the treating study physician in line with approved indications. Prescribed treatments are dispensed by a pharmacy of the participant's choice reflecting routine clinical care. Participants chose their own pharmacy per usual care to receive their medications, were responsible for paying an equalized out-of-pocket cost to mimic the typical prescription fill process, and no study-specific medication adherence methods were employed.

Follow-up domain

Follow-up, defined by how closely participants are followed up via visits and assessments, was scored 4, based on the rationale that there are three protocol-mandated visits that would not usually occur during routine clinical care. Furthermore, questionnaires assessing quality of life and other PROs are also not typically part of routine clinical practice.

Primary outcome domain

The primary outcome domain, defined as how relevant the end points and results are to trial participants, was scored 4. The steering group reported that composite end points are not considered to be highly pragmatic. The end point of the proportion of participants achieving HbA1c <7.0% was considered a payer-centric end point and not directly relevant to participants, but it has been reported that individuals with diabetes do regard HbA1c as an important metric.[11] In real-world practice and supported by treatment guidelines,[24] flexibility is often applied to these cut-offs. The inclusion of secondary end points such as achievement of individualized HbA1c targets determined by the treating study physician before randomization and change from baseline in HbA1c was deemed highly pragmatic. Measuring use of healthcare resource utilization is both relevant and pragmatic.

Primary analysis domain

Primary analysis, defined by what data are included in the analyses, was rated as 5 as the ITT population will be used for at least the primary estimand analysis.

DISCUSSION

SEPRA is a pragmatic clinical trial comparing the effects of once-weekly subcutaneous semaglutide versus standard of care when used as treatment intensification, in a real-world population of adults with T2D across a variety of practice settings in the USA. The trial was self-assessed using the PRECIS-2 tool and scored 4–5 in all nine domains suggesting a highly pragmatic study. The participants recruited demonstrated high variability across specific baseline characteristics (including a wide distribution of baseline HbA1c values and BMI). Recruitment challenges were mitigated using different approaches and, encouragingly, most participants screened were enrolled, adding to the generalizability of study findings to the wider US population.

Several clinical trials described as pragmatic have been completed to date in T2D, including the EXSCEL study, which assessed the effect of exenatide once weekly versus placebo on CV outcomes in 14 752 participants[34] and the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) study, in which 5047 participants on metformin monotherapy were randomized to add-on glimepiride, sitagliptin, liraglutide, or insulin glargine.[35] Highly pragmatic clinical trials are typically carried out in real clinical practice following usual care and build on explanatory clinical trial findings by generating real-world evidence on the comparative effectiveness of an intervention in routine clinical practice.[27] In contrast, highly explanatory clinical trials are designed to produce the highest level of clinical evidence available for assessing the clinical efficacy of an intervention and typically recruit a very specific patient group.[36] A continuum exists between explanatory and pragmatic clinical trials.[27] To quantify the degree of pragmatism of SEPRA, the PRECIS-2 tool was used and scored 4–5 across all domains.[27]

A key strength of this study is the relatively high level of pragmatism, as illustrated by the retrospective assessment using the PRECIS-2 tool, which enhanced real-world representativeness. The eligibility criteria were minimally restrictive and aligned with the indication for once-weekly subcutaneous semaglutide in T2D, allowing evaluation of treatment intervention in real-life daily practice in randomized participants. However, operational challenges resulted in a slower enrollment rate than originally projected. To mitigate this, the eligibility criteria were amended to include: (i) participants with T2D receiving two or fewer oral antidiabetes medications (excluding oral semaglutide), rather than metformin alone and (ii) participants with any health plan with pharmacy benefits, instead of Anthem-affiliated plans only. The changes were judged to increase the pragmatism of the eligibility domain by broadening the study population to become more heterogenous and more representative of a real-world setting. Another key operational challenge was the emergence of the COVID-19 pandemic that led to a national lockdown in the USA and reduced the study recruitment rate. An operational decision was

made to amend the exclusion criteria to allow enrollment of study sites with prior experience of semaglutide research. This increased the recruitment rate and also broadened the setting and recruitment domains within the study, making the study more explanatory (ie, less pragmatic). While the overall effect of the COVID-19 pandemic is unknown at this time, it may have impacted follow-up in some patients. While protocol amendments may thus have affected the level of pragmatism of some of the domains in potentially either direction, we believe the overall score remains the same.

