Cover Page for Protocol

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Official title of study:	Long Term Comparative Effectiveness of Once Weekly Semaglutide Versus Standard of Care in a Real World Adult US Population With Type 2 Diabetes - a Randomized Pragmatic Trial
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16.1.1 Protocol and protocol amendments

16.1.1.1 Protocol

Redacted protocol
Includes redaction of personal identifiable information only.

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[redacted]

Long term comparative effectiveness of once weekly semaglutide versus standard of care in a real world adult US population with type 2 diabetes - a randomized pragmatic clinical trial

Trial ID NN9535-4416

Novo Nordisk

March 13, 2018

Version 1.0

Trial Phase: 4
Investigational Substance: Semaglutide

[redacted]

[redacted]

STUDY APPROVALS
Protocol No: NN9535-4416
13-MAR-2018

Sponsor Approval:

Name: [redacted]
Title: [redacted]
Novo Nordisk

Signature: _____

Date: _____

Name: [redacted]
Title: [redacted]
Novo Nordisk

Signature: _____

Date: _____

[redacted]

Principal Study Physician Agreement:

I have read the protocol "Long term comparative effectiveness of once weekly semaglutide versus standard of care in a real world adult US population with type 2 diabetes - a randomized pragmatic clinical trial" and agree to ensure that all staff members involved in the conduct of this study are informed of their obligations and that they meet the commitments of the protocol in accordance with Good Clinical Practice (GCP) requirements. I have familiarized myself with the prescribing information corresponding with the study drugs associated with this study.

I acknowledge that I am responsible for overall study conduct. I understand GCP requirements and agree to personally conduct or supervise the described pragmatic study in accordance with GCP.

Signature: _____

Print Name: _____

Date: _____

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SYNOPSIS

Title: Long term comparative effectiveness of once weekly semaglutide versus standard of care in a real world US adult population with type 2 diabetes – a randomized pragmatic clinical trial
Sponsor: Novo Nordisk **Study Treatment:** Semaglutide in a prefilled pen (Ozempic®) **Active Ingredient:** Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA) **Comparator Treatment:** Standard of Care (SOC) (excluding semaglutide)
Trial ID: NN9535-4416
Study Physician Sites: Participation of approximately 285 physician sites, including both primary care practitioners and endocrinologists, that have a population of patients with the target indication, type 2 diabetes mellitus (T2DM), actively enrolled in an [redacted] affiliated commercial health plan. **Country:** United States (US)
Patients: Eligible patients include adult T2DM patients on metformin monotherapy whose physician deems that they have inadequate glycemic control and need treatment intensification with an additional antidiabetic oral or injectable medication. Planned enrollment in this study is 2250. Patients will be randomized 1:1 to receive either semaglutide or SOC.
Study Objectives: The objectives of this study are as follows: 1.) The primary objective is to demonstrate superior long term effects of treatment with semaglutide compared to SOC both added to metformin on glycemic control when used as intensification in routine clinical practice in adult patients with T2DM. 2.) The secondary objectives are to compare the long term effect of semaglutide versus SOC both added to metformin and used as intensification in routine clinical practice in adult patients with T2DM with regards to: a. Weight loss b. Patient reported outcomes (PROs) and clinician reported outcomes (ClinROs) c. Hypoglycemia d. Healthcare Resource Utilization (HCRU) e. Adherence and persistence to treatment
Study Design: This is a 2-year, multi-center, randomized, open label, parallel group, active comparator pragmatic clinical trial (PCT) comparing semaglutide versus SOC when added to metformin monotherapy as treatment intensification among adult T2DM patients in the course of routine clinical practice. Patients will be randomized 1:1 to receive either semaglutide or SOC. The decision that further antidiabetic treatment intensification with oral or injectable antidiabetic medication is indicated is at the discretion of the study physician and will be made prior to and independent of enrollment in this study. The study physician will have determined the patient's suitability for treatment with semaglutide prior to signing informed consent, but the determination to initiate semaglutide versus SOC will be made by randomization. In keeping with the study objectives and pragmatic design to evaluate semaglutide versus SOC in real world, routine clinical practice, inclusion and exclusion criteria are minimally restrictive and there are few study-specific evaluations. Study physicians will follow and treat patients according to their

routine clinical practice and judgement. All oral and injectable antidiabetic medications are allowed at the study physicians' discretion, with the exception of semaglutide in the SOC group. Patients will be followed for 2 years, regardless of changes in antidiabetic treatment over the course of the study.

It is anticipated that patients will undergo medical evaluation at regular intervals over the course of the study duration as per standard of care, but the only dedicated study visits are at randomization, at year 1, and at year 2. The study will also capture clinical data collected at the sites during routine care visits, i.e., office visits and other patient contacts that occur as part of routine clinical practice. Assessments will be conducted according to the study physician's routine clinical practice, with a few study-specific assessments as outlined in Study Procedures. Additionally, medical and pharmacy claims data will be captured utilizing the HealthCore Integrated Research Database (HIRD^{SM}) for the 2 year study period. HIRD data for the 12 months prior to randomization will also be collected if available.

Participant Selection:

Inclusion Criteria:

Patients must meet all of the following inclusion criteria to be eligible for the study:

1.) Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study.
2.) Male or female, age ≥ 18 years at the time of signing informed consent.
3.) Type 2 diabetes mellitus diagnosis.
4.) Treatment with metformin as antidiabetic monotherapy
5.) Current member of an [redacted] affiliated commercial health plan.
6.) Recorded glycosylated hemoglobin A1c (HbAlc) value within the last 90 days prior to randomization.
7.) Further intensification with an additional antidiabetic oral or injectable medication is indicated to achieve glycemic target at the discretion of the study physician according to approved labelling.

Exclusion Criteria:

Patients presenting with any of the following exclusion criteria will not be eligible for the study:

1.) Previous randomization in this study.
2.) Treatment with any medication for the indication of diabetes other than metformin in a period of 30 days before the day of eligibility assessment. Temporary/emergency use of any type of insulin is allowed, as is prior insulin treatment for gestational diabetes.
3.) Contraindications to semaglutide according to the FDA approved label.
4.) Female who is pregnant, breastfeeding or intends to become pregnant.
5.) Participation in another clinical trial.

Study Procedures:

- Study physicians will identify eligible patients for participation.
- Study physicians will obtain written informed consent from patients and if eligible, patients will be randomized to either semaglutide or SOC.
- Study data will be collected on electronic Case Report Forms (eCRFs) via an electronic data capture (EDC) system.
- Study physicians or site personnel will collect demographic, clinical (i.e., height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP)), medical and T2DM specific

[redacted]

history, antidiabetic medications, and pre-specified concomitant medications related to cardiovascular risk data prior to or at randomization. Individualized HbA1c target will be set prior to randomization.

- Baseline HbA1c will be collected from physician sites during eligibility assessment and will be the value closest to the date of randomization, within 90 days. All post-randomization HbA1c values will be recorded as available per routine clinical practice during the 2 year study period. Post-randomization HbA1c values are required for the year 1 and year 2 dedicated study visits.
- PROs and ClinROs will be completed at randomization, year 1, and year 2.
- Study physicians will collect patient data (HbA1c, study and antidiabetic medication changes, pre-specified concomitant medications related to cardiovascular risk, weight, SBP, DBP, hypoglycemic events leading to inpatient admission or emergency room (ER) encounter, adverse events (AEs) leading to study drug discontinuation, serious adverse events (SAEs), and pregnancies at the dedicated year 1 and year 2 study visits, as well as at any routine care visits during the 2 year study period.
- Administrative medical claims, pharmacy claims and health plan eligibility data will be captured from the HIRD for the duration of the 2 year study period. HIRD data for the 12 months prior to study randomization will also be collected if available. This data will be used for HCRU measures, as well as adherence and persistence to treatment.

Study Duration: Planned patient time on study will be 2 years. Administrative claims data will also be captured during this time period. Patients will be followed for the full 2 year study period regardless of changes in or discontinuation of antidiabetic treatment, other than withdrawal of consent.

Questionnaires: Diabetes treatment satisfaction, generic health-related quality of life (HRQoL), work productivity, and patient and clinician global assessments will be measured at the randomization, year 1, and year 2 dedicated study visits.

Statistical Analysis: Two estimands, each targeting a unique research question, have been defined to adequately describe the effect of semaglutide as compared to SOC (excluding semaglutide).

The primary estimand for all objectives will be the "intention-to-treat" estimand evaluating the effectiveness of randomized treatment intervention, irrespective of adherence to this randomized intervention or changes to other antidiabetic medication.

The secondary estimand for all objectives, with the exception of the adherence and persistence to treatment objective, is the "if all patients had adhered" estimand. This estimand evaluates the effect of randomized treatment intervention for all randomized patients if all patients had adhered to randomized treatment, regardless of changes to other antidiabetic medication.

Baseline is defined as ≤ 90 days prior to randomization visit (week 0) for HbA1c. For secondary endpoint assessments, baseline is defined as ≤ 4 weeks prior to the randomization visit (week 0).

Primary completion date (PCD) is the date the last patient completes the year 1 dedicated study visit.

The primary endpoint is binary, with success represented by an HbA1c <7.0% (53 mmol/mol) at year 1 (yes/no). Confirmatory secondary endpoints include:

- Change in HbA1c (%-point) from baseline to year 1
- HbA1c <7.0% (53 mmol/mol) at year 2 (yes/no)
- Change in HbA1c (%-point) from baseline to year 2

This study is designed to have 90% power to jointly confirm superiority of the primary endpoint and the above three confirmatory secondary endpoints based on an analysis of the primary estimand for each of the endpoints.

The confirmatory endpoints will all be tested under multiplicity control via a hierarchical testing scheme according to the order given in the above bullet list.

The estimand informs choices about data foundation and statistical analysis including possible imputation of missing data, hereby ensuring that randomization is preserved as a sound basis for statistical inference; i.e., estimation of effect size, associated uncertainty, and statistical testing.

The full analysis set (FAS) comprising all randomized patients will be the analysis population for evaluation of both the primary and secondary estimands. For both estimands, the primary endpoint, HbA1c <7.0%, will be analyzed using a logistic regression model with a logit link function and will include treatment and baseline HbA1c as independent variables. Continuous endpoints will be analyzed using analysis of covariance (ANCOVA) and will include the same independent variables. Prior to analysis, missing data will be imputed by multiple imputation on the continuous HbA1c scale and subsequently dichotomized for the primary endpoint.

Supplementary Analyses: Two complete case analyses will complement the analyses for the primary and secondary estimands. The supplementary complete case analyses will be based on the subset of patients without missing endpoint data, i.e., patients that do not have their endpoint imputed in the two analyses used for the primary estimand and the secondary estimand, respectively.

Secondary Analyses: Secondary analyses will compare semaglutide versus SOC treatment groups in terms of change in body weight, SBP, DBP, and PRO and ClinRO measures, based on the similar analysis methods as for the primary and secondary estimands. Similarly, binary endpoints and other secondary endpoints will be compared statistically between treatment groups, including HCRU and adherence/persistence to treatment measures, hypoglycemic events leading to inpatient admission or ER encounter, as well as composite measures of HbA1c, weight loss, and hypoglycemia.

Safety: The principal study physician is responsible for monitoring the safety of participating patients. For the purposes of this study, AEs that do not meet the definition of an SAE will only be collected/recorded in the EDC if they lead to study drug discontinuation. Study physicians are responsible for reporting all SAEs and following the patient until the outcome of the SAE is closed out. All SAEs will be reported from randomization until end of study (EOS) at year 2 or patient study withdrawal. Study physicians are also responsible for recording all pregnancies in female patients from randomization until EOS at year 2 or patient study withdrawal. The patient will be followed for the duration of the pregnancy until one month post-delivery to report the pregnancy outcome and any AEs or SAEs observed in the fetus or newborn until 1 month of age. Safety will be summarized descriptively.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	American Diabetes Association
AE	Adverse Event
ANCOVA	Analysis of Covariance
eCCGs	Electronic Case Report Form Completion Guidelines
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinician Global Impression of Disease Severity
CI	Confidence Interval
ClinRO	Clinician Reported Outcome
eCRF	Electronic Case Report Form
DBP	Diastolic Blood Pressure
DPP-4	Dipeptidyl peptidase 4
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTSQc	Diabetes Treatment Satisfaction Questionnaire, change version
DTSQs	Diabetes Treatment Satisfaction Questionnaire, status version
EASD	European Association for the Study of Diabetes
EDC	Electronic Data Capture
EOS	End of Study
ER	Emergency Room
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonists
HbA1c	Glycosylated Hemoglobin A1c

HCRU	Healthcare Resource Utilization
HEDIS	Healthcare Effectiveness Data and Information Set
HIRD[SM]	HealthCore Integrated Research Database
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ID	Identifier
IRB	Institutional Review Board
ITT	Intent to Treat
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MCS-12	Mental Summary Component (of the Short Form 12-Item version 2)
MPR	Medication Possession Ratio
OR	Odds Ratio
PCD	Primary Completion Date
PCS-12	Physical Summary Component (of the Short Form 12-Item version 2)
PCT	Pragmatic Clinical Trial
PDC	Proportion Days Covered
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Disease Severity
PRO	Patient Reported Outcome
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SF-12v2	Short Form 12-Item version 2
SGLT-2	Sodium-Glucose Co-transporter 2
[redacted]	

SM	Service Mark
SOC	Standard of Care
SUSTAIN	Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes
T2DM	Type 2 Diabetes Mellitus
TD	Treatment Difference
US	United States
WPAI-GH	Work Productivity and Activity Impairment, General Health

LIST OF DEFINITIONS

Term	Definition
Administrative Claims Data	Medical, pharmacy, and health plan eligibility data created in the processing of medical and pharmacy claims. The claims data utilized in this study are obtained from the HealthCore Integrated Research Database (HIRD).
Baseline	Baseline refers to assessments conducted and patient data collected at or prior to randomization. Baseline HbAlc may be ≤ 90 days prior to randomization. Baseline for secondary endpoint assessments may be ≤ 4 weeks prior to randomization.
Baseline Endpoint	For continuous endpoints and endpoints derived from continuous sources, the baseline value is defined as the last assessment taken prior to or at the randomization visit *and* before first use of study drug.
Comparator Treatment	Standard of Care (SOC) (excluding semaglutide); Commercially available oral or injectable antidiabetic medication, excluding semaglutide, prescribed at the discretion of the study physician for antidiabetic treatment intensification following randomization.
Complete the Study	Complete the study at 52 weeks: Patient has year 1 HbA1c data Complete the study at 104 weeks: Patient has year 2 HbA1c data
Dedicated Study Visit	One of three required study visits: randomization, year 1, and year 2.
Enrollment	Randomization
Estimand	The estimate targeted to address the research question posed by the study objective, i.e., "what is to be estimated." [1] The estimand translates the study objective into a precise definition of the effect of treatment.
Healthcare Resource Utilization (HCRU)	Broad term encompassing use of healthcare services, including inpatient admissions, ER encounters, outpatient encounters including office visits, and pharmacy prescription fills.
Index Date	The date corresponding to an event of interest. In this study, index date is the date corresponding to a claims-based proxy for antidiabetic treatment intensification for 2 comparator populations, thus mimicking randomization date in the study population.
Principal Study Physician	Physician at study site who is responsible for the overall conduct and oversight of the study at their site, including: supervision of study personnel, monitoring the safety of all participating patients, ensuring the accurate and complete collection and reporting of study data, continued review of the IRB study approval, and maintenance of study

	records. This term is analogous to "Investigator" in Good Clinical Practice (GCP) requirements.
Randomization	The point at which a patient is assigned by chance to either semaglutide or standard of care (SOC).
Routine Care Visit	An office visit or other patient contact during the study period that occurs outside of the dedicated study visits (randomization, year 1, and year 2) according to routine clinical practice.
Study Physician	Physician at study site who participates in the conduct of the study.
Study/Trial	For the purposes of this protocol, study and trial are considered synonyms. Study is used throughout the body of the text as it reflects the post-regulatory approval setting and real world design. Trial is used in the title and in referring to the PCT acronym to maintain consistency with the industry standard Pragmatic Clinical Trial or PCT.
Study Drug	Study drug is the first antidiabetic oral or injectable medication prescribed for treatment intensification following randomization. A patient can start and stop study drug throughout the study. At any time during the duration of the study, if a patient is taking study drug as defined, they will be considered "on study drug" regardless of prior study drug discontinuations. • For the semaglutide treatment group, study drug is defined as semaglutide. • For the SOC treatment group, study drug is defined as the drug class of the first antidiabetic oral or injectable medication prescribed for treatment intensification following randomization. If a fixed dose combination (FDC) product is prescribed, one of the drugs will be chosen by the study physician to be the study drug. A patient randomized to the SOC treatment group will still be considered "on study drug" if they are taking a drug in the same drug class as their first study drug, even if it is not the same individual drug. This also applies to treatment intensification with a FDC product if one of the drugs is in the same drug class as the first study drug.
Study Drug Discontinuations	Study drug discontinuation is termination of the study drug. A patient can start and stop study drug throughout the study; therefore a patient's study drug discontinuation status can change throughout the duration of the study. At any time during the duration of the study, if a patient is not taking study drug as defined, they will be considered "off study drug."

1 INTRODUCTION

1.1 Background and Rationale

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) position statement recommends a patient-centric approach to the selection of pharmacological treatment for type 2 diabetes mellitus (T2DM), including considerations on effectiveness, hypoglycemia risk, impact on body weight, side effects, costs, and patient preferences. [2] Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are recommended for the management of hyperglycemia in T2DM, primarily in combination with other antidiabetic medications. [2] [3]

Semaglutide, a human GLP-1 analogue for once-weekly subcutaneous administration, has been shown to improve glycemic control in adults with T2DM as monotherapy when the use of metformin is considered inappropriate, or as add-on to other glucose lowering therapies including insulin. In the *Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes* (SUSTAIN) clinical development program, semaglutide demonstrated clinically relevant and superior glycemic control, as well as weight loss versus placebo and active comparators, both when used as mono- and combination therapy in inadequately controlled patients with T2DM. In addition, a significant reduction in cardiovascular risk was demonstrated for semaglutide versus placebo in patients with T2DM at high risk of cardiovascular events. The overall safety profile of semaglutide was consistent with the well-established GLP-1 RA safety profile. [4]

Pragmatic clinical trials (PCTs) are designed and conducted to reflect patient outcomes and to investigate how a product is used and performs in routine clinical practice. This type of study compares two or more medical interventions that are directly relevant to clinical care and strives to assess those interventions' effectiveness in real world practice. They use broad eligibility criteria and recruit patients from a variety of practice settings to ensure the inclusion of the type of patients whose care will be influenced by the study´s results. Such studies are increasingly important to generate evidence regarding real world treatment outcomes to inform and support appropriate market access. [5]

The current local US study serves the purpose of evaluating the long term comparative effectiveness of semaglutide with existing commercially available antidiabetic medications in a real world population and in a variety of practice settings, thereby maximizing external validity while balancing the internal validity of a randomized controlled trial. This will generate data to complement the findings from the SUSTAIN clinical development program. Taken together, these findings may provide important evidence for decision making by clinicians, payers, and policy makers in routine clinical practice.

This local US study will enroll adult patients with T2DM who have inadequate glycemic control on metformin as their only antidiabetic medication, as defined by the need for treatment intensification with an additional antidiabetic oral or injectable medication per the study physician´s discretion. The current study targets patients at this particular treatment point

[redacted]

because they represent the population inadequately controlled on the current ADA recommended first lines of treatment of T2DM. The addition of a GLP-1 RA as second-line treatment is in line with the ADA guidance from 2017. [6] In keeping with the ADA and EASD position statement recommending a patient-centric approach to treatment selection for T2DM patients, in addition to comparative effectiveness, this study will also evaluate hypoglycemia risk, body weight, healthcare resource utilization (HCRU), patient reported outcomes (PROs), and clinician reported outcomes (ClinROs). Adverse events (AEs) leading to study drug discontinuation will also be collected. [2]

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to demonstrate superior long term effects of treatment with semaglutide compared to standard of care (SOC) both added to metformin on glycemic control when used as intensification in routine clinical practice in adult patients with T2DM.