There are some limitations to note due to the pragmatic design. Enrolling sites that were mainly non-research, routine-care settings maximized the pragmatism of the setting domain but required provision of training on clinical trial procedures (ie, treatment randomization, data entry, and query resolution). The open-label design could encourage participants to be more compliant with treatment; however, the minimal protocol-mandated visits and assessments may reduce adherence compared with highly explanatory clinical trials. We also note that although study visits have been kept to a minimum, treating study physicians were required to capture data that would not be captured during usual visits (eg, PROs).

The study design sought to ensure equal access to the study medication regardless of participants' insurance status. External validity may increase if there is no reimbursement of participants' out-of-pocket costs, while internal validity may decrease if these costs differ between arms, which could affect participants' behavior, including adherence and persistence to medication. Thus, to balance internal and external validity, the equalized out-of-pocket cost for randomized treatment was applied. Finally, we anticipate that claims data will not be available for all participants.

In summary, SEPRA is a highly pragmatic study that has enrolled a study population with a broad range of demographic and clinical characteristics. The study is ongoing and will provide data on the effects of once-weekly subcutaneous semaglutide in a real-world population to bridge the gap between clinical trial evidence and clinical practice.

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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 data sets in a de-identified and anonymized format. Data will be made available after research completion and approval of the product and product use in the EU and the USA. Information about data access request proposals can be found at novonordisk-trials.com.

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Supplemental material

Study design and baseline profile for adults with type 2 diabetes in the once-weekly subcutaneous SEmaglutide randomized PRAgmatic (SEPRA) trial

Contents

Supplemental table 1 Study endpoints and other variables by data source

	Data source	
Endpoint/variable	**eCRF**	**Administrative claims data**
Study drug variables		
On/off study drug	X	
Treatment intensification	X	
Treatment change	X	
Anti-diabetes treatment patterns	X	
Primary endpoint		
HbA1c <7.0% at year 1	X	
Confirmatory endpoints		
Change in HbA1c (%-point) from baseline to year 1	X	
HbA1c <7.0% at year 2	X	
Change in HbA1c (%-point) from baseline to year 1	X	
Supportive secondary endpoint assessment		
Individualized HbA1c target attained at year 1	X	
HbA1c <7.0% (53 mmol/mol) or at least 1%-point improvement in HbA1c at year 1	X	
HbA1c target attainment per HEDIS criteria (<8.0% if age ≥65 years or with defined comorbidities, otherwise <7.0%) at year 1	X	X
Change in body weight from baseline to year 1, lb	X	
Change in body weight from baseline to year 1, %	X	
Change in SBP from baseline to year 1, mmHg	X	
Change in DBP from baseline to year 1, mmHg	X	
Time to first study drug discontinuation during 2 years, day	X	
Time to first treatment intensification (add-on) or change (switch) after randomization during 2 years, day	X	
Study drug medication adherence for the first year of the study, as measured by medication possession ratio, %		X
Number of hypoglycemic episodes leading to an inpatient admission or ER encounter from baseline to year 2	X	
DTSQc, total treatment satisfaction score at year 1	X	
DTSQc, total treatment satisfaction score at year 2	X	
Change from baseline in SF-12 v2, PCS-12 score at year 1	X	
Change from baseline in SF-12 v2, PCS-12 score at year 2	X	
Change from baseline in SF-12 v2, MCS-12 score at year 1	X	
Change from baseline in SF-12 v2, MCS-12 score at year 2	X	
Change from baseline in WPAI-GH absenteeism (work time missed) score at year 1	X	
Change from baseline in WPAI-GH absenteeism (work time missed) score at year 2	X	
Change from baseline in WPAI-GH presenteeism (impairment at work/reduced on-the-job effectiveness) score at year 1	X	
Change from baseline in WPAI-GH presenteeism (impairment at	X	