2.2 Secondary Objectives

The secondary objectives are to compare the long term effect of semaglutide versus SOC both added to metformin and used as intensification in routine clinical practice in adult patients with T2DM with regards to:

- Weight loss
- Patient reported outcomes (PROs) and clinician reported outcomes (ClinROs)
- Hypoglycemia
- Healthcare Resource Utilization (HCRU)
- Adherence and persistence to treatment

3 STUDY ENDPOINTS

3.1 Baseline

Baseline is defined as ≤ 90 days prior to randomization visit (week 0) for glycosylated hemoglobin A1c (HbA1c). For secondary endpoint assessments, baseline is defined as ≤ 4 weeks prior to the randomization visit (week 0).

3.2 Primary Endpoint

Primary completion date (PCD) is the date the last patient completes the year 1 dedicated study visit.

The primary endpoint of this study is:

[redacted]

- HbA1c <7.0% (53 mmol/mol) at year 1 (yes/no)

3.3 Secondary Endpoints

3.3.1 Confirmatory Secondary Endpoints

Confirmatory secondary endpoints of this study include:

- Change in HbA1c (%-point) from baseline to year 1
- HbA1c <7.0% (53 mmol/mol) at year 2 (yes/no)
- Change in HbA1c (%-point) from baseline to year 2

3.3.2 Supportive Secondary Endpoints

Supportive secondary endpoints of this study include:

- Individualized HbA1c target attained at year 1 (yes/no)
- HbA1c <7.0% (53mmol/mol) or at least 1% point improvement in HbA1c compared to baseline at year 1 (yes/no)
- HbA1c target attainment per Healthcare Effectiveness Data and Information Set (HEDIS) criteria (<8.0% if age ≥65 years or with defined comorbidities, otherwise <7.0%) at year 1 (yes/no)
- Change in body weight (lb) from baseline to year 1
- Change in body weight (%) from baseline to year 1
- Change in systolic blood pressure (SBP; mm Hg) from baseline to year 1
- Change in diastolic blood pressure (DBP; mm Hg) from baseline to year 1
- Time to first study drug discontinuation during 2 years (day)
- Time to first treatment intensification (add-on) or change (switch) after randomization during 2 years (day)
- Study drug medication adherence for the first year of the study, as measured by medication possession ratio (MPR) (%)
- Number of hypoglycemic episodes leading to an inpatient admission or emergency room (ER) encounter from baseline to year 2
- Diabetes Treatment Satisfaction Questionnaire, change version (DTSQc), Total treatment satisfaction score measured at year 1
- DTSQc, Total treatment satisfaction score measured at year 2
- Change from baseline in Short Form 12-Item Version 2 Survey (SF-12 v2), Physical summary component (PCS-12) score at year 1

- Change from baseline in SF-12 v2, PCS-12 score at year 2
- Change from baseline in SF-12 v2, Mental summary component (MCS-12) score at year 1
- Change from baseline in SF-12 v2, MCS-12 score at year 2
- Change from baseline in Work Productivity and Activity Impairment, General Health questionnaire (WPAI-GH) Absenteeism (work time missed) score at year 1
- Change from baseline in WPAI-GH Absenteeism (work time missed) score at year 2
- Change from baseline in WPAI-GH Presenteeism (impairment at work / reduced on-the-job effectiveness) score at year 1
- Change from baseline in WPAI-GH Presenteeism (impairment at 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
- Change from baseline in WPAI-GH Work productivity loss (overall work impairment / absenteeism plus presenteeism) score at year 2
- Change from baseline in WPAI-GH Activity Impairment score at year 1
- Change from baseline in WPAI-GH Activity Impairment score at year 2

All cause healthcare resource utilization (HCRU) from baseline to year 2:

- Number of inpatient admissions
- Cumulative length of stay for inpatient admissions (days)
- Number of ER encounters
- Number of outpatient encounters
- Number of medications
- Occurrence of inpatient admission (yes/no)
- Occurrence of ER encounter (yes/no)
- Occurrence of outpatient encounter (yes/no)

Diabetes related HCRU from baseline to year 2:

- Number of diabetes related inpatient admissions
- Cumulative length of stay for diabetes related inpatient admissions (days)
- Number of diabetes related ER encounters

[redacted]

- Number of diabetes related outpatient encounters
- Number of diabetes related medications
- Occurrence of diabetes related inpatient admission (yes/no)
- Occurrence of diabetes related ER encounter (yes/no)
- Occurrence of diabetes related outpatient encounter (yes/no)

3.3.3 Exploratory Endpoints

Not applicable.

4 STUDY DESIGN

4.1 Overview

This is a 2-year, multi-center, randomized, open label, parallel group, active comparator PCT comparing semaglutide versus SOC when added to metformin monotherapy as treatment intensification among adult T2DM patients in the course of routine clinical practice. Patients will be randomized 1:1 to receive either semaglutide or SOC.

The decision that further antidiabetic treatment intensification with an additional oral or injectable antidiabetic medication is indicated is at the discretion of the study physician and will be made prior to and independent of enrollment in this study. The study physician will have determined the patient's suitability for treatment with semaglutide prior to inviting them to participate in the study. However, the determination to initiate semaglutide versus SOC will be made by randomization.

Patients will be followed for 2 years, regardless of changes in antidiabetic treatment over the course of the study. Data collection will continue for the full 2 year study period unless a patient withdraws informed consent. Patients who enroll in the study agree to the release of health information, and to answer questions about their health during the course of the study. Additionally, medical and pharmacy claims data will be extracted for the 2 year study period, as well as up to 12 months prior to randomization as available.

In keeping with the study objectives and pragmatic design to evaluate semaglutide versus SOC in real world, routine clinical practice, inclusion and exclusion criteria are minimally restrictive and there are few study-specific evaluations. Study physicians will follow and treat patients according to their routine clinical practice and judgement. All oral and injectable antidiabetic medications are allowed at the study physicians' discretion, with the exception of semaglutide in the SOC group. It is anticipated that patients will undergo medical evaluation at regular intervals over the course of the study duration as per standard of care, but the only dedicated study visits are at randomization, at year 1, and at year 2. The study will also capture clinical data collected at the sites during routine care visits, i.e., office visits and other patient contacts that occur as part

of routine clinical practice. Assessments will be conducted according to the study physician's routine clinical practice, with a few study-specific assessments as described in section 5. The data available may differ from site to site and patient to patient. To ensure flexibility, the dedicated year 1 and year 2 study visits have a window of ±6 weeks.

4.2 Practice and Patient Selection

The target population for this study consists of adult, commercially-insured, T2DM patients on metformin mono-therapy who are in need of treatment intensification with an additional antidiabetic oral or injectable medication. Physician practice and participant eligibility criteria were guided by feasibility data from the HealthCore Integrated Research Database (HIRD^{SM}) prior to protocol development.

Physician sites recruited for the study will be those who provide care for members of [redacted] health plans, one of the largest healthcare insurance providers in the US. [redacted] provides medical coverage for roughly 1 in 8 Americans, and although this is mostly concentrated in the employer-supported, commercially-insured market, the data in the HIRD are overall representative of the entire US population. [7] Study site recruitment will target both primary care practitioners and specialized endocrinologists to reflect diverse treatment settings and patient populations. Potential sites will be evaluated regarding feasibility of their participation in the study, including having a T2DM population of [redacted] members to meet enrollment goals, based on the initial data analysis from the HIRD. Potential sites will be tiered based on their estimated number of eligible study patients, and outreach will begin with all sites that meet a pre-determined minimum number of potentially eligible patients. Outreach and follow-up will be performed until the requisite number of physician sites is enrolled. Study-specific assessments have been kept to a minimum, thereby decreasing burden on study sites and increasing participation to a wide range of sites.

[redacted] health plans serve a large population of T2DM patients. In feasibility data from the HIRD, the number of patients with T2DM, at least one claim for metformin in the most recent 6 months, and without prior use of other antidiabetic drug classes (per study exclusion criterion #2), amounts to circa 300,000 potential eligible patients distributed across 61,803 unique providers.

4.2.1 Physician Practice Eligibility

Participation of approximately 285 physician sites in the US, including both general practitioners and endocrinologists that have a T2DM population, is anticipated. Physician sites will be limited to those that participate in the care of patients who are actively enrolled in an [redacted] health plan (hence forth referred to as [redacted] health plans).

[redacted]

4.2.2 Patient Recruitment and Eligibility

Eligible patients include adult T2DM patients whose physicians determine that they have inadequate glycemic control on metformin antidiabetic monotherapy. Inadequate glycemic control is defined by the need for T2DM treatment intensification with an additional antidiabetic oral or injectable medication, as determined by the study physician. Patients must also meet all of the inclusion criteria (section 4.2.3) and none of the exclusion criteria (section 4.2.4). Inclusion and exclusion criteria are minimally restrictive to ensure a broad population of adult T2DM patients to generate data in a population that reflects the heterogeneity of a real world population treated in general practice, and support the study objectives to evaluate semaglutide versus SOC in real world, routine clinical practice.

4.2.3 Patient Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for the study:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study.
2. Male or female, age ≥ 18 years at the time of signing informed consent.
3. Type 2 diabetes mellitus diagnosis.
4. Treatment with metformin as antidiabetic monotherapy.
5. Current member of an [redacted] affiliated commercial health plan.
6. Recorded HbAlc value within last 90 days prior to randomization.
7. Further intensification with an additional antidiabetic oral or injectable medication is indicated to achieve glycemic target at the discretion of the study physician according to approved labelling.

4.2.4 Patient Exclusion Criteria

Patients presenting with any of the following exclusion criteria will not be eligible for the study:

1. Previous randomization in this study.
2. Treatment with any medication for the indication of diabetes other than metformin in a period of 30 days before the day of eligibility assessment. Temporary/emergency use of any type of insulin is allowed, as is prior insulin treatment for gestational diabetes.
3. Contraindications to semaglutide according to the FDA approved label.
4. Female who is pregnant, breastfeeding or intends to become pregnant.
5. Participation in another clinical trial.

4.2.5 Patient Enrollment

Planned number of patients to be randomized: 2250

[redacted]

Expected number of patients to complete the study after 52 weeks: 1687

Expected number of patients to complete the study after 104 weeks: 1260

4.2.6 Patient Randomization

Study patients will be randomized to either semaglutide or SOC in a 1:1 ratio. The study design and patient randomization is depicted in Figure 1.

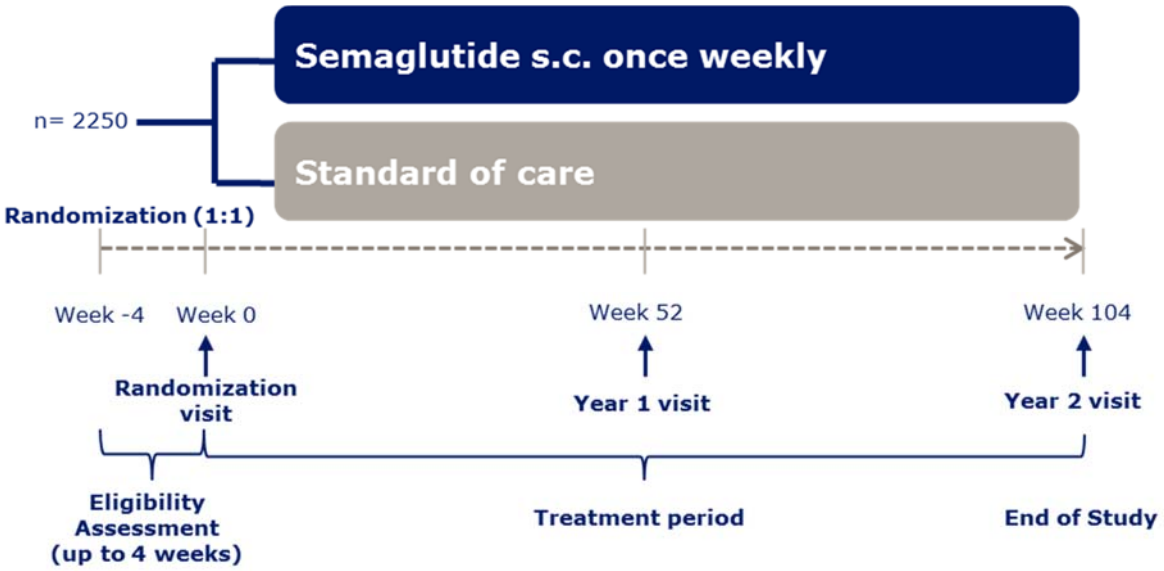

Figure 1 Study design diagram. Patients will be randomized in a 1:1 manner using centralized allocation to receive semaglutide or SOC as add-on to metformin.

5 STUDY PROCEDURES

The study visit schedule is summarized in Appendix 1.

5.1 Enrollment Procedures

The determination that a patient has inadequate glycemic control on metformin antidiabetic monotherapy, and the subsequent decision to intensify antidiabetic treatment with an additional oral or injectable antidiabetic medication, will be made by the study physician during the course of routine clinical practice. Following the decision to initiate treatment intensification, the study physician will determine the patient's suitability for the study. Suitability for the study will be assessed using the current inclusion and exclusion criteria, including the approved label for semaglutide. Only patients who are eligible for treatment intensification and have been found suitable for treatment with semaglutide, as determined by the study physician, are in scope for randomization. Prior to being randomized, patients must be willing to intensify with an antidiabetic medication, including GLP-1 receptor agonists. Study physicians will set and document an individualized HbA1c target for patients prior to randomization based on their

clinical judgement and knowledge of the patient. To preserve the real-world nature of the study, patients will be approached for potential enrollment into the study when they present to their physician as part of their standard care.

Informed consent will be obtained prior to any study related activities. The most recent HbA1c completed in the course of routine care up to 90 days prior to and including the date of randomization will be considered a baseline assessment and does not need to be repeated.

Study physicians or site personnel will collect patient characteristics and study data at each study visit as outlined in the Time and Events Schedule (Appendix 1), either directly from the patient or abstracted from the patient's medical records, and enter them into the electronic Case Report Form (eCRF).

5.2 Randomization Visit

Following informed consent and confirmation of inclusion/exclusion criteria, patients will be randomized to either semaglutide or SOC. Data collection at the randomization visit will include inclusion/exclusion criteria as well as the data outlined in the sections below. PRO and ClinRO questionnaires will also be administered (section 5.3).

5.2.1 Patient Characteristics

Baseline assessments at the randomization visit will include: demographic data, medical history, diabetes history including antidiabetic medications and diabetes complications, pre-specified concomitant medications related to cardiovascular risk, and clinical data (weight, height, HbA1c, SBP, DBP). Individualized HbA1c target will be set prior to randomization. The baseline HbA1c will be the patient's most recent HbA1c within 90 days of randomization.

5.2.2 Treatments

To preserve the real-world nature of the study, the patient experience will be as close to routine care as possible. The study physician will be one of the patient's own treating physicians, who may make treatment adjustments according to their clinical judgement. The study physician can make repeat prescriptions of the study drug as usual, which are collected by patients from the pharmacy of their choice. Patients will be randomized to either semaglutide or SOC. Treatment details will be recorded in the eCRF.

Semaglutide Group

Patients randomized to the semaglutide group will be prescribed commercially available semaglutide in a prefilled pen injector and will be instructed to initiate treatment with semaglutide according to the approved label. The study physician will determine the intended maintenance dose of semaglutide, as well as changes to the maintenance dose thereafter. Add-on, discontinuation or dose modification of antidiabetic medication, including semaglutide, during the study is allowed at the discretion of the study physician.

Semaglutide Study Drug: For patients randomized to the semaglutide group, study drug is

[redacted]

defined as semaglutide.

SOC Group

SOC is defined as commercially available oral or injectable antidiabetic medication (see current representative list below) other than semaglutide. Patients randomized to SOC will be prescribed and instructed to initiate commercially available antidiabetic medication according to the approved label and, if relevant for the specific antidiabetic medication, adjusted at the discretion of the study physician. Patients randomized to SOC may discontinue SOC, add-on to the SOC or switch to another antidiabetic medication during the study, with the exception of semaglutide which is not allowed in the SOC group for the duration of the study.

SOC Study Drug: For patients randomized to the SOC group, study drug is defined as the drug class of the first antidiabetic oral or injectable medication prescribed for treatment intensification following randomization. If a fixed dose combination (FDC) product is prescribed, one of the drugs will be chosen by the study physician to be the study drug. A patient randomized to the SOC treatment group will still be considered "on study drug" if they are taking a drug in the same class as their first study drug, even if it is not the same individual drug. This also applies to treatment intensification with a FDC product if one of the drugs is in the same class as the first study drug.

Study Drug: Start/Stop, Discontinuations

Study drug discontinuation is termination of the study drug. A patient can stop or start study drug throughout the study; therefore a patient's study drug discontinuation status can change throughout the duration of the study. At any time during the duration of the study, if a patient is not taking study drug as defined, they will be considered "off study drug." Conversely, at any time during the duration of the study, if a patient is taking study drug as defined, they will be considered "on study drug," regardless of prior study drug discontinuations.

If a participating patient becomes pregnant, the study physician will review the patient's antidiabetic treatment regimen and make any changes necessary according to standard care of patients with T2DM during pregnancy. Semaglutide will be discontinued and will not be restarted unless the patient is no longer pregnant or breast-feeding. All study drug copay assistance will end.

Copay assistance

The study products will be handled and dispensed by the patients' pharmacy(s) per their preference and health plan benefits. In order to minimize the impact of any differential in out-of-pocket costs between the treatment groups, an out-of-pocket maximum will be provided by Novo Nordisk as part of the study. In both treatment groups, the patient's copay will be up to the specified maximum for the study drug (as defined above) and ancillary needles (if required to administer the study drug). Copay assistance will only apply to the study drug as defined above (i.e., not to any subsequent add-on treatment or treatment changes outside the study drug

definition). Because patients can start and stop study drug throughout the study, copay assistance may also start and stop throughout the study. For the duration of the study, any time a patient is "on study drug" they will receive copay assistance, and any time a patient is "off study drug" they will not receive copay assistance. The only exceptions are if a patient initiates prescription coverage through Medicare or Medicaid, at which point all copay assistance will end.

Products

A current representative list of the products used in this study is below. All treatments will be used in accordance with local clinical practice and guidelines. Products with more than one active substance i.e., FDC products, can be used in this study.

Semaglutide: Semaglutide in a prefilled pen (Ozempic®)

Oral antidiabetic drugs: The oral antidiabetic drug classes included in this study are the commercially available options (listed in alphabetic order):

- Alpha-glucosidase inhibitors
- Dipeptidyl peptidase 4 (DPP-4) inhibitors
- Meglitinides
- Sodium-glucose co-transporter 2 (SGLT-2) inhibitors
- Sulfonylureas
- Thiazolidinediones
- Other
    - Bromocriptine
    - Colesevelam

Injectable antidiabetic drugs: The injectable antidiabetic drug classes included in this study are the commercially available options (listed in alphabetic order):

- GLP-1 RAs
- Basal Insulin
    - Long acting insulin
    - Intermediate acting insulin including premix
- Prandial Insulin
    - Short acting insulin
    - Rapid acting insulin
- Other
    - Pramlintide

[redacted]

Background medication: The following treatment is considered background medication: metformin. Patients may discontinue metformin at any time during the study. Patients may change the pre-study dose and frequency of metformin at any time during the study. Background medication will not be provided nor reimbursed by Novo Nordisk.

5.3 Patient Reported Outcomes, Clinician Reported Outcomes, and Diabetes Treatment Satisfaction

Diabetes treatment satisfaction, generic health-related quality of life (HRQoL), work productivity, and patient and clinician global assessments will be assessed by the following instruments at randomization, year 1, and year 2. Patients will self-administer these instruments on paper. Site study personnel will review for completeness and enter responses into the eCRF.

5.3.1 PRO and Treatment Satisfaction questionnaires

5.3.1.1 Diabetes Treatment Satisfaction Questionnaire (DTSQ) [8] [9] [10] [11]

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) evaluates patient satisfaction with treatment. The DTSQ status version (DTSQs) will be completed at the randomization visit and the DTSQ change version (DTSQc) will be completed at the year 1 and year 2 dedicated study visits.

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

The SF-12 v2 is a generic HRQoL questionnaire that assesses physical and mental functioning and overall HRQoL. The SF-12v2 standard 4-week recall period questionnaire will be completed at the randomization, year 1, and year 2 dedicated study visits.

5.3.1.3 Work Productivity and Activity Impairment: General Health (WPAI-GH) Questionnaire [13]

The WPAI-GH questionnaire assesses both absenteeism (i.e., work time missed) and presenteeism (i.e., impairment at work or reduced on-the-job effectiveness) as well as daily activity impairment (e.g., work around the house, shopping, exercising, childcare, studying) attributable to general health. The WPAI-GH will be administered at the randomization, year 1, and year 2 dedicated study visits.

5.3.1.4 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, i.e., normal, mild, moderate, or severe, whereas 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, i.e., very much better, much better, a little better, no change, a little worse, much worse, or very much worse. The PGI-S will be administered at the randomization visit and the PGI-C will be administered at the year 1 and year 2 dedicated study visits.

[redacted]

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

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 symptoms, i.e., normal, mild, moderate, or severe, whereas 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, i.e., very much better, much better, a little better, no change, a little worse, much worse, or very much worse. The study physician will complete the CGI-S at the randomization visit and the CGI-C at the year 1 and year 2 dedicated study visits.

5.4 Study Period

Patients will be followed from randomization to end of study (EOS) at 2 years, during which study physicians or trained site personnel will collect study data and record it in the eCRF at dedicated study visits (randomization, year 1, year 2) and routine care visits. Patients will be followed for the full 2 year study period regardless of treatment changes or discontinuation during the study period, other than withdrawal of consent. If a patient leaves the [redacted] health plan network during the 2 year study period, administrative claims data will be collected from randomization through the date they leave the health plan. In this scenario, site-based study data collection will continue without change.

On-study data collection at dedicated study visits and routine care visits (if available per local clinical practice) will include: clinical data (weight, HbA1c, SBP, DBP), treatment details (study drug, other antidiabetic medication, pre-specified concomitant medications related to cardiovascular risk, reasons for treatment discontinuation as applicable), hypoglycemia leading to inpatient admission or ER encounter, AEs leading to study drug discontinuation, pregnancy, and serious adverse events (SAEs). Additionally, PRO and ClinRO instruments will be completed at randomization, year 1, and year 2.

EOS visit is 2 years (±6 weeks) after randomization.

5.5 Administrative Claims Data – HIRD^{SM}

In addition to prospectively collected clinical data and PROs, this study will also utilize claims data from the HIRD for all study patients. Data collected will include integrated medical claims, pharmacy claims, and health plan eligibility files for the 2 years after the respective patient's study randomization. Extraction of this data will take place approximately 3 months after the last patient's last visit (LPLV) to allow for data lags in the claims. Administrative claims data will also be collected for up to 12 months prior to study randomization, if available. The prospectively collected eCRF study data and claims data will be merged into one dataset via a study-specific patient identifier (ID) for analysis.

5.6 Withdrawals

5.6.1 Physician Practices

Novo Nordisk and/or the Institutional Review Board (IRB) reserve the right to terminate the study any time. In this event, all data collection will end. After the collected data is received, study physicians will be compensated as contractually agreed.

The IRB reserves the right to terminate participation of individual study sites at any time. Individual study sites may also be terminated for cause by Novo Nordisk per contractual agreement. In such cases, all data collection at terminated study sites will end. After the collected data is received, the study physicians will be compensated as contractually agreed.

5.6.2 Patients

Participation in the study is voluntary, and all patients are free to terminate their participation at any time. A patient will only be withdrawn from the study if they withdraw consent. In the event of study withdrawal, the study physician will record the reason for study withdrawal and continue to follow-up with the patient for any unresolved SAEs or pregnancies, if patient agrees. Upon patient withdrawal from the study, all data collection will end, but all study data collected up to withdrawal will be included in the study database.

6 STATISTICAL METHODS

6.1 Introduction

Patients are randomized 1:1 to semaglutide or SOC. The data analyses for this study will be outlined in further detail in a Statistical Analysis Plan (SAP) developed prior to database lock at year 1.

For continuous endpoints and categorical endpoints derived from continuous sources, the baseline value is defined as the last assessment taken prior to or at the randomization visit *and* before first use of study drug.

If endpoint data is missing then any routine care data that are collected within ±10 weeks of the dedicated study visit will be used.

The significance level used in all statistical analyses will be 5% (two-sided).

6.1.1 Estimands

Two estimands, each targeting a unique research question, have been defined to adequately describe the effect of semaglutide as compared to SOC (excluding semaglutide).

The primary estimand for all objectives will be the “intention-to-treat” (ITT) estimand evaluating the effectiveness of randomized treatment intervention irrespective of adherence to this randomized intervention or changes to other antidiabetic medication during follow-up. The

purpose of this estimand is to quantify the expected effect size in the commercially-insured health plan population upon adoption of semaglutide as compared SOC (excluding semaglutide), and is as such relevant to inform and support appropriate market access and population based treatment guidance.

The secondary estimand for all objectives with the exception of the adherence and persistence to treatment objective, is the "if all patients had adhered" estimand. This estimand evaluates the effect of randomized treatment intervention for all randomized patients if all patients had adhered to randomized treatment, regardless of changes to other (i.e., non-study drug) antidiabetic medication. The purpose of this estimand lies in quantifying the expected effect size for an individual patient in the commercially-insured health plan population who is prescribed, initiates, and continues treatment with semaglutide as compared to SOC (excluding semaglutide). The relevance of this effect measure is to inform decision making for individual patients and prescribing physicians.

6.1.2 Confirmatory Endpoints and Hypotheses

The primary endpoint is HbA1c <7.0% (53 mmol/mol) at year 1 (yes/no). This is a binary endpoint. Confirmatory secondary endpoints include:

- Change in HbA1c (%-point) from baseline to year 1
- HbA1c <7.0% (53 mmol/mol) at year 2 (yes/no)
- Change in HbA1c (%-point) from baseline to year 2

The primary and confirmatory endpoints will all be tested for superiority under multiplicity control via a hierarchical testing scheme according to the order given in the above bullet list. Confirmatory testing will only be performed for the primary estimand with the secondary estimand being supportive. The testing procedure will be stopped the first time an analysis fails to confirm superiority of the endpoint in question using a two-sided significance level of 5%.

Superiority on HbA1c <7.0% will be evaluated with respect to the odds ratio (OR) (odds semaglutide / odds SOC):

$$H_0: OR \leq 1 \text{ against } H_a: OR > 1$$

Superiority on change in HbA1c (year 1 – baseline; year 2 – baseline) will be evaluated with respect to the mean treatment difference (TD) (semaglutide – SOC):

$$H_0: TD \geq 0 \text{ against } H_a: TD < 0$$

6.1.3 Study Populations

The following analysis set will be defined:

Full analysis set (FAS): Includes all randomized patients analyzed according to the treatment group to which they were assigned at randomization.

[redacted]

6.2 Sample Size Determination

6.2.1 Power and Sample Size for Primary Objective

Assumptions for the sample size were based on input from the HIRD claims/laboratory results database. In line with the primary ITT estimand, the assumptions for the proportion of patients with HbA1c < 7.0% at year 1 and year 2, and for the change from baseline in HbA1c, were based on the claims/laboratory results data within the [redacted] population for all patients initiating treatment intensification, regardless of whether patients adhered to this treatment. Specifically, for semaglutide, assumptions were based on data for liraglutide and dulaglutide. For SOC, assumptions were based on all intensifications in the claims database. The study sample size of 2,250 was calculated based on the following assumptions, informed from HIRD data: 10% difference in proportion patients with HbA1c < 7.0% at year 1 and year 2 (60% semaglutide versus 50% SOC), absolute difference in change from baseline HbA1c of 0.5%-point (SD=2.3%) between treatment groups, 90% power, and an overall alpha leve1 of 5%. Sample size calculations, including different sample size scenarios and a summary of the data from the HIRD, will be documented in the SAP.

The proportion of missing data for the confirmatory endpoints was estimated to be 25% after one year and 44% after two years. In the sample size calculation, it was assumed that only non-missing data at year 1 and year 2 would be used for the respective analyses. This is considered conservative, since the use of imputed data in the actual primary analysis (see 6.3) will increase the power. When accounting for missing data, randomizing 2250 patients will contribute 1687 patients for the year 1 analyses and 1260 patients for the year 2 analyses, achieving a total power of 90% for confirming all 4 confirmatory hypotheses. The corresponding marginal powers for presence of HbA1c < 7.0% at year 1, change in HbA1c to 1 year, presence of HbA1c < 7.0% at year 2, and change in HbA1c to 2 years are 99%, 99%, 95%, and 97% respectively.

6.3 Statistical Analysis for the Primary Estimand

The primary estimand will be estimated based on the FAS using data from all patients with observations at the dedicated study visit (year 1 for the primary endpoint), with the exception of patients who, in violation of the protocol, have initiated semaglutide in the SOC treatment group. The data collected following initiation of semaglutide from these patients will be censored and imputed together with missing data. The primary endpoint, HbA1c < 7.0%, will be analyzed with a logistic regression model with a logit link function, treatment as a categorical effect, and baseline HbA1c as covariate. From the model, the estimated OR (semaglutide versus SOC) will be presented. The underlying continuous endpoint of change in HbA1c will be analyzed using analysis of covariance (ANCOVA) that will include the same independent variables. From the model, the estimated mean difference in change from baseline to dedicated study visit (semaglutide versus SOC) will be presented. The estimated treatment effect from each of these analyses will be complemented with associated 95% confidence interval (CI) and two-sided p-value for testing the null-hypothesis of no difference.

Prior to analysis, missing data will be imputed by multiple imputation on the continuous HbA1c scale and subsequently dichotomized for the primary endpoint. 500 complete data sets will be generated to adequately account for the uncertainty due to missing data. Missing endpoint data will be imputed separately by treatment group and based on patients who remained in the study according to study drug treatment status, i.e., according to whether these patients are on or off study drug at the dedicated study visit. Data will be imputed based on the assumption that, within treatment groups, patients with missing endpoint data will behave like patients with the same study drug treatment status at endpoint as the missing patients' last registered treatment status prior to the missing endpoint. For example, for patients withdrawing from the study with an "off study drug" treatment status, data will be imputed based on the assumption that the withdrawn patients will behave like patients who remain in the study but are not receiving study drug at the dedicated study visit. Technically, the imputation model will be an ANCOVA for the endpoint data. The ANCOVA will include baseline HbA1c, diabetes duration, age, and sex as independent variables. After this model has been used to predict missing values, each of the now 500 complete data sets will be analyzed as described above. Finally, the multiple analysis results will be combined using Rubin's rule. [14] For the OR the results will be combined on the logarithm scale.

Superiority for the primary endpoint, HbA1c <7.0% at year 1, will be considered established if the OR 95% CI is greater than 1, or similarly if the two-sided p-value is significant on a 5% level and the treatment OR is in favor of semaglutide.

If the hierarchical testing scheme allows, superiority for change from baseline to dedicated study visit in HbA1c will be considered established if the 95% CI for the estimated treatment difference is smaller than 0, or similarly if the two-sided p-value is significant on a 5% level and the treatment difference is in favor of semaglutide.

6.4 Statistical Analysis for the Secondary Estimand

The secondary estimand will be estimated based on the FAS. The analysis is similar to the primary analysis for the primary endpoint, but varies with regards to the data used and the imputation of missing data. Specifically, data will only be used from the subset of patients who are receiving study drug at the dedicated study visit (year 1 for the primary endpoint), in order to estimate the treatment effect if all patients had continued treatment. Patients who no longer are receiving study drug will be censored and imputed together with missing data. The same will apply to patients who, in violation of the protocol, have initiated semaglutide in the SOC group. Collectively, missing and censored data will be imputed separately by treatment group based on all patients who are on study drug at the dedicated study visit. Data will be imputed based on the assumption that withdrawn or censored patients behave like patients that remain in the study and continue on study drug.

The technical aspects of missing data imputation based on multiple imputation, the statistical analysis of the multiple complete data sets, and combination of the multiple results will be the same as that described for the primary estimand.

6.5 Supplementary Analyses

The HbA1c analyses described for the two estimands above will be complemented with two complete case analyses based on the subset of patients without missing endpoint data, i.e., patients that do not have their endpoint imputed in the two analyses used for the primary and secondary estimand.

Complete case analysis

This analysis will be based only on patients with available measurements at the dedicated study visit including measurements irrespective of whether patients discontinued study drug or not. The analysis will use the same analysis model as described under the primary estimand.

Complete case on-study drug analysis

The analysis will be based only on patients with available measurements at the dedicated study visit including only measurements for patients still on study drug. The analysis will use the same analysis model as described under the primary estimand.

6.6 PRO Analysis

PRO and physician assessments will be measured with the instruments described in Section 5.3. Analysis of these measures will address the secondary objective of this study to compare semaglutide versus SOC in the study's patient population as is relates to PRO, i.e., treatment satisfaction, generic health outcomes, work productivity, and patient and physician global assessment measures, over one and two year observation periods. PRO analysis will descriptively summarize these measures at baseline, year 1, and year 2, as well as compare semaglutide versus SOC for change from baseline to year 1 and year 2. The continuous change from baseline endpoints will be analyzed using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis section. Details will be fully described in the SAP.

6.7 Safety Analysis

SAEs and AEs will be collected as described in Section 7. No formal safety analyses are planned for this study. SAEs, AEs leading to study drug discontinuation, and pregnancies will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and descriptively summarized by System Organ Class and Preferred Term (PT).

6.8 Other Analyses

The following analyses are planned to further support the primary objective to compare semaglutide versus SOC in glycemic control. They will also address the secondary objectives of

this study to compare semaglutide versus SOC in the study's patient population over one and two year observation periods as is relates to body weight loss, hypoglycemia, HCRU, and adherence and persistence to treatment. The binary and continuous endpoints will be analyzed using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections. Further details of these analyses and details for analyses of other endpoint types will be fully described in the SAP.

6.8.1 Supportive Analyses of Glycemic Control

The proportion of patients achieving the secondary endpoints related to glycemic control at year 1 as defined in section 3.3.2 (individualized HbA1c target, HbA1c <7.0% (53mmol/mol) or at least 1% point improvement in HbA1c from baseline, HbA1c target attainment per HEDIS criteria) will be compared between semaglutide and SOC treatment groups using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections.

Additionally, derived outcome variables for supportive measures of glycemic control (Appendix 2) will be utilized to support these analyses.

6.8.2 Weight Loss

Change in patient weight from baseline to year one will be calculated in pounds and percentage as defined in section 3.3.2. Mean change in weight will be compared between semaglutide and SOC treatment groups using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections.

Additionally, derived outcome variables for supportive measures of body weight loss (Appendix 2) will be utilized to support these analyses.

6.8.3 Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP)

Change in patient SBP and DBP from baseline to year 1 and baseline to year 2 will be calculated as defined in section 3.3.2 and Appendix 2. Mean change in SBP and DBP will be compared between semaglutide and SOC treatment groups using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections.

6.8.4 Hypoglycemia

The number of hypoglycemic episodes leading to an inpatient admission or ER encounter will be reported by patients and compared by semaglutide and SOC treatment groups utilizing a negative binomial model.

Additionally, derived outcome variables for supportive measures of hypoglycemia (Appendix 2) will be utilized to support these analyses.

6.8.5 Healthcare Resource Utilization (HCRU)

HCRU analyses will compare all-cause and diabetes-related HCRU (inpatient admissions, ER

encounters, outpatient encounters, and pharmacy utilization) as defined in section 3.3.2 from the HIRD by semaglutide and SOC treatment group from baseline to year 2.

The details of claims data definitions and calculations will be fully described in the SAP.

6.8.6 Adherence and Persistence to Treatment

Adherence and persistence to the study drug will be calculated and compared between semaglutide and SOC treatment groups.

Medication adherence refers to a patient's conformance to the provider's recommendation with respect to timing, dosage, and frequency of medication taken during the prescribed length of time. In claims, adherence is typically measured using either medication possession ratio (MPR) or proportion of days covered (PDC).

Medication persistence refers to whether a patient stays on therapy or the time from initiation to discontinuation of therapy. In claims, persistence is typically defined as the duration of time from initiation of the therapy to discontinuation or switching, whichever comes first.

Adherence and persistence will be further defined in the SAP.

6.8.7 Antidiabetic Treatment Patterns

Antidiabetic treatment patterns will be assessed and compared between semaglutide and SOC treatment groups. This analysis will summarize the number and classification type of antidiabetic medications taken during the study period.

6.8.8 Exploratory Predictive Analysis

An exploratory predictive analysis will be performed within and between the semaglutide and SOC treatment groups to identify predictors of treatment adherence and persistence and glycemic control. The objectives of the exploratory predictive analyses are to identify within and between treatment groups: 1) patients less likely to discontinue treatment and 2) patients more likely to reach clinical target.

6.8.9 Evaluation of the Study Population

To evaluate the generalizability of the study results, an analysis of the study population will be performed. The primary objective of this analysis is to evaluate the external validity of the study and to understand how the study population fits into the larger T2DM populations within study sites and [redacted] as a whole. Two claims-based T2DM patient populations will be described and compared to the study population: (1) commercially-insured [redacted] T2DM patients treated with metformin who undergo an antidiabetic treatment intensification, and (2) within the study sites, commercially-insured [redacted] T2DM patients treated with metformin who are not enrolled in the study, but who undergo an antidiabetic treatment intensification. The analysis will compare the demographics, HCRU, and HbA1c between the study population and the two comparator populations during the 12 month period prior to randomization (for study population) or prior to a claims-based proxy for antidiabetic treatment intensification index date (for comparators).

[redacted]

Additionally, treatment patterns of non-enrolled T2DM patients within the practices from which the study patients are recruited will be evaluated to identify any relevant patterns of care suggesting channeling of certain types to patients away from the study. These analyses will help to contextualize study results within the T2DM population broadly.

The details of this analysis will be fully described in the SAP.

7 Adverse Event Collection

The principal study physician is responsible for monitoring the safety of participating patients. All SAEs reported by the patients during the study observational period are required to be documented on the appropriate SAE reporting form. For the purposes of this study, AEs that do not meet the definition of SAE will only be collected if they lead to study drug discontinuation.

7.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product or medical device, which does not necessarily have to have a causal relationship to the product of device. Study physicians will follow AEs that occur in any patient during this study in a manner consistent with routine clinical practice. For the purposes of this study, AEs that do not meet the definition of an SAE (section 7.2) will only be collected in the eCRF if they lead to study drug discontinuation.