	Data source	
Endpoint/variable	**eCRF**	**Administrative claims data**
work/reduced on-the-job effectiveness) score at year 2		
Change from baseline in WPAI-GH work productivity loss (overall work impairment/absenteeism plus presenteeism) score at year 1	X	
Change from baseline in WPAI-GH work productivity loss (overall work impairment/absenteeism plus presenteeism) score at year 2	X	
Change from baseline in WPAI-GH activity impairment score at year 1	X	
Change from baseline in WPAI-GH activity impairment score at year 2	X	
All cause HCRU from baseline to year 2		
Number of inpatient admissions		X
Length of stay for inpatient admissions (days) per inpatient admission		X
Cumulative length of stay for inpatient admissions (days)		X
Number of ER encounters		X
Number of physician office visits		X
Number of other outpatient encounters (overall, and by category: tests – lab, imaging, procedures, OT/speech, medication and related services, durable medication equipment, physician other services, tests – other, other)		X
Number of medications		X
Occurrence of inpatient admission		X
Occurrence of ER encounter		X
Occurrence of physician office visits		X
Occurrence of other outpatient encounter (yes/no) (overall, and by category: tests – lab, imaging, procedures, OT/speech, medication and related services, durable medication equipment, physician other services, tests – other, other)		X
Diabetes-related HCRU from baseline to year 2		
Number of diabetes-related inpatient admissions		X
Length of stay for diabetes-related inpatient admissions (days) per diabetes-related inpatient admissions		X
Cumulative length of stay for diabetes-related inpatient admissions (days)		X
Number of diabetes-related ER encounters		X
Number of diabetes-related physician office visits		X
Number of diabetes-related other outpatient encounters (overall, and by category: tests – lab, imaging, procedures, OT/speech, medication and related services, durable medication equipment, physician other services, tests – other, other)		X
Number of diabetes-related medications		X
Occurrence of diabetes-related inpatient admission		X
Occurrence of diabetes-related ER encounter		X
Occurrence of diabetes-related physician office visits		X
Occurrence of diabetes-related outpatient encounter (yes/no) (overall, and by category: tests – lab, imaging, procedures, OT/speech, medication and related services, durable medication equipment, physician other services, tests – other, other)		X

	Data source	
Endpoint/variable	**eCRF**	**Administrative claims data**
Additional derived outcome variables for supportive analyses		
Supportive measures of glycemic control		
Individualized HbA1c target attained at year 2	X	
HbA1c <7.0% (53 mmol/mol) or at least 1%-point improvement in HbA1c compared to baseline at year 2	X	
HbA1c <8.0% (64 mmol/mol) at year 1	X	
HbA1c <8.0% (64 mmol/mol) at year 2	X	
HbA1c <7.0% (53 mmol/mol) and no further anti-diabetes medication intensification after randomization at year 1	X	
HbA1c <7.0% (53 mmol/mol) and no further anti-diabetes medication intensification after randomization at year 2	X	
HbA1c target attainment per HEDIS criteria (<8.0% if age ≥65 years or with defined comorbidities, otherwise <7.0%) at year 2	X	X
HbA1c <7.0% (53 mmol/mol) at year 1 in patients with HbA1c >9.0% at baseline	X	
HbA1c <7.0% (53 mmol/mol) at year 2 in patients with HbA1c >9.0% at baseline	X	
HbA1c <8.0% (64 mmol/mol) at year 1 in patients with HbA1c >9.0% at baseline	X	
HbA1c <8.0% (64 mmol/mol) at year 2 in patients with HbA1c >9.0% at baseline	X	
Body weight loss		
Change in body weight (%) from baseline to year 2	X	
Change in body weight (lb) from baseline to year 2	X	
Blood pressure		
Change in SBP (mmHg) from baseline to year 2	X	
Change in DBP (mmHg) from baseline to year 2	X	
Hypoglycemia		
Reported hypoglycemia leading to inpatient admission or ER encounter during year 1	X	
Reported hypoglycemia leading to inpatient admission or ER encounter during year 2	X	
Composite variables		
HbA1c <7.0% (53 mmol/mol) without experiencing hypoglycemia leading to inpatient admission or ER encounter and body weight loss of ≥5% vs baseline at year 1	X	
Absolute HbA1c reduction of ≥0.5% without experiencing hypoglycemia leading to inpatient admission or ER encounter and a body weight loss of ≥5% vs baseline at year 1	X	
HbA1c <7.0% (53 mmol/mol) without experiencing hypoglycemia leading to inpatient admission or ER encounter and body weight loss of ≥5% vs baseline at year 2	X	
Absolute HbA1c reduction of ≥0.5% without experiencing hypoglycemia leading to inpatient admission or ER encounter and a body weight loss of	X	