7.2 Serious Adverse Events

All AEs meeting the definition of SAE will be collected in the eCRF. SAEs will be reported from the time a patient is randomized until EOS at year 2, or until the patient withdraws from the study. An SAE is defined as any AE which results in at least one of the following outcomes:

- Initial inpatient admission or prolongation of existing inpatient admission
- A life-threatening event, i.e., an event in which the patient was at immediate risk of dying at the time of the event; not an event that hypothetically could have caused death had it been more severe
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect in offspring
- Death
- Is deemed serious for any other reason, i.e., if it is an important medical event based on appropriate medical judgement which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other listed outcomes.

7.2.1 Collection Period of Serious Adverse Events

SAEs will be reported from the time a patient is randomized until EOS at year 2, or until the patient withdraws from the study. The principal study physician is responsible for alerting Novo Nordisk or its designee to any SAE within 24 hours of becoming aware of it via electronic data capture (EDC) entry. The patient should be followed until the outcome of the event is closed out. Follow-up information should be reported within 24 hours of it becoming available. Requests for follow-up information should be resolved within 14 calendar days.

At each visit (both routine care visits and dedicated study visits), patients will be asked about AEs including hypoglycemic events, e.g. “Have you experienced any problems since the last contact?”

If an investigator becomes aware of SAEs after EOS at year 2 that are possibly related to the study product, these should be reported as spontaneous events.

7.3 Pregnancy

Any abnormal pregnancy outcome (e.g., spontaneous miscarriage, fetal death, congenital anomaly/birth defect, etc.) is considered an SAE. For the purposes of this study, any pregnancies in participating female patients will be reported, along with pregnancy outcome and any AEs or SAEs observed in the fetus or newborn until 1 month of age.

7.3.1 Reporting Period of Pregnancy

Pregnancies will be reported from the time a patient is randomized until EOS at year 2 or until the patient withdraws from the study. The principal study physician is responsible for alerting Novo Nordisk or its designee to any drug exposure during pregnancy within 14 days of the first knowledge of the pregnancy via the pregnancy reporting form. The study physician will follow the patient for the duration of the pregnancy.

7.4 Technical Complaints

Technical complaints may be reported as per usual practice. However, any SAEs resulting from a technical complaint must be reported via EDC.

8 DATA COLLECTION

8.1 Data Sources

Data sources include primary data collected prospectively by study sites at study visits (demographic and clinical data, patient-completed PRO data, and physician reported global assessments) as well as secondary data collection utilizing administrative claims data from the HIRD. In order to maintain patient confidentiality, each patient will be assigned a unique patient study ID number upon signing informed consent to use in place of patient name or any other identifying information (e.g., medical record number). Clinical study data, PROs/ClinROs and

claims-derived variables will be integrated into one analysis dataset via this confidential patient ID.

8.2 Electronic Case Report Forms (eCRFs)

All clinical study data will be collected at the physician office and entered into eCRF by trained site study personnel through a fully validated, 21 CFR 11 and HIPAA compliant EDC system. Patients will complete PRO questionnaires on paper and the site study personnel will enter the completed forms into the EDC system. Site users will be provided eCRF Completion Guidelines (eCCGs) to assist with study data collection and entry. Study personnel will access the EDC system through a secure study website.

Some clinical assessments utilized in this study may be completed in the course of routine clinical practice by site personnel not affiliated with study (e.g., blood pressure), however any activities completed solely for the study (e.g., data entry, PRO administration) must be done by trained site study personnel. For example, a nurse not affiliated with the study may measure blood pressure as part of routine care. The data from this assessment may be used for this study, but must be extracted from the patient's medical record and entered into the eCRF by trained site study personnel.

The principal study physician has the ultimate responsibility for the collection and reporting of all clinical and patient data through the eCRFs, as well as ensuring that they are accurate and complete to the extent possible.

8.3 Year One Database Lock

The primary analysis for this study is a year 1 analysis. Once data collection for year 1 has completed, a database lock and year 1 analysis will be performed. The year 1 analysis will not be integrated with HCRU and will be limited to year 1 endpoints derived from eCRF data, including PRO data. To maintain study integrity for the remaining study period, data from year 1 will be used for limited and confidential communications while complying with public disclosure requirements. All other analyses will be conducted following a second database lock once data collection for the entire study is complete.

9 STUDY MANAGEMENT

9.1 Regulatory and Ethical Consideration

All study activities will be conducted in accordance with Good Clinical Practice (GCP) guidelines. Study personnel at physician sites will be provided training on the study protocol, the Informed Consent Form (ICF), data collection, and data entry to ensure both the protection of potential study patients as well as the scientific integrity of the study. Site monitoring will be conducted by [redacted] staff.

[redacted]

9.1.1 Institutional Review Board (IRB)

The principal study physician will have prospective IRB approval of the study protocol, ICF, and any patient information or recruiting materials prior to commencement of any study activities at their site. In the case of a protocol amendment, the study physician must sign the revised protocol and submit the amendment to the IRB for review and approval prior to implementation of any changes specified in the protocol amendment. All changes in research activity and all unanticipated problems involving risk to human patients or others must be reported to the IRB as required.

The principal study physician will obtain continued review of the IRB study approval at intervals not to exceed one year or otherwise specified by the IRB.

9.1.2 Informed Consent

An ICF describing the purpose, procedures, and potential risks and benefits of the study will be developed and approved by the IRB prior to study initiation. The principal study physician must ensure that each study patient is informed of the study and authorizes release of health information prior to study-related activities. The study physician, or study personnel designated by the study physician, will obtain written informed consent from each patient prior to initiation of any study-related procedures. Each patient will be given a copy of the signed ICF. The principal study physician will retain the original signed ICF for each patient.

The IRB must prospectively approve the ICF and any changes to the ICF during the course of the study before use. If a protocol amendment increases the potential risk to the patient, the ICF must be revised and submitted to the IRB for review and approval prior to implementation. The revised ICF must then be used to obtain consent from new patients entering the study as well as from currently enrolled patients if they are affected by the amendment, per IRB guidance.

9.2 Record Retention and Access

This study may be subject to audits or inspections by regulatory authorities or Novo Nordisk (or its designee). To enable such inspections and/or audits, the principal study physician must agree to maintain and allow access to required patient and study records. The principal study physician agrees to keep the identity of all participating patients (sufficient information to link records, e.g., hospital records), all original signed ICFs, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls, reports). The principal study physician should retain records according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

10 PUBLICATION OF STUDY RESULTS

All information related to this study is considered confidential information belonging to Novo Nordisk and [redacted] as consistent with contractual agreement. A final study report will be

[redacted]

generated following completion of data collection and analysis. Results and findings will be submitted to conferences and for publication in peer-reviewed scientific journals with authorship following the International Committee of Medical Journal Editors (ICMJE) guidelines.

Information regarding the study will be disclosed at clinicaltrials.gov and novonordisk-trials.com. Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of studies regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this study will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

11 INDEMNIFICATION

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the trial or by persons for whom the said site or investigator are responsible.

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Appendix 1: Time and Events Schedule

Study NN9535-4416	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]					
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				
Individualized HbA1c target[d]	X				
Type of glucose-lowering medication including semaglutide	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[e]	X	X	X	X
SAEs, pregnancies, and AEs leading to study drug discontinuation		X	X	X	X
Healthcare resource utilization[f]		X	X	X	X
Hypoglycemia leading to inpatient admission or ER encounter		X	X	X	X

[redacted]

Study NN9535-4416	Dedicated Study visit, Randomization	Routine Care visits, Year 1	Dedicated Study visit, Year 1	Routine Care visits, Year 2	Dedicated Study visit, Year 2
PROs and Physician Completed Assessments					
DTSQs	X				
DTSQc			X		X
SF-12v2	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 mediations will be collected at the randomization visit.
** The year 1 and year 2 routine care visit windows are determined by the date of the patient's dedicated year 1 study visit. The year 1 routine care visit window will end immediately prior to the dedicated year 1 study visit. The year 2 routine 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 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. Additionally, PRO and ClinRO 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 the HIRD and will not be entered into the eCRF.

[a] Routine 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 care visits will be collected as available/according to local clinical practice in eCRF.

[redacted]

[c] Informed consent must be obtained before any study related activities.
[d] Individualized HbA1c target must be set and documented prior to randomization.
[e] The HbA1c value is based on historical data collected from the study physician and is the value closest to the date of randomization, within the last 90 days.
[f] Data from the HIRD. Data will be extracted from the HIRD at the end of the study, but will include data from patient randomization through EOS or withdrawal.

Appendix 2: Additional Derived Outcome Variables for Supportive Analyses

Supportive Measures of Glycemic Control

- Individualized HbA1c target attained at year 2 (yes/no)
- HbA1c <7.0% (53 mmol/mol) or at least 1% point improvement in HbA1c compared to baseline at year 2 (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 1 (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 2 (yes/no)
- HbA1c <7.0% (53 mmol/mol) and no further antidiabetic medication intensification after randomization at year 1 (yes/no)
- HbA1c <7.0% (53 mmol/mol) and no further antidiabetic medication intensification after randomization at year 2 (yes/no)
- HbA1c target attainment per HEDIS criteria (<8.0% if age ≥65 years or with defined comorbidities, otherwise <7.0%) at year 2 (yes/no)
- HbA1c <7.0% (53 mmol/mol) at year 1 in patients with HbA1c >9.0% at baseline (yes/no)
- HbA1c <7.0% (53 mmol/mol) at year 2 in patients with HbA1c >9.0% at baseline (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 1 in patients with HbA1c >9.0% at baseline (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 2 in patients with HbA1c >9.0% at baseline (yes/no)

Body Weight Loss

- Change in body weight (%) from baseline to year 2
- Change in body weight (lb) from baseline to year 2

Blood Pressure

- Change in SBP (mm Hg) from baseline to year 2
- Change in DPB (mm Hg) from baseline to year 2

Hypoglycemia

- Reported hypoglycemia leading to inpatient admission or ER encounter during year 1 (yes/no)

- Reported hypoglycemia leading to inpatient admission or ER encounter during year 2 (yes/no)

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 (yes/no)

- 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 (yes/no)

- 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 (yes/no)

- 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 2 (yes/no)

- 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 (yes/no)

- 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 (yes/no)

Adherence to Treatment

- Study drug medication adherence for the two years of the study, as measured by the medication possession ratio (MPR)

Appendix 3: Patient Reported Outcome Additional Information

DTSQc

The DTSQc provides a measure of how satisfied patients are with their current diabetes treatment compared with previous treatment. It consists of 8 questions, which are to be answered on a Likert scale from -3 to +3 (-3 = much less satisfied now to +3 = much more satisfied now), with 0 (midpoint), representing no change. Six questions are summed 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.

SF-12 v2

The SF-12v2 is a 12-item generic health-related quality of life measure that assesses physical and mental functioning. The items will be scored using the scoring software that will be provided with the license. The following two summary scores are used as endpoints: Physical Component Summary (PCS) Score and Mental Component Summary (MCS) Score. The scores are norm-scored such that the scores range from 0-100 with a mean of 50 and standard deviation of 10. A higher score is associated with better quality of life and a lower score, poorer quality of life.

WPAI-GH

The WPAI-GH yields four types of scores: Absenteeism (work time missed), Presenteeism (impairment at work / reduced on-the-job effectiveness), Work productivity loss (overall work impairment / absenteeism plus presenteeism), and Activity Impairment. WPAI outcomes are expressed as percentages, with higher numbers indicating greater impairment and less productivity, i.e., 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).

16.1.1.2 Protocol Amendments

[redacted]

Long term comparative effectiveness of once weekly semaglutide versus standard of care in a real world adult US population with type 2 diabetes - a randomized pragmatic clinical trial

Trial ID NN9535-4416

Novo Nordisk

March 27, 2019

Version 2.0

Trial Phase: 4
Investigational Substance: Semaglutide

[redacted]

[redacted]

STUDY APPROVALS
Protocol No: NN9535-4416
27-MAR-2019

Sponsor Approval:

Name: [redacted]
Title: [redacted]
Novo Nordisk

Signature [redacted]

Date: [redacted]

Name: [redacted]
Title: [redacted] Statistician
Novo Nordisk

Signature: [redacted]

Date: [redacted]

Principal Study Physician Agreement:

I have read the protocol "Long term comparative effectiveness of once weekly semaglutide versus standard of care in a real world adult US population with type 2 diabetes - a randomized pragmatic clinical trial" and agree to ensure that all staff members involved in the conduct of this study are informed of their obligations and that they meet the commitments of the protocol in accordance with Good Clinical Practice (GCP) requirements. I have familiarized myself with the prescribing information corresponding with the study drugs associated with this study.

I acknowledge that I am responsible for overall study conduct. I understand GCP requirements and agree to personally conduct or supervise the described pragmatic study in accordance with GCP.

Signature: _____

Print Name: _____

Date: _____

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[redacted]

[redacted]

[redacted]

SYNOPSIS

Title: Long term comparative effectiveness of once weekly semaglutide versus standard of care in a real world US adult population with type 2 diabetes – a randomized pragmatic clinical trial

Sponsor: Novo Nordisk

Study Treatment: Semaglutide in a prefilled pen (Ozempic®)

Active Ingredient: Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA)

Comparator Treatment: Standard of Care (SOC) (excluding semaglutide)

Trial ID: NN9535-4416

Study Physician Sites: Participation of approximately 285 physician sites, including both primary care practitioners and endocrinologists, that have a population of patients with the target indication, type 2 diabetes mellitus (T2DM), actively enrolled in an [redacted] affiliated commercial health plan.

Country: United States (US)

Patients: Eligible patients include adult T2DM patients on up to 2 oral antidiabetic medications whose physician deems that they have inadequate glycemic control and need treatment intensification with an additional antidiabetic oral or injectable medication.

Planned enrollment in this study is 2250. Patients will be randomized 1:1 to receive either semaglutide or SOC.

Study Objectives: The objectives of this study are as follows:

1.) The primary objective is to demonstrate superior long term effects of treatment with semaglutide compared to SOC both added to up to 2 oral antidiabetic medications on glycemic control when used as intensification in routine clinical practice in adult patients with T2DM.

2.) The secondary objectives are to compare the long term effect of semaglutide versus SOC both added to up to 2 oral antidiabetic medications and used as intensification in routine clinical practice in adult patients with T2DM with regards to:
   a. Weight loss
   b. Patient reported outcomes (PROs) and clinician reported outcomes (ClinROs)
   c. Hypoglycemia
   d. Healthcare Resource Utilization (HCRU)
   e. Adherence and persistence to treatment

Study Design: This is a 2-year, multi-center, randomized, open label, parallel group, active comparator pragmatic clinical trial (PCT) comparing semaglutide versus SOC when added to up to 2 oral antidiabetic medications as treatment intensification among adult T2DM patients in the course of routine clinical practice. Patients will be randomized 1:1 to receive either semaglutide or SOC. The decision that further antidiabetic treatment intensification with oral or injectable antidiabetic medication is indicated is at the discretion of the study physician and will be made prior to and independent of enrollment in this study. The study physician will have determined the patient's suitability for treatment with semaglutide prior to signing informed consent, but the determination to initiate semaglutide versus SOC will be made by randomization.

In keeping with the study objectives and pragmatic design to evaluate semaglutide versus SOC in real world, routine clinical practice, inclusion and exclusion criteria are minimally restrictive and there are few study-specific evaluations. Study physicians will follow and treat patients according to their

routine clinical practice and judgement. All oral and injectable antidiabetic medications are allowed at the study physicians' discretion, with the exception of semaglutide in the SOC group. Patients will be followed for 2 years, regardless of changes in antidiabetic treatment over the course of the study.

It is anticipated that patients will undergo medical evaluation at regular intervals over the course of the study duration as per standard of care, but the only dedicated study visits are at randomization, at year 1, and at year 2. The study will also capture clinical data collected at the sites during routine care visits, i.e., office visits and other patient contacts that occur as part of routine clinical practice. Assessments will be conducted according to the study physician's routine clinical practice, with a few study-specific assessments as outlined in Study Procedures. Additionally, medical and pharmacy claims data will be captured utilizing the HealthCore Integrated Research Database (HIRD^{SM}) for the 2 year study period. HIRD data for the 12 months prior to randomization will also be collected if available.

Participant Selection:

Inclusion Criteria:

Patients must meet all of the following inclusion criteria to be eligible for the study:

1.) Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study.
2.) Male or female, age ≥ 18 years at the time of signing informed consent.
3.) Type 2 diabetes mellitus diagnosis.
4.) Treatment with either 1 or 2 oral antidiabetic medications.
5.) Current member of an [redacted] affiliated commercial health plan with pharmacy benefits.
6.) Recorded glycosylated hemoglobin A1c (HbAlc) value within the last 90 days prior to randomization.
7.) Further intensification with an additional antidiabetic oral or injectable medication is indicated to achieve glycemic target at the discretion of the study physician according to approved labelling.

Exclusion Criteria:

Patients presenting with any of the following exclusion criteria will not be eligible for the study:

1.) Previous randomization in this study.
2.) Treatment with more than 2 oral antidiabetic medications or any injectable medication in a period of 30 days before the day of eligibility assessment. Temporary/emergency use of any type of insulin is allowed, as is prior insulin treatment for gestational diabetes.
3.) Contraindications to semaglutide according to the FDA approved label.
4.) Female who is pregnant, breastfeeding or intends to become pregnant.
5.) Participation in another clinical trial.

Study Procedures:

- Study physicians will identify eligible patients for participation.
- Study physicians will obtain written informed consent from patients and if eligible, patients will be randomized to either semaglutide or SOC.
- Study data will be collected on electronic Case Report Forms (eCRFs) via an electronic data capture (EDC) system.
- Study physicians or site personnel will collect demographic, clinical (i.e., height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP)), medical and T2DM specific

[redacted]

history, antidiabetic medications, and pre-specified concomitant medications related to cardiovascular risk data prior to or at randomization. Individualized HbA1c target will be set prior to randomization.

- Baseline HbA1c will be collected from physician sites during eligibility assessment and will be the value closest to the date of randomization, within 90 days. All post-randomization HbA1c values will be recorded as available per routine clinical practice during the 2 year study period. Post-randomization HbA1c values are required for the year 1 and year 2 dedicated study visits.
- PROs and ClinROs will be completed at randomization, year 1, and year 2.
- Study physicians will collect patient data (HbA1c, study and antidiabetic medication changes, pre-specified concomitant medications related to cardiovascular risk, weight, SBP, DBP, hypoglycemic events leading to inpatient admission or emergency room (ER) encounter, adverse events (AEs) leading to study drug discontinuation, serious adverse events (SAEs), and pregnancies at the dedicated year 1 and year 2 study visits, as well as at any routine care visits during the 2 year study period.
- Administrative medical claims, pharmacy claims and health plan eligibility data will be captured from the HIRD for the duration of the 2 year study period. HIRD data for the 12 months prior to study randomization will also be collected if available. This data will be used for HCRU measures, as well as adherence and persistence to treatment.

Study Duration: Planned patient time on study will be 2 years. Administrative claims data will also be captured during this time period. Patients will be followed for the full 2 year study period regardless of changes in or discontinuation of antidiabetic treatment, other than withdrawal of consent.

Questionnaires: Diabetes treatment satisfaction, generic health-related quality of life (HRQoL), work productivity, and patient and clinician global assessments will be measured at the randomization, year 1, and year 2 dedicated study visits.

Statistical Analysis: Two estimands, each targeting a unique research question, have been defined to adequately describe the effect of semaglutide as compared to SOC (excluding semaglutide).

The primary estimand for all objectives will be the "intention-to-treat" estimand evaluating the effectiveness of randomized treatment intervention, irrespective of adherence to this randomized intervention or changes to other antidiabetic medication.