	Data source	
Endpoint/variable	**eCRF**	**Administrative claims data**
≥5% vs baseline at year 2		
HbA1c <7.0% (53 mmol/mol) without experiencing hypoglycemia leading to inpatient admission or ER encounter and no body weight gain vs baseline at year 1	X	
HbA1c <7.0% (53 mmol/mol) without experiencing hypoglycemia leading to inpatient admission or ER encounter and no body weight gain vs baseline at year 2	X	
Adherence to treatment		
Study drug medication adherence for the 2 years of the study, as measured by the medication possession ratio (%)		X

DBP, diastolic blood pressure; DTSQc, Diabetes Treatment Satisfaction Questionnaire, change version; eCRF, electronic case report form; ER, emergency room; HbA1c, glycated hemoglobin; HCRU, Healthcare Resource Utilization; HEDIS, Healthcare Effectiveness Data and Information Set; MCS-12, Mental Component Summary; OT, occupational therapy; PCS-12, Physical Component Summary; SBP, systolic blood pressure; SF-12 v2, Short Form 12-Item version 2 Survey; WPAI-GH, Work Productivity and Activity Impairment: General Health questionnaire.

Supplemental table 2 Summary of assessments

SePra	Dedicated study visit, randomization	Routine care visits, Year 1	Dedicated study visit, Year 1	Routine care visits, Year 2	Dedicated study visit, Year 2
Time of visit (weeks)[a]	0*	0–52**	52±6	52–104**	104±6
Patient and treatment-related assessments[b]	X				
Informed consent[c]	X				
Inclusion/exclusion criteria	X				
Demographics (date of birth, gender, race, ethnicity)	X				
Selected medical history	X				
Diabetes history and diabetes complications	X				
Indivisualised HbA1c target[d]	X				
Type of glucose-lowering medication including semaglutide[e]	X	X	X	X	X
Concomitant cardiovascular medication	X	X	X	X	X
Reason for discontinuation of any glucose-lowering medication		X	X	X	X
Effectiveness and safety-related assessments					
Body weight	X	X	X	X	X
Height	X				
SBP/DBP	X	X	X	X	X
HbA1c	X[f]	X	X	X	X
SAEs, pregnancies, and AEs leading to study drug continuation[g]		X	X	X	X
Healthcare resource utilization[h]		X	X	X	X
Hypoglycemia leading to inpatient admission or ER encounter		X	X	X	X
Hypoglycemia leading to inpatient admission or ER		X	X	X	X

SePra	Dedicated study visit, randomization	Routine care visits, Year 1	Dedicated study visit, Year 1	Routine care visits, Year 2	Dedicated study visit, Year 2
encounter					
PROs and physician-completed assessments					
DTSQs	X				
DTSQc			X		X
SF-12 v2	X		X		X
WPAI-GH	X		X		X
PGI-S	X				
PGI-C			X		X
CGI-S	X				
CGI-C			X		X
End of study					
End of study					X

*Eligibility assessment may take place up to 4 weeks prior to the randomization visit. If eligibility assessment occurs prior to the randomization visit, any changes in collected medical history, diabetes history, diabetes complications, glucose-lowering medications and concomitant cardiovascular medications will be collected at the randomization visit.

**The year 1 and year 2 routine diabetic care visit windows are determined by the date of the participant's dedicated year 1 study visit. The year 1 routine diabetic care visit window will end immediately prior to the dedicated year 1 study visit. The year 2 routine diabetic care visit window will begin immediately following the dedicated year 1 study visit.

Note: In this study, data will be collected from two different data sources:

1) Data entered into the eCRF will be collected at dedicated study visits and routine diabetic care visits (if available per local clinical practice) and will include demographics, selected medical history, diabetes medical history and diabetes complications, individualized HbA1c target, type of glucose-lowing medication, concomitant cardiovascular medication, reason for discontinuation of any glucose-lowering medication, body weight, height, SBP, DBP, HbA1c, AEs leading to study drug discontinuation, SAEs, pregnancies and hypoglycemia leading to inpatient admission or ER encounter. Of note, AEs leading to study drug discontinuation or SAEs will be collected from all interactions with the participant, as well as if discovered when reviewing documents from healthcare encounters with other providers. Additionally, PRO and clinician-reported outcome data will be collected at the dedicated study visits and entered into the eCRF.

2) Healthcare resource utilization and pharmacy prescription data will be extracted from health plan medical and pharmacy claims and will not be entered into the eCRF.

[a]Routine diabetic care visits will follow standard of care frequency and any available data will be entered in the eCRF.

[b]Assessments at dedicated study visits will be collected in eCRF. Assessments at routine diabetic care visits will be collected as available/according to local clinical practice in eCRF.

[c]Informed consent must be obtained before any study related activities.

[d]Individualized HbA1c target must be set and documented prior to randomization.

[e]Medication data (glucose-lowering medications and/or concomitant cardiovascular medications) collected at study visits only include medications that are current at time of study visit.

[f]The HbA1c value is based on historical data collected from the treating study physician and is the value closest to the date of randomization, within the last 90 days.

[g]Any SAE identified from any encounter or notation at any time must be reported.

[h]Data from health plan medical and pharmacy claims. Data will be extracted at €the end of the study but will include data from participant randomization through end of study or withdrawal.

AE, adverse event; CGI-C, Clinical Global Impression-Change; CGI-S, Clinical Global Impression-Severity; DBP, diastolic blood pressure; DTSQc, Diabetes Treatment Satisfaction Questionnaire, change version; DTSQs, Diabetes Treatment Satisfaction Questionnaire, status version; eCRF, electronic case report form; ER, emergency room; PGI-C, Patient Global Impression-Change; PGI-S, Patient Global Impression-Severity; PRO, patient-reported outcome; SAE, serious adverse event; SBP, systolic blood pressure; SF-12 v2, Short Form 12-Item version 2; WPAI-GH, Work Productivity and Activity Impairment: General Health questionnaire.

Supplemental table 3 Geographical distribution and specialty of participating study sites

	Overall (N=1278), %
Geographic region	
Northeast	167 (13.1)
Midwest	333 (26.1)
South	561 (43.9)
West	217 (17.0)
	Overall (N=138), %
Site specialty	
Primary care, internal medicine, family medicine	100 (72.5)
Endocrinology	38 (27.5)
Sites with semaglutide research experience	
Yes	32 (23.2)*
No	106 (76.8)