The secondary estimand for all objectives, with the exception of the adherence and persistence to treatment objective, is the "if all patients had adhered" estimand. This estimand evaluates the effect of randomized treatment intervention for all randomized patients if all patients had adhered to randomized treatment, regardless of changes to other antidiabetic medication.

Baseline is defined as ≤ 90 days prior to randomization visit (week 0) for HbA1c. For secondary endpoint assessments, baseline is defined as ≤ 4 weeks prior to the randomization visit (week 0).

Primary completion date (PCD) is the date the last patient completes the year 1 dedicated study visit.

The primary endpoint is binary, with success represented by an HbA1c <7.0% (53 mmol/mol) at year 1 (yes/no). Confirmatory secondary endpoints include:

- Change in HbA1c (%-point) from baseline to year 1
- HbA1c <7.0% (53 mmol/mol) at year 2 (yes/no)
- Change in HbA1c (%-point) from baseline to year 2

This study is designed to have 90% power to jointly confirm superiority of the primary endpoint and the above three confirmatory secondary endpoints based on an analysis of the primary estimand for each of the endpoints.

The confirmatory endpoints will all be tested under multiplicity control via a hierarchical testing scheme according to the order given in the above bullet list.

The estimand informs choices about data foundation and statistical analysis including possible imputation of missing data, hereby ensuring that randomization is preserved as a sound basis for statistical inference; i.e., estimation of effect size, associated uncertainty, and statistical testing.

The full analysis set (FAS) comprising all randomized patients will be the analysis population for evaluation of both the primary and secondary estimands. For both estimands, the primary endpoint, HbA1c <7.0%, will be analyzed using a logistic regression model with a logit link function and will include treatment and baseline HbA1c as independent variables. Continuous endpoints will be analyzed using analysis of covariance (ANCOVA) and will include the same independent variables. Prior to analysis, missing data will be imputed by multiple imputation on the continuous HbA1c scale and subsequently dichotomized for the primary endpoint.

Supplementary Analyses: Two complete case analyses will complement the analyses for the primary and secondary estimands. The supplementary complete case analyses will be based on the subset of patients without missing endpoint data, i.e., patients that do not have their endpoint imputed in the two analyses used for the primary estimand and the secondary estimand, respectively.

Secondary Analyses: Secondary analyses will compare semaglutide versus SOC treatment groups in terms of change in body weight, SBP, DBP, and PRO and ClinRO measures, based on the similar analysis methods as for the primary and secondary estimands. Similarly, binary endpoints and other secondary endpoints will be compared statistically between treatment groups, including HCRU and adherence/persistence to treatment measures, hypoglycemic events leading to inpatient admission or ER encounter, as well as composite measures of HbA1c, weight loss, and hypoglycemia.

Safety: The principal study physician is responsible for monitoring the safety of participating patients. For the purposes of this study, AEs that do not meet the definition of an SAE will only be collected/recorded in the EDC if they lead to study drug discontinuation. Study physicians are responsible for reporting all SAEs and following the patient until the outcome of the SAE is closed out. All SAEs will be reported from randomization until end of study (EOS) at year 2 or patient study withdrawal. Study physicians are also responsible for recording all pregnancies in female patients from randomization until EOS at year 2 or patient study withdrawal. The patient will be followed for the duration of the pregnancy until one month post-delivery to report the pregnancy outcome and any AEs or SAEs observed in the fetus or newborn until 1 month of age. Safety will be summarized descriptively.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	American Diabetes Association
AE	Adverse Event
ANCOVA	Analysis of Covariance
eCCGs	Electronic Case Report Form Completion Guidelines
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinician Global Impression of Disease Severity
CI	Confidence Interval
ClinRO	Clinician Reported Outcome
eCRF	Electronic Case Report Form
DBP	Diastolic Blood Pressure
DPP-4	Dipeptidyl peptidase 4
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTSQc	Diabetes Treatment Satisfaction Questionnaire, change version
DTSQs	Diabetes Treatment Satisfaction Questionnaire, status version
EASD	European Association for the Study of Diabetes
EDC	Electronic Data Capture
EOS	End of Study
ER	Emergency Room
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonists
HbA1c	Glycosylated Hemoglobin A1c

HCRU	Healthcare Resource Utilization
HEDIS	Healthcare Effectiveness Data and Information Set
HIRD[SM]	HealthCore Integrated Research Database
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ID	Identifier
IRB	Institutional Review Board
ITT	Intent to Treat
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MCS-12	Mental Summary Component (of the Short Form 12-Item version 2)
MPR	Medication Possession Ratio
OR	Odds Ratio
PCD	Primary Completion Date
PCS-12	Physical Summary Component (of the Short Form 12-Item version 2)
PCT	Pragmatic Clinical Trial
PDC	Proportion Days Covered
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Disease Severity
PRO	Patient Reported Outcome
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SF-12v2	Short Form 12-Item version 2
SGLT-2	Sodium-Glucose Co-transporter 2
[redacted]	

SM	Service Mark
SOC	Standard of Care
SUSTAIN	Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes
T2DM	Type 2 Diabetes Mellitus
TD	Treatment Difference
US	United States
WPAI-GH	Work Productivity and Activity Impairment, General Health

LIST OF DEFINITIONS

Term	Definition
Administrative Claims Data	Medical, pharmacy, and health plan eligibility data created in the processing of medical and pharmacy claims. The claims data utilized in this study are obtained from the HealthCore Integrated Research Database (HIRD).
Baseline	Baseline refers to assessments conducted and patient data collected at or prior to randomization. Baseline HbAlc may be ≤ 90 days prior to randomization. Baseline for secondary endpoint assessments may be ≤ 4 weeks prior to randomization.
Baseline Endpoint	For continuous endpoints and endpoints derived from continuous sources, the baseline value is defined as the last assessment taken prior to or at the randomization visit *and* before first use of study drug.
Comparator Treatment	Standard of Care (SOC) (excluding semaglutide); Commercially available oral or injectable antidiabetic medication, excluding semaglutide, prescribed at the discretion of the study physician for antidiabetic treatment intensification following randomization.
Complete the Study	Complete the study at 52 weeks: Patient has year 1 HbA1c data Complete the study at 104 weeks: Patient has year 2 HbA1c data
Dedicated Study Visit	One of three required study visits: randomization, year 1, and year 2.
Enrollment	Randomization
Estimand	The estimate targeted to address the research question posed by the study objective, i.e., "what is to be estimated." [1] The estimand translates the study objective into a precise definition of the effect of treatment.
Healthcare Resource Utilization (HCRU)	Broad term encompassing use of healthcare services, including inpatient admissions, ER encounters, outpatient encounters including office visits, and pharmacy prescription fills.
Index Date	The date corresponding to an event of interest. In this study, index date is the date corresponding to a claims-based proxy for antidiabetic treatment intensification for 2 comparator populations, thus mimicking randomization date in the study population.
Principal Study Physician	Physician at study site who is responsible for the overall conduct and oversight of the study at their site, including: supervision of study personnel, monitoring the safety of all participating patients, ensuring the accurate and complete collection and reporting of study data, continued review of the IRB study approval, and maintenance of study

[redacted]

	records. This term is analogous to "Investigator" in Good Clinical Practice (GCP) requirements.
Randomization	The point at which a patient is assigned by chance to either semaglutide or standard of care (SOC).
Routine Care Visit	An office visit or other patient contact during the study period that occurs outside of the dedicated study visits (randomization, year 1, and year 2) according to routine clinical practice.
Study Physician	Physician at study site who participates in the conduct of the study.
Study/Trial	For the purposes of this protocol, study and trial are considered synonyms. Study is used throughout the body of the text as it reflects the post-regulatory approval setting and real world design. Trial is used in the title and in referring to the PCT acronym to maintain consistency with the industry standard Pragmatic Clinical Trial or PCT.
Study Drug	Study drug is the first antidiabetic oral or injectable medication prescribed for treatment intensification following randomization. A patient can start and stop study drug throughout the study. At any time during the duration of the study, if a patient is taking study drug as defined, they will be considered "on study drug" regardless of prior study drug discontinuations. • For the semaglutide treatment group, study drug is defined as semaglutide. • For the SOC treatment group, study drug is defined as the drug class of the first antidiabetic oral or injectable medication prescribed for treatment intensification following randomization. If a fixed dose combination (FDC) product is prescribed, one of the drugs will be chosen by the study physician to be the study drug. A patient randomized to the SOC treatment group will still be considered "on study drug" if they are taking a drug in the same drug class as their first study drug, even if it is not the same individual drug. This also applies to treatment intensification with a FDC product if one of the drugs is in the same drug class as the first study drug.
Study Drug Discontinuations	Study drug discontinuation is termination of the study drug. A patient can start and stop study drug throughout the study; therefore a patient's study drug discontinuation status can change throughout the duration of the study. At any time during the duration of the study, if a patient is not taking study drug as defined, they will be considered "off study drug."

1 INTRODUCTION

1.1 Background and Rationale

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) position statement recommends a patient-centric approach to the selection of pharmacological treatment for type 2 diabetes mellitus (T2DM), including considerations on effectiveness, hypoglycemia risk, impact on body weight, side effects, costs, and patient preferences. [2] Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are recommended for the management of hyperglycemia in T2DM, primarily in combination with other antidiabetic medications. [2] [3]

Semaglutide, a human GLP-1 analogue for once-weekly subcutaneous administration, has been shown to improve glycemic control in adults with T2DM as monotherapy when the use of metformin is considered inappropriate, or as add-on to other glucose lowering therapies including insulin. In the *Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes* (SUSTAIN) clinical development program, semaglutide demonstrated clinically relevant and superior glycemic control, as well as weight loss versus placebo and active comparators, both when used as mono- and combination therapy in inadequately controlled patients with T2DM. In addition, a significant reduction in cardiovascular risk was demonstrated for semaglutide versus placebo in patients with T2DM at high risk of cardiovascular events. The overall safety profile of semaglutide was consistent with the well-established GLP-1 RA safety profile. [4]

Pragmatic clinical trials (PCTs) are designed and conducted to reflect patient outcomes and to investigate how a product is used and performs in routine clinical practice. This type of study compares two or more medical interventions that are directly relevant to clinical care and strives to assess those interventions' effectiveness in real world practice. They use broad eligibility criteria and recruit patients from a variety of practice settings to ensure the inclusion of the type of patients whose care will be influenced by the study´s results. Such studies are increasingly important to generate evidence regarding real world treatment outcomes to inform and support appropriate market access. [5]

The current local US study serves the purpose of evaluating the long term comparative effectiveness of semaglutide with existing commercially available antidiabetic medications in a real world population and in a variety of practice settings, thereby maximizing external validity while balancing the internal validity of a randomized controlled trial. This will generate data to complement the findings from the SUSTAIN clinical development program. Taken together, these findings may provide important evidence for decision making by clinicians, payers, and policy makers in routine clinical practice.

This local US study will enroll adult patients with T2DM who have inadequate glycemic control on up to 2 oral antidiabetic medications, as defined by the need for treatment intensification with an additional antidiabetic oral or injectable medication per the study physician´s discretion. The current study targets patients at this particular treatment point because they represent the

population inadequately controlled on the current ADA recommended first lines of treatment of T2DM. The addition of a GLP-1 RA as second-line treatment is in line with the ADA guidance from 2017. [6] In keeping with the ADA and EASD position statement recommending a patient-centric approach to treatment selection for T2DM patients, in addition to comparative effectiveness, this study will also evaluate hypoglycemia risk, body weight, healthcare resource utilization (HCRU), patient reported outcomes (PROs), and clinician reported outcomes (ClinROs). Adverse events (AEs) leading to study drug discontinuation will also be collected. [2]

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to demonstrate superior long term effects of treatment with semaglutide compared to standard of care (SOC) both added to up to 2 oral antidiabetic medications on glycemic control when used as intensification in routine clinical practice in adult patients with T2DM.

2.2 Secondary Objectives

The secondary objectives are to compare the long term effect of semaglutide versus SOC both added to up to 2 oral antidiabetic medications and used as intensification in routine clinical practice in adult patients with T2DM with regards to:

- Weight loss
- Patient reported outcomes (PROs) and clinician reported outcomes (ClinROs)
- Hypoglycemia
- Healthcare Resource Utilization (HCRU)
- Adherence and persistence to treatment

3 STUDY ENDPOINTS

3.1 Baseline

Baseline is defined as ≤ 90 days prior to randomization visit (week 0) for glycosylated hemoglobin A1c (HbA1c). For secondary endpoint assessments, baseline is defined as ≤ 4 weeks prior to the randomization visit (week 0).

3.2 Primary Endpoint

Primary completion date (PCD) is the date the last patient completes the year 1 dedicated study visit.

The primary endpoint of this study is:

[redacted]

- HbA1c <7.0% (53 mmol/mol) at year 1 (yes/no)

3.3 Secondary Endpoints

3.3.1 Confirmatory Secondary Endpoints

Confirmatory secondary endpoints of this study include:

- Change in HbA1c (%-point) from baseline to year 1
- HbA1c <7.0% (53 mmol/mol) at year 2 (yes/no)
- Change in HbA1c (%-point) from baseline to year 2

3.3.2 Supportive Secondary Endpoints

Supportive secondary endpoints of this study include:

- Individualized HbA1c target attained at year 1 (yes/no)
- HbA1c <7.0% (53mmol/mol) or at least 1% point improvement in HbA1c compared to baseline at year 1 (yes/no)
- HbA1c target attainment per Healthcare Effectiveness Data and Information Set (HEDIS) criteria (<8.0% if age ≥65 years or with defined comorbidities, otherwise <7.0%) at year 1 (yes/no)
- Change in body weight (lb) from baseline to year 1
- Change in body weight (%) from baseline to year 1
- Change in systolic blood pressure (SBP; mm Hg) from baseline to year 1
- Change in diastolic blood pressure (DBP; mm Hg) from baseline to year 1
- Time to first study drug discontinuation during 2 years (day)
- Time to first treatment intensification (add-on) or change (switch) after randomization during 2 years (day)
- Study drug medication adherence for the first year of the study, as measured by medication possession ratio (MPR) (%)
- Number of hypoglycemic episodes leading to an inpatient admission or emergency room (ER) encounter from baseline to year 2
- Diabetes Treatment Satisfaction Questionnaire, change version (DTSQc), Total treatment satisfaction score measured at year 1
- DTSQc, Total treatment satisfaction score measured at year 2
- Change from baseline in Short Form 12-Item Version 2 Survey (SF-12 v2), Physical summary component (PCS-12) score at year 1

- Change from baseline in SF-12 v2, PCS-12 score at year 2
- Change from baseline in SF-12 v2, Mental summary component (MCS-12) score at year 1
- Change from baseline in SF-12 v2, MCS-12 score at year 2
- Change from baseline in Work Productivity and Activity Impairment, General Health questionnaire (WPAI-GH) Absenteeism (work time missed) score at year 1
- Change from baseline in WPAI-GH Absenteeism (work time missed) score at year 2
- Change from baseline in WPAI-GH Presenteeism (impairment at work / reduced on-the-job effectiveness) score at year 1
- Change from baseline in WPAI-GH Presenteeism (impairment at 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
- Change from baseline in WPAI-GH Work productivity loss (overall work impairment / absenteeism plus presenteeism) score at year 2
- Change from baseline in WPAI-GH Activity Impairment score at year 1
- Change from baseline in WPAI-GH Activity Impairment score at year 2

All cause healthcare resource utilization (HCRU) from baseline to year 2:

- Number of inpatient admissions
- Cumulative length of stay for inpatient admissions (days)
- Number of ER encounters
- Number of outpatient encounters
- Number of medications
- Occurrence of inpatient admission (yes/no)
- Occurrence of ER encounter (yes/no)
- Occurrence of outpatient encounter (yes/no)

Diabetes related HCRU from baseline to year 2:

- Number of diabetes related inpatient admissions
- Cumulative length of stay for diabetes related inpatient admissions (days)
- Number of diabetes related ER encounters

[redacted]

- Number of diabetes related outpatient encounters
- Number of diabetes related medications
- Occurrence of diabetes related inpatient admission (yes/no)
- Occurrence of diabetes related ER encounter (yes/no)
- Occurrence of diabetes related outpatient encounter (yes/no)

3.3.3 Exploratory Endpoints

Not applicable.

4 STUDY DESIGN

4.1 Overview

This is a 2-year, multi-center, randomized, open label, parallel group, active comparator PCT comparing semaglutide versus SOC when added to up to 2 oral antidiabetic medications as treatment intensification among adult T2DM patients in the course of routine clinical practice. Patients will be randomized 1:1 to receive either semaglutide or SOC.

The decision that further antidiabetic treatment intensification with an additional oral or injectable antidiabetic medication is indicated is at the discretion of the study physician and will be made prior to and independent of enrollment in this study. The study physician will have determined the patient's suitability for treatment with semaglutide prior to inviting them to participate in the study. However, the determination to initiate semaglutide versus SOC will be made by randomization.

Patients will be followed for 2 years, regardless of changes in antidiabetic treatment over the course of the study. Data collection will continue for the full 2 year study period unless a patient withdraws informed consent. Patients who enroll in the study agree to the release of health information, and to answer questions about their health during the course of the study. Additionally, medical and pharmacy claims data will be extracted for the 2 year study period, as well as up to 12 months prior to randomization as available.

In keeping with the study objectives and pragmatic design to evaluate semaglutide versus SOC in real world, routine clinical practice, inclusion and exclusion criteria are minimally restrictive and there are few study-specific evaluations. Study physicians will follow and treat patients according to their routine clinical practice and judgement. All oral and injectable antidiabetic medications are allowed at the study physicians' discretion, with the exception of semaglutide in the SOC group. It is anticipated that patients will undergo medical evaluation at regular intervals over the course of the study duration as per standard of care, but the only dedicated study visits are at randomization, at year 1, and at year 2. The study will also capture clinical data collected at the sites during routine care visits, i.e., office visits and other patient contacts that occur as part

of routine clinical practice. Assessments will be conducted according to the study physician's routine clinical practice, with a few study-specific assessments as described in section 5. The data available may differ from site to site and patient to patient. To ensure flexibility, the dedicated year 1 and year 2 study visits have a window of ±6 weeks.

4.2 Practice and Patient Selection

The target population for this study consists of adult, commercially-insured, T2DM patients on up to 2 oral antidiabetic medications who are in need of treatment intensification with an additional antidiabetic oral or injectable medication. Physician practice and participant eligibility criteria were guided by feasibility data from the HealthCore Integrated Research Database (HIRD[SM]) prior to protocol development.

Physician sites recruited for the study will be those who provide care for members of [redacted] health plans, one of the largest healthcare insurance providers in the US. [redacted] provides medical coverage for roughly 1 in 8 Americans, and although this is mostly concentrated in the employer-supported, commercially-insured market, the data in the HIRD are overall representative of the entire US population. [7] Study site recruitment will target both primary care practitioners and specialized endocrinologists to reflect diverse treatment settings and patient populations. Potential sites will be evaluated regarding feasibility of their participation in the study, including having a T2DM population of [redacted] members to meet enrollment goals, based on the initial data analysis from the HIRD. Potential sites will be tiered based on their estimated number of eligible study patients, and outreach will begin with all sites that meet a pre-determined minimum number of potentially eligible patients. Outreach and follow-up will be performed until the requisite number of physician sites is enrolled. Study-specific assessments have been kept to a minimum, thereby decreasing burden on study sites and increasing participation to a wide range of sites.

4.2.1 Physician Practice Eligibility

Participation of approximately 285 physician sites in the US, including both general practitioners and endocrinologists that have a T2DM population, is anticipated. Physician sites will be limited to those that participate in the care of patients who are actively enrolled in an [redacted] health plan (hence forth referred to as [redacted] health plans).

4.2.2 Patient Recruitment and Eligibility

Eligible patients include adult T2DM patients whose physicians determine that they have inadequate glycemic control on 1 or 2 oral antidiabetic medications. Inadequate glycemic control is defined by the need for T2DM treatment intensification with an additional antidiabetic oral or injectable medication, as determined by the study physician. Patients must also meet all of the inclusion criteria (section 4.2.3) and none of the exclusion criteria (section 4.2.4). Inclusion and exclusion criteria are minimally restrictive to ensure a broad population of adult T2DM patients

[redacted]

to generate data in a population that reflects the heterogeneity of a real world population treated in general practice, and support the study objectives to evaluate semaglutide versus SOC in real world, routine clinical practice.

4.2.3 Patient Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for the study:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study.
2. Male or female, age ≥ 18 years at the time of signing informed consent.
3. Type 2 diabetes mellitus diagnosis.
4. Treatment with either 1 or 2 oral antidiabetic medications.
5. Current member of an [redacted] affiliated commercial health plan with pharmacy benefits.
6. Recorded HbAlc value within last 90 days prior to randomization.
7. Further intensification with an additional antidiabetic oral or injectable medication is indicated to achieve glycemic target at the discretion of the study physician according to approved labelling.

4.2.4 Patient Exclusion Criteria

Patients presenting with any of the following exclusion criteria will not be eligible for the study:

1. Previous randomization in this study.
2. Treatment with more than 2 oral antidiabetic medications or any injectable antidiabetic medication in a period of 30 days before the day of eligibility assessment. Temporary/emergency use of any type of insulin is allowed, as is prior insulin treatment for gestational diabetes.
3. Contraindications to semaglutide according to the FDA approved label.
4. Female who is pregnant, breastfeeding or intends to become pregnant.
5. Participation in another clinical trial.

4.2.5 Patient Enrollment

Planned number of patients to be randomized: 2250

Expected number of patients to complete the study after 52 weeks: 1687

Expected number of patients to complete the study after 104 weeks: 1260

4.2.6 Patient Randomization

Study patients will be randomized to either semaglutide or SOC in a 1:1 ratio. The study design and patient randomization is depicted in Figure 1.

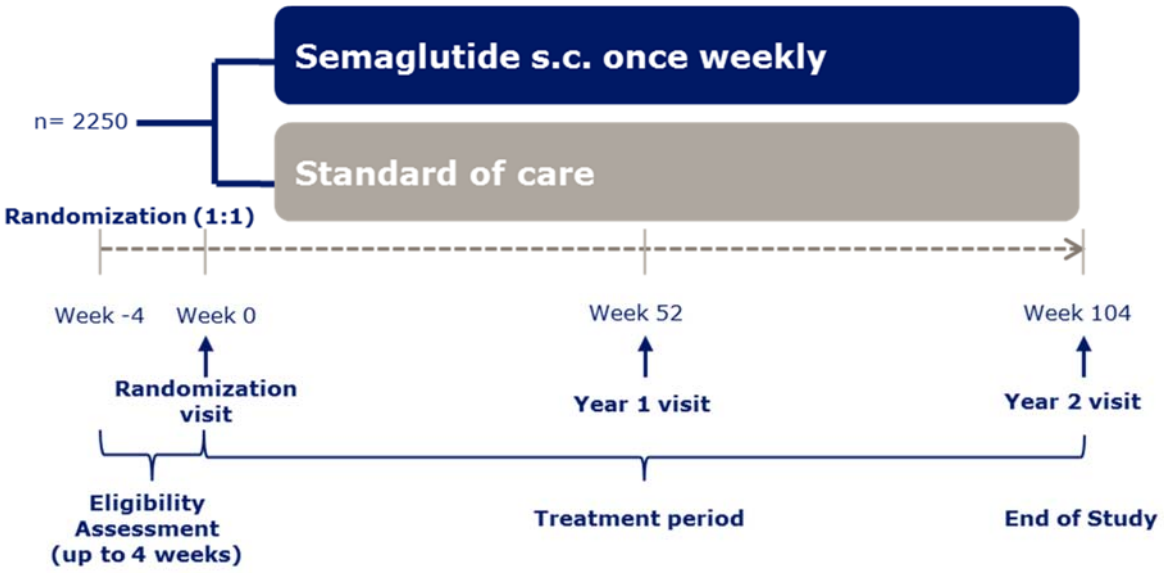

Figure 1 Study design diagram. Patients will be randomized in a 1:1 manner using centralized allocation to receive semaglutide or SOC as add-on to up to 2 oral antidiabetic medications.

5 STUDY PROCEDURES

The study visit schedule is summarized in Appendix 1.

5.1 Enrollment Procedures

The determination that a patient has inadequate glycemic control on up to 2 oral antidiabetic medications, and the subsequent decision to intensify antidiabetic treatment with an additional oral or injectable antidiabetic medication, will be made by the study physician during the course of routine clinical practice. Following the decision to initiate treatment intensification, the study physician will determine the patient's suitability for the study. Suitability for the study will be assessed using the current inclusion and exclusion criteria, including the approved label for semaglutide. Only patients who are eligible for treatment intensification and have been found suitable for treatment with semaglutide, as determined by the study physician, are in scope for randomization. Prior to being randomized, patients must be willing to intensify with an antidiabetic medication, including GLP-1 receptor agonists. Study physicians will set and document an individualized HbA1c target for patients prior to randomization based on their clinical judgement and knowledge of the patient. To preserve the real-world nature of the study, patients will be approached for potential enrollment into the study when they present to their physician as part of their standard care.

Informed consent will be obtained prior to any study related activities. The most recent HbA1c completed in the course of routine care up to 90 days prior to and including the date of randomization will be considered a baseline assessment and does not need to be repeated.

Study physicians or site personnel will collect patient characteristics and study data at each study visit as outlined in the Time and Events Schedule (Appendix 1), either directly from the patient or abstracted from the patient's medical records, and enter them into the electronic Case Report Form (eCRF).

5.2 Randomization Visit

Following informed consent and confirmation of inclusion/exclusion criteria, patients will be randomized to either semaglutide or SOC. Data collection at the randomization visit will include inclusion/exclusion criteria as well as the data outlined in the sections below. PRO and ClinRO questionnaires will also be administered (section 5.3).

5.2.1 Patient Characteristics

Baseline assessments at the randomization visit will include: demographic data, medical history, diabetes history including antidiabetic medications and diabetes complications, pre-specified concomitant medications related to cardiovascular risk, and clinical data (weight, height, HbA1c, SBP, DBP). Individualized HbA1c target will be set prior to randomization. The baseline HbA1c will be the patient's most recent HbA1c within 90 days of randomization.

5.2.2 Treatments

To preserve the real-world nature of the study, the patient experience will be as close to routine care as possible. The study physician will be one of the patient's own treating physicians, who may make treatment adjustments according to their clinical judgement. The study physician can make repeat prescriptions of the study drug as usual, which are collected by patients from the pharmacy of their choice. Patients will be randomized to either semaglutide or SOC. Treatment details will be recorded in the eCRF.

Semaglutide Group

Patients randomized to the semaglutide group will be prescribed commercially available semaglutide in a prefilled pen injector and will be instructed to initiate treatment with semaglutide according to the approved label. The study physician will determine the intended maintenance dose of semaglutide, as well as changes to the maintenance dose thereafter. Add-on, discontinuation or dose modification of antidiabetic medication, including semaglutide, during the study is allowed at the discretion of the study physician.

> *Semaglutide Study Drug*: For patients randomized to the semaglutide group, study drug is defined as semaglutide.

SOC Group

SOC is defined as commercially available oral or injectable antidiabetic medication (see current representative list below) other than semaglutide. Patients randomized to SOC will be prescribed and instructed to initiate commercially available antidiabetic medication according to the approved label and, if relevant for the specific antidiabetic medication, adjusted at the discretion

of the study physician. Patients randomized to SOC may discontinue SOC, add-on to the SOC or switch to another antidiabetic medication during the study, with the exception of semaglutide which is not allowed in the SOC group for the duration of the study.

> *SOC Study Drug*: For patients randomized to the SOC group, study drug is defined as the drug class of the first antidiabetic oral or injectable medication prescribed for treatment intensification following randomization. If a fixed dose combination (FDC) product is prescribed, one of the drugs will be chosen by the study physician to be the study drug. A patient randomized to the SOC treatment group will still be considered "on study drug" if they are taking a drug in the same class as their first study drug, even if it is not the same individual drug. This also applies to treatment intensification with a FDC product if one of the drugs is in the same class as the first study drug.

Study Drug: Start/Stop, Discontinuations

Study drug discontinuation is termination of the study drug. A patient can stop or start study drug throughout the study; therefore a patient's study drug discontinuation status can change throughout the duration of the study. At any time during the duration of the study, if a patient is not taking study drug as defined, they will be considered "off study drug." Conversely, at any time during the duration of the study, if a patient is taking study drug as defined, they will be considered "on study drug," regardless of prior study drug discontinuations.

If a participating patient becomes pregnant, the study physician will review the patient's antidiabetic treatment regimen and make any changes necessary according to standard care of patients with T2DM during pregnancy. Semaglutide will be discontinued and will not be restarted unless the patient is no longer pregnant or breast-feeding. All study drug copay assistance will end.

Copay assistance

The study products will be handled and dispensed by the patients' pharmacy(s) per their preference and health plan benefits. In order to minimize the impact of any differential in out-of-pocket costs between the treatment groups, an out-of-pocket maximum will be provided by Novo Nordisk as part of the study. In both treatment groups, the patient's copay will be up to the specified maximum for the study drug (as defined above) and ancillary needles (if required to administer the study drug). Copay assistance will only apply to the study drug as defined above (i.e., not to any subsequent add-on treatment or treatment changes outside the study drug definition). Because patients can start and stop study drug throughout the study, copay assistance may also start and stop throughout the study. For the duration of the study, any time a patient is "on study drug" they will receive copay assistance, and any time a patient is "off study drug" they will not receive copay assistance. The only exceptions are if a patient initiates prescription coverage through Medicare or Medicaid, at which point all copay assistance will end.

Products

A current representative list of the products used in this study is below. All treatments will be used in accordance with local clinical practice and guidelines. Products with more than one active substance i.e., FDC products, can be used in this study.

Semaglutide: Semaglutide in a prefilled pen (Ozempic®)

Oral antidiabetic drugs: The oral antidiabetic drug classes included in this study are the commercially available options (listed in alphabetic order):

- Alpha-glucosidase inhibitors
- Dipeptidyl peptidase 4 (DPP-4) inhibitors
- Meglitinides
- Metformin
- Sodium-glucose co-transporter 2 (SGLT-2) inhibitors
- Sulfonylureas
- Thiazolidinediones
- Other
    - Bromocriptine
    - Colesevelam

Injectable antidiabetic drugs: The injectable antidiabetic drug classes included in this study are the commercially available options (listed in alphabetic order):

- GLP-1 RAs
- Basal Insulin
    - Long acting insulin
    - Intermediate acting insulin including premix
- Prandial Insulin
    - Short acting insulin
    - Rapid acting insulin
- Other
    - Pramlintide

Background medication: The (up to 2) oral antidiabetic medication(s) taken prior to randomization and treatment intensification is considered background medication. Patients may discontinue background medication at any time during the study. Patients may change the pre-

study dose and frequency of background medication at any time during the study. Background medication will not be provided nor reimbursed by Novo Nordisk.

5.3 Patient Reported Outcomes, Clinician Reported Outcomes, and Diabetes Treatment Satisfaction

Diabetes treatment satisfaction, generic health-related quality of life (HRQoL), work productivity, and patient and clinician global assessments will be assessed by the following instruments at randomization, year 1, and year 2. Patients will self-administer these instruments on paper. Site study personnel will review for completeness and enter responses into the eCRF.

5.3.1 PRO and Treatment Satisfaction questionnaires

5.3.1.1 Diabetes Treatment Satisfaction Questionnaire (DTSQ) [8] [9] [10] [11]

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) evaluates patient satisfaction with treatment. The DTSQ status version (DTSQs) will be completed at the randomization visit and the DTSQ change version (DTSQc) will be completed at the year 1 and year 2 dedicated study visits.

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

The SF-12 v2 is a generic HRQoL questionnaire that assesses physical and mental functioning and overall HRQoL. The SF-12v2 standard 4-week recall period questionnaire will be completed at the randomization, year 1, and year 2 dedicated study visits.

5.3.1.3 Work Productivity and Activity Impairment: General Health (WPAI-GH) Questionnaire [13]

The WPAI-GH questionnaire assesses both absenteeism (i.e., work time missed) and presenteeism (i.e., impairment at work or reduced on-the-job effectiveness) as well as daily activity impairment (e.g., work around the house, shopping, exercising, childcare, studying) attributable to general health. The WPAI-GH will be administered at the randomization, year 1, and year 2 dedicated study visits.

5.3.1.4 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, i.e., normal, mild, moderate, or severe, whereas 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, i.e., very much better, much better, a little better, no change, a little worse, much worse, or very much worse. The PGI-S will be administered at the randomization visit and the PGI-C will be administered at the year 1 and year 2 dedicated study visits.

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

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 symptoms, i.e., normal, mild, moderate, or severe, whereas 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, i.e., very much better, much better, a little better, no change, a little worse, much worse, or very much worse. The study physician will complete the CGI-S at the randomization visit and the CGI-C at the year 1 and year 2 dedicated study visits.

5.4 Study Period

Patients will be followed from randomization to end of study (EOS) at 2 years, during which study physicians or trained site personnel will collect study data and record it in the eCRF at dedicated study visits (randomization, year 1, year 2) and routine care visits. Patients will be followed for the full 2 year study period regardless of treatment changes or discontinuation during the study period, other than withdrawal of consent. If a patient leaves the [redacted] health plan network during the 2 year study period, administrative claims data will be collected from randomization through the date they leave the health plan. In this scenario, site-based study data collection will continue without change.

On-study data collection at dedicated study visits and routine care visits (if available per local clinical practice) will include: clinical data (weight, HbA1c, SBP, DBP), treatment details (study drug, other antidiabetic medication, pre-specified concomitant medications related to cardiovascular risk, reasons for treatment discontinuation as applicable), hypoglycemia leading to inpatient admission or ER encounter, AEs leading to study drug discontinuation, pregnancy, and serious adverse events (SAEs). Additionally, PRO and ClinRO instruments will be completed at randomization, year 1, and year 2.

EOS visit is 2 years (±6 weeks) after randomization.

5.5 Administrative Claims Data – HIRD^{SM}

In addition to prospectively collected clinical data and PROs, this study will also utilize claims data from the HIRD for all study patients. Data collected will include integrated medical claims, pharmacy claims, and health plan eligibility files for the 2 years after the respective patient's study randomization. Extraction of this data will take place approximately 3 months after the last patient's last visit (LPLV) to allow for data lags in the claims. Administrative claims data will also be collected for up to 12 months prior to study randomization, if available. The prospectively collected eCRF study data and claims data will be merged into one dataset via a study-specific patient identifier (ID) for analysis.

5.6 Withdrawals

5.6.1 Physician Practices

Novo Nordisk and/or the Institutional Review Board (IRB) reserve the right to terminate the study any time. In this event, all data collection will end. After the collected data is received, study physicians will be compensated as contractually agreed.

The IRB reserves the right to terminate participation of individual study sites at any time. Individual study sites may also be terminated for cause by Novo Nordisk per contractual agreement. In such cases, all data collection at terminated study sites will end. After the collected data is received, the study physicians will be compensated as contractually agreed.

5.6.2 Patients

Participation in the study is voluntary, and all patients are free to terminate their participation at any time. A patient will only be withdrawn from the study if they withdraw consent. In the event of study withdrawal, the study physician will record the reason for study withdrawal and continue to follow-up with the patient for any unresolved SAEs or pregnancies, if patient agrees. Upon patient withdrawal from the study, all data collection will end, but all study data collected up to withdrawal will be included in the study database.

6 STATISTICAL METHODS

6.1 Introduction

Patients are randomized 1:1 to semaglutide or SOC. The data analyses for this study will be outlined in further detail in a Statistical Analysis Plan (SAP) developed prior to database lock at year 1.

For continuous endpoints and categorical endpoints derived from continuous sources, the baseline value is defined as the last assessment taken prior to or at the randomization visit *and* before first use of study drug.

If endpoint data is missing then any routine care data that are collected within ±10 weeks of the dedicated study visit will be used.

The significance level used in all statistical analyses will be 5% (two-sided).

6.1.1 Estimands

Two estimands, each targeting a unique research question, have been defined to adequately describe the effect of semaglutide as compared to SOC (excluding semaglutide).

The primary estimand for all objectives will be the “intention-to-treat” (ITT) estimand evaluating the effectiveness of randomized treatment intervention irrespective of adherence to this randomized intervention or changes to other antidiabetic medication during follow-up. The

purpose of this estimand is to quantify the expected effect size in the commercially-insured health plan population upon adoption of semaglutide as compared SOC (excluding semaglutide), and is as such relevant to inform and support appropriate market access and population based treatment guidance.

The secondary estimand for all objectives with the exception of the adherence and persistence to treatment objective, is the "if all patients had adhered" estimand. This estimand evaluates the effect of randomized treatment intervention for all randomized patients if all patients had adhered to randomized treatment, regardless of changes to other (i.e., non-study drug) antidiabetic medication. The purpose of this estimand lies in quantifying the expected effect size for an individual patient in the commercially-insured health plan population who is prescribed, initiates, and continues treatment with semaglutide as compared to SOC (excluding semaglutide). The relevance of this effect measure is to inform decision making for individual patients and prescribing physicians.

6.1.2 Confirmatory Endpoints and Hypotheses

The primary endpoint is HbA1c <7.0% (53 mmol/mol) at year 1 (yes/no). This is a binary endpoint. Confirmatory secondary endpoints include:

- Change in HbA1c (%-point) from baseline to year 1
- HbA1c <7.0% (53 mmol/mol) at year 2 (yes/no)
- Change in HbA1c (%-point) from baseline to year 2

The primary and confirmatory endpoints will all be tested for superiority under multiplicity control via a hierarchical testing scheme according to the order given in the above bullet list. Confirmatory testing will only be performed for the primary estimand with the secondary estimand being supportive. The testing procedure will be stopped the first time an analysis fails to confirm superiority of the endpoint in question using a two-sided significance level of 5%.

Superiority on HbA1c <7.0% will be evaluated with respect to the odds ratio (OR) (odds semaglutide / odds SOC):

$$H_0: OR \leq 1 \text{ against } H_a: OR > 1$$

Superiority on change in HbA1c (year 1 – baseline; year 2 – baseline) will be evaluated with respect to the mean treatment difference (TD) (semaglutide – SOC):

$$H_0: TD \geq 0 \text{ against } H_a: TD < 0$$

6.1.3 Study Populations

The following analysis set will be defined:

Full analysis set (FAS): Includes all randomized patients analyzed according to the treatment group to which they were assigned at randomization.

[redacted]

6.2 Sample Size Determination

6.2.1 Power and Sample Size for Primary Objective

Assumptions for the sample size were based on input from the HIRD claims/laboratory results database. In line with the primary ITT estimand, the assumptions for the proportion of patients with HbA1c < 7.0% at year 1 and year 2, and for the change from baseline in HbA1c, were based on the claims/laboratory results data within the [redacted] population for all patients initiating treatment intensification, regardless of whether patients adhered to this treatment. Specifically, for semaglutide, assumptions were based on data for liraglutide and dulaglutide. For SOC, assumptions were based on all intensifications in the claims database. The study sample size of 2,250 was calculated based on the following assumptions, informed from HIRD data: 10% difference in proportion patients with HbA1c < 7.0% at year 1 and year 2 (60% semaglutide versus 50% SOC), absolute difference in change from baseline HbA1c of 0.5%-point (SD=2.3%) between treatment groups, 90% power, and an overall alpha leve1 of 5%. Sample size calculations, including different sample size scenarios and a summary of the data from the HIRD, will be documented in the SAP.