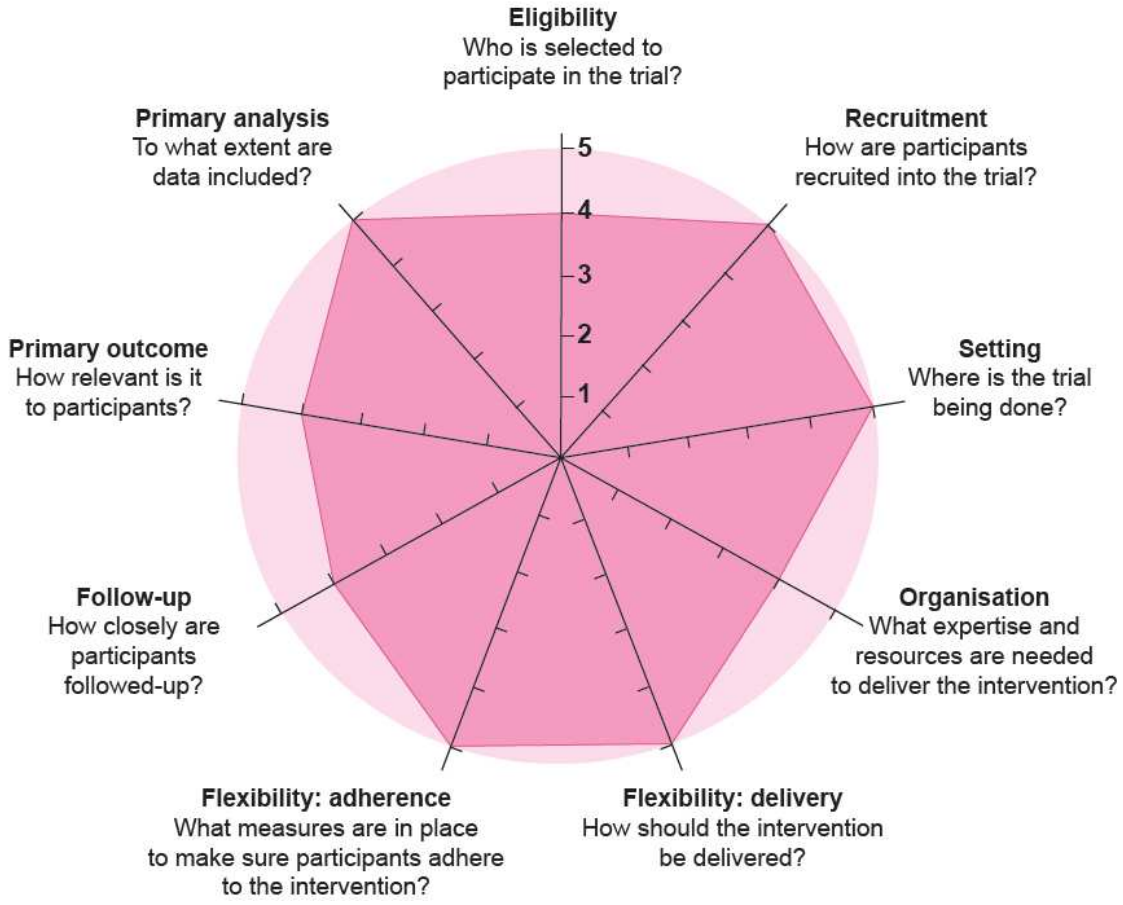
*Of the 32 study physicians at research-experienced sites, 29 were primary care physicians and three were endocrinologists.

Supplemental table 4 Summary of the independently assessed PRECIS-2 scores from each individual in the study steering group and the overall consensus reached following discussions during a workshop meeting in December 2018.