The proportion of missing data for the confirmatory endpoints was estimated to be 25% after one year and 44% after two years. In the sample size calculation, it was assumed that only non-missing data at year 1 and year 2 would be used for the respective analyses. This is considered conservative, since the use of imputed data in the actual primary analysis (see 6.3) will increase the power. When accounting for missing data, randomizing 2250 patients will contribute 1687 patients for the year 1 analyses and 1260 patients for the year 2 analyses, achieving a total power of 90% for confirming all 4 confirmatory hypotheses. The corresponding marginal powers for presence of HbA1c < 7.0% at year 1, change in HbA1c to 1 year, presence of HbA1c < 7.0% at year 2, and change in HbA1c to 2 years are 99%, 99%, 95%, and 97% respectively.

6.3 Statistical Analysis for the Primary Estimand

The primary estimand will be estimated based on the FAS using data from all patients with observations at the dedicated study visit (year 1 for the primary endpoint), with the exception of patients who, in violation of the protocol, have initiated semaglutide in the SOC treatment group. The data collected following initiation of semaglutide from these patients will be censored and imputed together with missing data. The primary endpoint, HbA1c < 7.0%, will be analyzed with a logistic regression model with a logit link function, treatment as a categorical effect, and baseline HbA1c as covariate. From the model, the estimated OR (semaglutide versus SOC) will be presented. The underlying continuous endpoint of change in HbA1c will be analyzed using analysis of covariance (ANCOVA) that will include the same independent variables. From the model, the estimated mean difference in change from baseline to dedicated study visit (semaglutide versus SOC) will be presented. The estimated treatment effect from each of these analyses will be complemented with associated 95% confidence interval (CI) and two-sided p-value for testing the null-hypothesis of no difference.

Prior to analysis, missing data will be imputed by multiple imputation on the continuous HbA1c scale and subsequently dichotomized for the primary endpoint. 500 complete data sets will be generated to adequately account for the uncertainty due to missing data. Missing endpoint data will be imputed separately by treatment group and based on patients who remained in the study according to study drug treatment status, i.e., according to whether these patients are on or off study drug at the dedicated study visit. Data will be imputed based on the assumption that, within treatment groups, patients with missing endpoint data will behave like patients with the same study drug treatment status at endpoint as the missing patients' last registered treatment status prior to the missing endpoint. For example, for patients withdrawing from the study with an "off study drug" treatment status, data will be imputed based on the assumption that the withdrawn patients will behave like patients who remain in the study but are not receiving study drug at the dedicated study visit. Technically, the imputation model will be an ANCOVA for the endpoint data. The ANCOVA will include baseline HbA1c, diabetes duration, age, and sex as independent variables. After this model has been used to predict missing values, each of the now 500 complete data sets will be analyzed as described above. Finally, the multiple analysis results will be combined using Rubin's rule. [14] For the OR the results will be combined on the logarithm scale.

Superiority for the primary endpoint, HbA1c <7.0% at year 1, will be considered established if the OR 95% CI is greater than 1, or similarly if the two-sided p-value is significant on a 5% level and the treatment OR is in favor of semaglutide.

If the hierarchical testing scheme allows, superiority for change from baseline to dedicated study visit in HbA1c will be considered established if the 95% CI for the estimated treatment difference is smaller than 0, or similarly if the two-sided p-value is significant on a 5% level and the treatment difference is in favor of semaglutide.

6.4 Statistical Analysis for the Secondary Estimand

The secondary estimand will be estimated based on the FAS. The analysis is similar to the primary analysis for the primary endpoint, but varies with regards to the data used and the imputation of missing data. Specifically, data will only be used from the subset of patients who are receiving study drug at the dedicated study visit (year 1 for the primary endpoint), in order to estimate the treatment effect if all patients had continued treatment. Patients who no longer are receiving study drug will be censored and imputed together with missing data. The same will apply to patients who, in violation of the protocol, have initiated semaglutide in the SOC group. Collectively, missing and censored data will be imputed separately by treatment group based on all patients who are on study drug at the dedicated study visit. Data will be imputed based on the assumption that withdrawn or censored patients behave like patients that remain in the study and continue on study drug.

The technical aspects of missing data imputation based on multiple imputation, the statistical analysis of the multiple complete data sets, and combination of the multiple results will be the same as that described for the primary estimand.

6.5 Supplementary Analyses

The HbA1c analyses described for the two estimands above will be complemented with two complete case analyses based on the subset of patients without missing endpoint data, i.e., patients that do not have their endpoint imputed in the two analyses used for the primary and secondary estimand.

Complete case analysis

This analysis will be based only on patients with available measurements at the dedicated study visit including measurements irrespective of whether patients discontinued study drug or not. The analysis will use the same analysis model as described under the primary estimand.

Complete case on-study drug analysis

The analysis will be based only on patients with available measurements at the dedicated study visit including only measurements for patients still on study drug. The analysis will use the same analysis model as described under the primary estimand.

6.6 PRO Analysis

PRO and physician assessments will be measured with the instruments described in Section 5.3. Analysis of these measures will address the secondary objective of this study to compare semaglutide versus SOC in the study's patient population as is relates to PRO, i.e., treatment satisfaction, generic health outcomes, work productivity, and patient and physician global assessment measures, over one and two year observation periods. PRO analysis will descriptively summarize these measures at baseline, year 1, and year 2, as well as compare semaglutide versus SOC for change from baseline to year 1 and year 2. The continuous change from baseline endpoints will be analyzed using the same analysis approach as described under the complete case and complete case on-study drug analyses in Section 6.5. Details will be fully described in the SAP.

6.7 Safety Analysis

SAEs and AEs will be collected as described in Section 7. No formal safety analyses are planned for this study. SAEs, AEs leading to study drug discontinuation, and pregnancies will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and descriptively summarized by System Organ Class and Preferred Term (PT).

6.8 Other Analyses

The following analyses are planned to further support the primary objective to compare semaglutide versus SOC in glycemic control. They will also address the secondary objectives of

this study to compare semaglutide versus SOC in the study's patient population over one and two year observation periods as is relates to body weight loss, hypoglycemia, HCRU, and adherence and persistence to treatment. The binary and continuous endpoints that include HbA1c, weight, SBP, or DBP data will be analyzed using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections. All other endpoints will be analyzed using the same analysis approach as described under the complete case and complete case on-study drug analyses in Section 6.5. Further details of these analyses and details for analyses of other endpoint types will be fully described in the SAP.

6.8.1 Supportive Analyses of Glycemic Control

The proportion of patients achieving the secondary endpoints related to glycemic control at year 1 as defined in section 3.3.2 (individualized HbA1c target, HbA1c <7.0% (53mmol/mol) or at least 1% point improvement in HbA1c from baseline, HbA1c target attainment per HEDIS criteria) will be compared between semaglutide and SOC treatment groups using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections.

Additionally, derived outcome variables for supportive measures of glycemic control (Appendix 2) will be utilized to support these analyses.

6.8.2 Weight Loss

Change in patient weight from baseline to year one will be calculated in pounds and percentage as defined in section 3.3.2. Mean change in weight will be compared between semaglutide and SOC treatment groups using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections.

Additionally, derived outcome variables for supportive measures of body weight loss (Appendix 2) will be utilized to support these analyses.

6.8.3 Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP)

Change in patient SBP and DBP from baseline to year 1 and baseline to year 2 will be calculated as defined in section 3.3.2 and Appendix 2. Mean change in SBP and DBP will be compared between semaglutide and SOC treatment groups using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections.

6.8.4 Hypoglycemia

The number of hypoglycemic episodes leading to an inpatient admission or ER encounter will be reported by patients and compared by semaglutide and SOC treatment groups utilizing a negative binomial model.

Additionally, derived outcome variables for supportive measures of hypoglycemia (Appendix 2) will be utilized to support these analyses.

6.8.5 Healthcare Resource Utilization (HCRU)

HCRU analyses will compare all-cause and diabetes-related HCRU (inpatient admissions, ER encounters, outpatient encounters, and pharmacy utilization) as defined in section 3.3.2 from the HIRD by semaglutide and SOC treatment group from baseline to year 2.

The details of claims data definitions and calculations will be fully described in the SAP.

6.8.6 Adherence and Persistence to Treatment

Adherence and persistence to the study drug will be calculated and compared between semaglutide and SOC treatment groups.

Medication adherence refers to a patient's conformance to the provider's recommendation with respect to timing, dosage, and frequency of medication taken during the prescribed length of time. In claims, adherence is typically measured using either medication possession ratio (MPR) or proportion of days covered (PDC).

Medication persistence refers to whether a patient stays on therapy or the time from initiation to discontinuation of therapy. In claims, persistence is typically defined as the duration of time from initiation of the therapy to discontinuation or switching, whichever comes first.

Adherence and persistence will be further defined in the SAP.

6.8.7 Antidiabetic Treatment Patterns

Antidiabetic treatment patterns will be assessed and compared between semaglutide and SOC treatment groups. This analysis will summarize the number and classification type of antidiabetic medications taken during the study period.

6.8.8 Exploratory Predictive Analysis

An exploratory predictive analysis will be performed within and between the semaglutide and SOC treatment groups to identify predictors of treatment adherence and persistence and glycemic control. The objectives of the exploratory predictive analyses are to identify within and between treatment groups: 1) patients less likely to discontinue treatment and 2) patients more likely to reach clinical target.

6.8.9 Evaluation of the Study Population

To evaluate the generalizability of the study results, an analysis of the study population will be performed. The primary objective of this analysis is to evaluate the external validity of the study and to understand how the study population fits into the larger T2DM populations within study sites and [redacted] as a whole. Two claims-based T2DM patient populations will be described and compared to the study population: (1) commercially-insured [redacted] T2DM patients treated with up to 2 oral antidiabetic medications who undergo an antidiabetic treatment intensification, and (2) within the study sites, commercially-insured [redacted] T2DM patients treated with up to 2 oral antidiabetic medications who are not enrolled in the study, but who undergo an antidiabetic

[redacted]

treatment intensification. The analysis will compare the demographics, HCRU, and HbA1c between the study population and the two comparator populations during the 12 month period prior to randomization (for study population) or prior to a claims-based proxy for antidiabetic treatment intensification index date (for comparators). Additionally, treatment patterns of non-enrolled T2DM patients within the practices from which the study patients are recruited will be evaluated to identify any relevant patterns of care suggesting channeling of certain types to patients away from the study. These analyses will help to contextualize study results within the T2DM population broadly.

The details of this analysis will be fully described in the SAP.

7 Adverse Event Collection

The principal study physician is responsible for monitoring the safety of participating patients. All SAEs reported by the patients during the study observational period are required to be documented on the appropriate SAE reporting form. For the purposes of this study, AEs that do not meet the definition of SAE will only be collected if they lead to study drug discontinuation.

7.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product or medical device, which does not necessarily have to have a causal relationship to the product of device. Study physicians will follow AEs that occur in any patient during this study in a manner consistent with routine clinical practice. For the purposes of this study, AEs that do not meet the definition of an SAE (section 7.2) will only be collected in the eCRF if they lead to study drug discontinuation.

7.2 Serious Adverse Events

All AEs meeting the definition of SAE will be collected in the eCRF. SAEs will be reported from the time a patient is randomized until EOS at year 2, or until the patient withdraws from the study. An SAE is defined as any AE which results in at least one of the following outcomes:

- Initial inpatient admission or prolongation of existing inpatient admission
- A life-threatening event, i.e., an event in which the patient was at immediate risk of dying at the time of the event; not an event that hypothetically could have caused death had it been more severe
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect in offspring
- Death

- Is deemed serious for any other reason, i.e., if it is an important medical event based on appropriate medical judgement which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other listed outcomes.

7.2.1 Collection Period of Serious Adverse Events

SAEs will be reported from the time a patient is randomized until EOS at year 2, or until the patient withdraws from the study. The principal study physician is responsible for alerting Novo Nordisk or its designee to any SAE within 24 hours of becoming aware of it via electronic data capture (EDC) entry. The patient should be followed until the outcome of the event is closed out. Follow-up information should be reported within 24 hours of it becoming available. Requests for follow-up information should be resolved within 14 calendar days.

At each visit (both routine care visits and dedicated study visits), patients will be asked about AEs including hypoglycemic events, e.g. “Have you experienced any problems since the last contact?”

If an investigator becomes aware of SAEs after EOS at year 2 that are possibly related to the study product, these should be reported as spontaneous events.

7.3 Pregnancy

Any abnormal pregnancy outcome (e.g., spontaneous miscarriage, fetal death, congenital anomaly/birth defect, etc.) is considered an SAE. For the purposes of this study, any pregnancies in participating female patients will be reported, along with pregnancy outcome and any AEs or SAEs observed in the fetus or newborn until 1 month of age.

7.3.1 Reporting Period of Pregnancy

Pregnancies will be reported from the time a patient is randomized until EOS at year 2 or until the patient withdraws from the study. The principal study physician is responsible for alerting Novo Nordisk or its designee to any drug exposure during pregnancy within 14 days of the first knowledge of the pregnancy via the pregnancy reporting form. The study physician will follow the patient for the duration of the pregnancy.

7.4 Technical Complaints

Technical complaints may be reported as per usual practice. However, any SAEs resulting from a technical complaint must be reported via EDC.

8 DATA COLLECTION

8.1 Data Sources

Data sources include primary data collected prospectively by study sites at study visits (demographic and clinical data, patient-completed PRO data, and physician reported global assessments) as well as secondary data collection utilizing administrative claims data from the

[redacted]

HIRD. In order to maintain patient confidentiality, each patient will be assigned a unique patient study ID number upon signing informed consent to use in place of patient name or any other identifying information (e.g., medical record number). Clinical study data, PROs/ClinROs and claims-derived variables will be integrated into one analysis dataset via this confidential patient ID.

8.2 Electronic Case Report Forms (eCRFs)

All clinical study data will be collected at the physician office and entered into eCRF by trained site study personnel through a fully validated, 21 CFR 11 and HIPAA compliant EDC system. Patients will complete PRO questionnaires on paper and the site study personnel will enter the completed forms into the EDC system. Site users will be provided eCRF Completion Guidelines (eCCGs) to assist with study data collection and entry. Study personnel will access the EDC system through a secure study website.

Some clinical assessments utilized in this study may be completed in the course of routine clinical practice by site personnel not affiliated with study (e.g., blood pressure), however any activities completed solely for the study (e.g., data entry, PRO administration) must be done by trained site study personnel. For example, a nurse not affiliated with the study may measure blood pressure as part of routine care. The data from this assessment may be used for this study, but must be extracted from the patient's medical record and entered into the eCRF by trained site study personnel.

The principal study physician has the ultimate responsibility for the collection and reporting of all clinical and patient data through the eCRFs, as well as ensuring that they are accurate and complete to the extent possible.

8.3 Year One Database Lock

The primary analysis for this study is a year 1 analysis. Once data collection for year 1 has completed, a database lock and year 1 analysis will be performed. The year 1 analysis will not be integrated with HCRU and will be limited to year 1 endpoints derived from eCRF data, including PRO data. To maintain study integrity for the remaining study period, data from year 1 will be used for limited and confidential communications while complying with public disclosure requirements. All other analyses will be conducted following a second database lock once data collection for the entire study is complete.

9 STUDY MANAGEMENT

9.1 Regulatory and Ethical Consideration

All study activities will be conducted in accordance with Good Clinical Practice (GCP) guidelines. Study personnel at physician sites will be provided training on the study protocol, the Informed Consent Form (ICF), data collection, and data entry to ensure both the protection of

potential study patients as well as the scientific integrity of the study. Site monitoring will be conducted by [redacted] staff.

9.1.1 Institutional Review Board (IRB)

The principal study physician will have prospective IRB approval of the study protocol, ICF, and any patient information or recruiting materials prior to commencement of any study activities at their site. In the case of a protocol amendment, the study physician must sign the revised protocol and submit the amendment to the IRB for review and approval prior to implementation of any changes specified in the protocol amendment. All changes in research activity and all unanticipated problems involving risk to human patients or others must be reported to the IRB as required.

The principal study physician will obtain continued review of the IRB study approval at intervals not to exceed one year or otherwise specified by the IRB.

9.1.2 Informed Consent

An ICF describing the purpose, procedures, and potential risks and benefits of the study will be developed and approved by the IRB prior to study initiation. The principal study physician must ensure that each study patient is informed of the study and authorizes release of health information prior to study-related activities. The study physician, or study personnel designated by the study physician, will obtain written informed consent from each patient prior to initiation of any study-related procedures. Each patient will be given a copy of the signed ICF. The principal study physician will retain the original signed ICF for each patient.

The IRB must prospectively approve the ICF and any changes to the ICF during the course of the study before use. If a protocol amendment increases the potential risk to the patient, the ICF must be revised and submitted to the IRB for review and approval prior to implementation. The revised ICF must then be used to obtain consent from new patients entering the study as well as from currently enrolled patients if they are affected by the amendment, per IRB guidance.

9.2 Record Retention and Access

This study may be subject to audits or inspections by regulatory authorities or Novo Nordisk (or its designee). To enable such inspections and/or audits, the principal study physician must agree to maintain and allow access to required patient and study records. The principal study physician agrees to keep the identity of all participating patients (sufficient information to link records, e.g., hospital records), all original signed ICFs, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls, reports). The principal study physician should retain records according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

10 PUBLICATION OF STUDY RESULTS

All information related to this study is considered confidential information belonging to Novo Nordisk and [redacted] as consistent with contractual agreement. A final study report will be generated following completion of data collection and analysis. Results and findings will be submitted to conferences and for publication in peer-reviewed scientific journals with authorship following the International Committee of Medical Journal Editors (ICMJE) guidelines.

Information regarding the study will be disclosed at clinicaltrials.gov and novonordisk-trials.com. Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of studies regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this study will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

11 INDEMNIFICATION

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the trial or by persons for whom the said site or investigator are responsible.

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Appendix 1: Time and Events Schedule

Study NN9535-4416	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]					
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				
Individualized HbA1c target[d]	X				
Type of glucose-lowering medication including semaglutide	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[e]	X	X	X	X
SAEs, pregnancies, and AEs leading to study drug discontinuation		X	X	X	X
Healthcare resource utilization[f]		X	X	X	X
Hypoglycemia leading to inpatient admission or ER encounter		X	X	X	X

[redacted]

Study NN9535-4416	Dedicated Study visit, Randomization	Routine Care visits, Year 1	Dedicated Study visit, Year 1	Routine Care visits, Year 2	Dedicated Study visit, Year 2
PROs and Physician Completed Assessments					
DTSQs	X				
DTSQc			X		X
SF-12v2	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 mediations will be collected at the randomization visit.
** The year 1 and year 2 routine care visit windows are determined by the date of the patient's dedicated year 1 study visit. The year 1 routine care visit window will end immediately prior to the dedicated year 1 study visit. The year 2 routine 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 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. Additionally, PRO and ClinRO 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 the HIRD and will not be entered into the eCRF.

[a] Routine 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 care visits will be collected as available/according to local clinical practice in eCRF.

[redacted]

[c] Informed consent must be obtained before any study related activities.
[d] Individualized HbA1c target must be set and documented prior to randomization.
[e] The HbA1c value is based on historical data collected from the study physician and is the value closest to the date of randomization, within the last 90 days.
[f] Data from the HIRD. Data will be extracted from the HIRD at the end of the study, but will include data from patient randomization through EOS or withdrawal.