Domain	A	B	C	D	E	F	G	H	I	J	K	Consensus score
Eligibility criteria	5	4	4	4	4	4	5	5	4	3–4	4	4
Recruitment path	4	5	5	4	4	5	5	4	4	5	3	5
Setting	5	5	5	4	5	5	5	5	5	4	5	5
Organisation	4	4	4	4	5	5	4	5	4	4	4	4
Flexibility: delivery	5	5	4	5	5	5	5	5	5	4	5	5
Flexibility: adherence	5	5	5	5	5	5	5	5	5	4	4	5
Follow-up	4	4	5	4	4	4	4	4	4	5	2	4
Outcome	5	4	5	4	4	4	4	4	4	3–4	4	4
Analysis	5	5	5	5	5	5	3	5	5	5	3	5

PRECIS-2, PRagmatic Explanatory Continuum Indicator Summary-2.

Supplemental figure 1 The PRECIS-2 assessment of the SEPRA trial



The tool uses a 5-point Likert scale, where 1 = very explanatory and 5 = very pragmatic.[1]

PRECIS-2, PRagmatic Explanatory Continuum Indicator Summary-2.

Appendix 1. Description of patient reported outcomes, clinician reported outcomes, and diabetes treatment satisfaction

Diabetes Treatment Satisfaction Questionnaire (DTSQ)[2-5]

The DTSQ was included in the trial to evaluate patient satisfaction with treatment compared with prior treatment. The DTSQ status version was completed at randomization and the DTSQ change (DTSQc) version will be completed at year 1 and year 2. The DTSQc version employs eight questions that are answered using a Likert scale from –3 to +3 (–3 = much less satisfied now to +3 = much more satisfied now) with 0 (midpoint), representing no change. The scores to six questions are added together to produce a total treatment satisfaction score. The remaining two questions concern perceived frequency of hyperglycemia and perceived frequency of hypoglycemia, respectively. The DTSQc total treatment satisfaction score ranges from –18 to +18, with higher scores associated with greater treatment satisfaction.

Short Form 12-Item version 2 (SF-12 v2) Health Survey[6]

The SF-12 v2 questionnaire was included in the trial to assess physical and mental functioning and overall health-related quality of life. The following two summary scores are used as endpoints: Physical Component Summary score and Mental Component Summary score. The scores are norm scored such that the scores range from 0–100 with a mean of 50 and standard deviation of 10. The higher the score, the better quality of life; the lower the score, the poorer quality of life.

Work Productivity and Activity Impairment: General Health (WPAI-GH) questionnaire[7]

The WPAI-GH assesses work productivity and activity impairment attributable to general health. There are four types of scores: absenteeism (ie, work time missed), presenteeism (ie, impairment at work/reduced on-the-job effectiveness), work productivity loss (ie, overall work impairment/absenteeism plus presenteeism), and activity impairment (eg, work around the house, shopping, exercising, childcare, studying). Outcomes are expressed as percentages with higher numbers indicating greater impairment and less productivity, ie, worse outcomes (percent work time missed due to health, percent impairment while working due to health, percent overall work impairment due to health, percent activity impairment due to health).

Patient Global Impression of Disease Severity (PGI-S) and Patient Global Impression of Change (PGI-C)

The PGI-S is a 1-item measure that assesses the patient's impression of disease severity based on their present diabetes symptoms (ie, normal, mild, moderate, or severe). The PGI-C assesses the patient's impression of changes in diabetes symptoms, based on their diabetes symptoms now, compared with how they were before they began taking the study drug (ie, very much better, much better, a little better, no change, a little worse, much worse, or very much worse).

Clinician Global Impression of Disease Severity (CGI-S) and Clinician Global Impression of Change (CGI-C)

The CGI-S and CGI-C were included in the study to assess disease severity from the treating study physician's perspective. The CGI-S is a 1-item measure that assesses the clinician's impression of the patient's disease severity, based on the patient's present diabetes symptom (ie, normal, mild, moderate, or severe). The CGI-C assesses the clinician's impression of change in the patient's diabetes symptoms, based on the patient's diabetes symptoms now, compared with how they were before they began taking the study drug (ie, very much better, much better, a little better, no change, a little worse, much worse, or very much worse).

Appendix 2. Study investigators

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