Appendix 2: Additional Derived Outcome Variables for Supportive Analyses

Supportive Measures of Glycemic Control

- Individualized HbA1c target attained at year 2 (yes/no)
- HbA1c <7.0% (53 mmol/mol) or at least 1% point improvement in HbA1c compared to baseline at year 2 (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 1 (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 2 (yes/no)
- HbA1c <7.0% (53 mmol/mol) and no further antidiabetic medication intensification after randomization at year 1 (yes/no)
- HbA1c <7.0% (53 mmol/mol) and no further antidiabetic medication intensification after randomization at year 2 (yes/no)
- HbA1c target attainment per HEDIS criteria (<8.0% if age ≥65 years or with defined comorbidities, otherwise <7.0%) at year 2 (yes/no)
- HbA1c <7.0% (53 mmol/mol) at year 1 in patients with HbA1c >9.0% at baseline (yes/no)
- HbA1c <7.0% (53 mmol/mol) at year 2 in patients with HbA1c >9.0% at baseline (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 1 in patients with HbA1c >9.0% at baseline (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 2 in patients with HbA1c >9.0% at baseline (yes/no)

Body Weight Loss

- Change in body weight (%) from baseline to year 2
- Change in body weight (lb) from baseline to year 2

Blood Pressure

- Change in SBP (mm Hg) from baseline to year 2
- Change in DPB (mm Hg) from baseline to year 2

Hypoglycemia

- Reported hypoglycemia leading to inpatient admission or ER encounter during year 1 (yes/no)

[redacted]

- Reported hypoglycemia leading to inpatient admission or ER encounter during year 2 (yes/no)

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 (yes/no)

- 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 (yes/no)

- 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 (yes/no)

- 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 2 (yes/no)

- 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 (yes/no)

- 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 (yes/no)

Adherence to Treatment

- Study drug medication adherence for the two years of the study, as measured by the medication possession ratio (MPR)

Appendix 3: Patient Reported Outcome Additional Information

DTSQc

The DTSQc provides a measure of how satisfied patients are with their current diabetes treatment compared with previous treatment. It consists of 8 questions, which are to be answered on a Likert scale from -3 to +3 (-3 = much less satisfied now to +3 = much more satisfied now), with 0 (midpoint), representing no change. Six questions are summed 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.

SF-12 v2

The SF-12v2 is a 12-item generic health-related quality of life measure that assesses physical and mental functioning. The items will be scored using the scoring software that will be provided with the license. The following two summary scores are used as endpoints: Physical Component Summary (PCS) Score and Mental Component Summary (MCS) Score. The scores are norm-scored such that the scores range from 0-100 with a mean of 50 and standard deviation of 10. A higher score is associated with better quality of life and a lower score, poorer quality of life.

WPAI-GH

The WPAI-GH yields four types of scores: Absenteeism (work time missed), Presenteeism (impairment at work / reduced on-the-job effectiveness), Work productivity loss (overall work impairment / absenteeism plus presenteeism), and Activity Impairment. WPAI outcomes are expressed as percentages, with higher numbers indicating greater impairment and less productivity, i.e., 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).

Summary of Amendments and Updates

Summary of Changes
NN95359-4416 Protocol Version 2.0, dated 27MAR2019

Number	Section/Page	Change	Rationale
1	Global Change, Study Population	Allow enrollment of patients treated with either 1 or 2 oral antidiabetic medications.	Expand study population from patients treated with metformin monotherapy to patients treated with either 1 or 2 oral antidiabetic medications to facilitate enrollment.
2	Global Change	**March ~~13~~27, ~~2018~~2019** Version ~~1~~2.0	Update protocol date and version.
3	Study Approvals, p. 2	**Name:** [redacted] **Title:** [redacted]	Study approval title update.
4	Study Approvals, p. 2	**Name:** [redacted] **Title:** [redacted] Statistician	Update to study statistician.
5	Patient Description, Synopsis, p. 7	Eligible patients include adult T2DM patients on ~~metformin monotherapy~~ up to 2 oral antidiabetic medications whose physician deems that they have inadequate glycemic control and need treatment intensification with an additional antidiabetic oral or injectable medication.	Update patient description to reflect expanded study population.

6	Primary Objective Synopsis, p. 7 Section 2.1, Primary Objective, p. 17	The primary objective is to demonstrate superior long term effects of treatment with semaglutide compared to SOC both added to ~~metformin~~ up to 2 oral antidiabetic medications on glycemic control when used as intensification in routine clinical practice in adult patients with T2DM.	Update primary objective to reflect expanded study population.
7	Secondary Objective Synopsis, p. 7 Section 2.2, Secondary Objectives, p. 17	The secondary objectives are to compare the long term effect of semaglutide versus SOC both added to ~~metformin~~ up to 2 oral antidiabetic medications and used as intensification in routine clinical practice in adult patients with T2DM with regards to:	Update secondary objectives to reflect expanded study population.
8	Study Design Synopsis, p. 7 Section 4.1, Study Design Overview, p. 20	This is a 2-year, multi-center, randomized, open label, parallel group, active comparator pragmatic clinical trial (PCT) comparing semaglutide versus SOC when added to ~~metformin monotherapy~~ up to 2 oral antidiabetic medications as treatment intensification among adult T2DM patients in the course of routine clinical practice.	Update study design to reflect expanded study population.
9	Inclusion Criteria, #4 Synopsis, p. 8 Section 4.2.3, Patient Inclusion Criteria, p. 22	4.) Treatment with ~~metformin as antidiabetic monotherapy~~ either 1 or 2 oral antidiabetic medications.	Expand study population from patient treated with metformin monotherapy to patients treated with either 1 or 2 oral antidiabetic medications to facilitate enrollment.
10	Inclusion Criteria, #5	5.) Current member of an [redacted] affiliated	Clarification of health plan requirements.

[redacted]

	Synopsis, p. 8 Section 4.2.3, Patient Inclusion Criteria, p. 22	commercial health plan with pharmacy benefits.	
11	Exclusion Criteria, #2 Synopsis, p. 8 Section 4.2.4, Patient Exclusion Criteria, p. 22	2.) Treatment with more than 2 oral antidiabetic medications or any injectable antidiabetic medication ~~any medication for the indication of diabetes other than metformin~~ in a period of 30 days before the day of eligibility assessment. Temporary/emergency use of any type of insulin is allowed, as is prior insulin treatment for gestational diabetes.	Update exclusion criterion #2 to be consistent with inclusion criterion #4.
12	Section 1, Introduction, p. 16	This local US study will enroll adult patients with T2DM who have inadequate glycemic control on ~~metformin as their only~~ up to 2 oral antidiabetic medications, as defined by the need for treatment intensification with an additional antidiabetic oral or injectable medication per the study physician´s discretion.	Update description of study to reflect expanded study population.
13	Section 4.2, Practice and Patient Selection, p. 21	The target population for this study consists of adult, commercially-insured, T2DM patients on ~~metformin mono-therapy~~ up to 2 oral antidiabetic medications who are in need of treatment intensification with an additional antidiabetic oral or injectable medication.	Update target population to reflect expanded study population.
14	Section 4.2, Practice and Patient Selection, p. 21	[redacted] ~~health plans serve a large population of T2DM patients. In feasibility data from the HIRD, the number of~~ [redacted]	Delete data based on metformin monotherapy as it is not relevant to updated inclusion criteria.

		~~patients with T2DM, at least one claim for metformin in the most recent 6 months, and without prior use of other antidiabetic drug classes (per study exclusion criterion #2), amounts to circa 300,000 potential eligible patients distributed across 61,803 unique providers.~~	
15	Section 4.2.2, Patient Recruitment and Eligibility, p. 21	Eligible patients include adult T2DM patients whose physicians determine that they have inadequate glycemic control on ~~metformin antidiabetic monotherapy~~1 or 2 oral antidiabetic medications.	Update description of eligible patients to reflect expanded study population.
16	Figure 1, Study design, p. 23	**Figure 1 Study design diagram**. Patients will be randomized in a 1:1 manner using centralized allocation to receive semaglutide or SOC as add-on to ~~metformin~~ up to 2 oral antidiabetic medications.	Update description of study design to reflect expanded study population.
17	Section 5.1, Enrollment Procedures, p. 23	The determination that a patient has inadequate glycemic control on ~~metformin antidiabetic monotherapy~~ up to 2 oral antidiabetic medications, and the subsequent decision to intensify antidiabetic treatment with an additional oral or injectable antidiabetic medication, will be made by the study physician during the course of routine clinical practice.	Update enrollment procedures to reflect expanded study population.
18	Section 5.2.2, Treatments, p. 26	• Metformin	Add metformin to the list of oral antidiabetic drugs included in this study to reflect expanded study population.

[redacted]

19	Section 5.2.2, Treatments, p. 26-27	**Background medication:** The (up to 2) oral antidiabetic medication(s) taken prior to randomization and treatment intensification ~~following treatment~~ is considered background medication~~: metformin~~. Patients may discontinue ~~metformin~~ background medication at any time during the study. Patients may change the pre-study dose and frequency of ~~metformin~~ background medication at any time during the study. Background medication will not be provided nor reimbursed by Novo Nordisk.	Update description of background medication to reflect expanded study population.
20	Section 6.6, PRO Analysis, p. 33	The continuous change from baseline endpoints will be analyzed using the same analysis approach as described under the complete case and complete case on-study drug analyses in ~~primary estimand, secondary estimand, and supplementary analysis~~ ~~s~~Section 6.5.	Update to planned PRO analyses, with no missing data imputation for PRO endpoints.
21	Section 6.8, Other Analyses, p. 34	The binary and continuous endpoints that include HbA1c, weight, SBP, or DBP data will be analyzed using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections. All other endpoints will be analyzed using the same analysis approach as described under the complete case and complete case	Update to planned analyses, with missing data imputation only for endpoints including HbA1c, weight, SBP, or DBP data.

[redacted]

		on-study drug analyses in Section 6.5.	
22	Section 6.8.9, Evaluation of Study Population, p. 35	Two claims-based T2DM patient populations will be described and compared to the study population: (1) commercially-insured [redacted] T2DM patients treated with ~~metformin~~ up to 2 oral antidiabetic medications who undergo an antidiabetic treatment intensification, and (2) within the study sites, commercially-insured [redacted] T2DM patients treated with ~~metformin~~ up to 2 oral antidiabetic medications who are not enrolled in the study, but who undergo an antidiabetic treatment intensification.	Update claims-based comparator population to reflect expanded study population.

Long term comparative effectiveness of once weekly semaglutide versus standard of care in a real world adult US population with type 2 diabetes - a randomized pragmatic clinical trial

Trial ID NN9535-4416

Novo Nordisk

August 21, 2019

Version 3.0

Trial Phase: 4
Investigational Substance: Semaglutide

[redacted]

[redacted]

STUDY APPROVALS
Protocol No: NN9535-4416
21-AUG-2019

Sponsor Approval:

Name: [redacted]
Title: [redacted]
Novo Nordisk

Signature: DocuSigned by: [redacted]

Date: 26-Aug-2019

Name: [redacted]
Title: [redacted] Statistician
Novo Nordisk

Signature: DocuSigned by: [redacted]

Date: 26-Aug-2019

Principal Study Physician Agreement:

I have read the protocol "Long term comparative effectiveness of once weekly semaglutide versus standard of care in a real world adult US population with type 2 diabetes - a randomized pragmatic clinical trial" and agree to ensure that all staff members involved in the conduct of this study are informed of their obligations and that they meet the commitments of the protocol in accordance with Good Clinical Practice (GCP) requirements. I have familiarized myself with the prescribing information corresponding with the study drugs associated with this study.

I acknowledge that I am responsible for overall study conduct. I understand GCP requirements and agree to personally conduct or supervise the described pragmatic study in accordance with GCP.

Signature: _____

Print Name: _____

Date: _____

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[redacted]

[redacted]

[redacted]

SYNOPSIS

Title: Long term comparative effectiveness of once weekly semaglutide versus standard of care in a real world US adult population with type 2 diabetes – a randomized pragmatic clinical trial
Sponsor: Novo Nordisk **Study Treatment:** Semaglutide in a prefilled pen (Ozempic®) **Active Ingredient:** Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA) **Comparator Treatment:** Standard of Care (SOC) (excluding semaglutide)
Trial ID: NN9535-4416
Study Physician Sites: Participation of approximately 200 physician sites, including both primary care practitioners and endocrinologists, that have a population of patients with the target indication, type 2 diabetes mellitus (T2DM), actively enrolled in a commercial or Medicare health plan with pharmacy benefits. **Country:** United States (US)
Patients: Eligible patients include adult T2DM patients on up to 2 oral antidiabetic medications whose physician deems that they have inadequate glycemic control and need treatment intensification with an additional antidiabetic oral or injectable medication. Planned enrollment in this study is 1387. Patients will be randomized 1:1 to receive either semaglutide or SOC.
Study Objectives: The objectives of this study are as follows: 1.) The primary objective is to demonstrate superior long term effects of treatment with semaglutide compared to SOC both added to up to 2 oral antidiabetic medications on glycemic control when used as intensification in routine clinical practice in adult patients with T2DM. 2.) The secondary objectives are to compare the long term effect of semaglutide versus SOC both added to up to 2 oral antidiabetic medications and used as intensification in routine clinical practice in adult patients with T2DM with regards to: a. Weight loss b. Patient reported outcomes (PROs) and clinician reported outcomes (ClinROs) c. Hypoglycemia d. Healthcare Resource Utilization (HCRU) e. Adherence and persistence to treatment
Study Design: This is a 2-year, multi-center, randomized, open label, parallel group, active comparator pragmatic clinical trial (PCT) comparing semaglutide versus SOC when added to up to 2 oral antidiabetic medications as treatment intensification among adult T2DM patients in the course of routine clinical practice. Patients will be randomized 1:1 to receive either semaglutide or SOC. The decision that further antidiabetic treatment intensification with oral or injectable antidiabetic medication is indicated is at the discretion of the study physician and will be made prior to and independent of enrollment in this study. The study physician will have determined the patient's suitability for treatment with semaglutide prior to signing informed consent, but the determination to

initiate semaglutide versus SOC will be made by randomization.

In keeping with the study objectives and pragmatic design to evaluate semaglutide versus SOC in real world, routine clinical practice, inclusion and exclusion criteria are minimally restrictive and there are few study-specific evaluations. Study physicians will follow and treat patients according to their routine clinical practice and judgement. All oral and injectable antidiabetic medications are allowed at the study physicians' discretion, with the exception of semaglutide in the SOC group. Patients will be followed for 2 years, regardless of changes in antidiabetic treatment over the course of the study.

It is anticipated that patients will undergo medical evaluation at regular intervals over the course of the study duration as per standard of care, but the only dedicated study visits are at randomization, at year 1, and at year 2. The study will also capture clinical data collected at the sites during routine diabetic care visits, i.e., office visits and other patient contacts that occur as part of routine clinical practice. Assessments will be conducted according to the study physician's routine clinical practice, with a few study-specific assessments as outlined in Study Procedures. Additionally, medical and pharmacy claims data will be captured utilizing the HealthCore Integrated Research Database (HIRD^{SM}) for [redacted] patients or requested, via patient written authorization, from a set of other health insurers for non-[redacted] patients for the 2 year study period. Claims data for the 12 months prior to randomization will also be collected if available.

Participant Selection:

Inclusion Criteria:

Patients must meet all of the following inclusion criteria to be eligible for the study:

1.) Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study.
2.) Male or female, age ≥ 18 years at the time of signing informed consent.
3.) Type 2 diabetes mellitus diagnosis.
4.) Treatment with either 1 or 2 oral antidiabetic medications.
5.) Current member of a commercial or Medicare health plan with pharmacy benefits.
6.) Recorded glycosylated hemoglobin A1c (HbAlc) value within the last 90 days prior to randomization.
7.) Further intensification with an additional antidiabetic oral or injectable medication is indicated to achieve glycemic target at the discretion of the study physician according to approved labelling.

Exclusion Criteria:

Patients presenting with any of the following exclusion criteria will not be eligible for the study:

1.) Previous randomization in this study.
2.) Treatment with more than 2 oral antidiabetic medications or any injectable medication in a period of 30 days before the day of eligibility assessment. Temporary/emergency use of any type of insulin is allowed, as is prior insulin treatment for gestational diabetes.
3.) Contraindications to semaglutide according to the FDA approved label.
4.) Female who is pregnant, breastfeeding or intends to become pregnant.
5.) Participation in another clinical trial.

Study Procedures:

- Study physicians will identify eligible patients for participation.

[redacted]

- Study physicians will obtain written informed consent from patients and if eligible, patients will be randomized to either semaglutide or SOC.
- Study data will be collected on electronic Case Report Forms (eCRFs) via an electronic data capture (EDC) system.
- Study physicians or site personnel will collect demographic, clinical (i.e., height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP)), medical and T2DM specific history, antidiabetic medications, and pre-specified concomitant medications related to cardiovascular risk data prior to or at randomization. Individualized HbA1c target will be set prior to randomization.
- Baseline HbA1c will be collected from physician sites during eligibility assessment and will be the value closest to the date of randomization, within 90 days. All post-randomization HbA1c values will be recorded as available per routine clinical practice during the 2 year study period. Post-randomization HbA1c values are required for the year 1 and year 2 dedicated study visits.
- PROs and ClinROs will be completed at randomization, year 1, and year 2.
- Study physicians will collect patient data (HbA1c, study and antidiabetic medication changes, pre-specified concomitant medications related to cardiovascular risk, weight, SBP, DBP, hypoglycemic events leading to inpatient admission or emergency room (ER) encounter, adverse events (AEs) leading to study drug discontinuation, serious adverse events (SAEs), and pregnancies at the dedicated year 1 and year 2 study visits, as well as at any routine diabetic care visits during the 2 year study period. Of note, AEs leading to study drug discontinuation or SAEs will be collected from all interactions with the patient, as well as if discovered when reviewing documents from healthcare encounters with other providers.
- Administrative medical claims, pharmacy claims and health plan eligibility data will be captured from the HIRD for [redacted] patients or requested, via patient written authorization, from a set of other health insurers for the duration of the 2 year study period. Claims data for the 12 months prior to study randomization will also be collected if available. This data will be used for HCRU measures, as well as adherence and persistence to treatment.

Study Duration: Planned patient time on study will be 2 years. Administrative claims data will also be captured during this time period. Patients will be followed for the full 2 year study period regardless of changes in or discontinuation of antidiabetic treatment, other than withdrawal of consent.

Questionnaires: Diabetes treatment satisfaction, generic health-related quality of life (HRQoL), work productivity, and patient and clinician global assessments will be measured at the randomization, year 1, and year 2 dedicated study visits.

Statistical Analysis: Two estimands, each targeting a unique research question, have been defined to adequately describe the effect of semaglutide as compared to SOC (excluding semaglutide).

The primary estimand for all objectives will be the "intention-to-treat" estimand evaluating the effectiveness of randomized treatment intervention, irrespective of adherence to this randomized intervention or changes to other antidiabetic medication.

The secondary estimand for all objectives, with the exception of the adherence and persistence to treatment objective, is the "if all patients had adhered" estimand. This estimand evaluates the effect of randomized treatment intervention for all randomized patients if all patients had adhered to randomized treatment, regardless of changes to other antidiabetic medication.

Baseline is defined as ≤ 90 days prior to randomization visit (week 0) for HbA1c. For secondary

endpoint assessments, baseline is defined as ≤ 4 weeks prior to the randomization visit (week 0).

Primary completion date (PCD) is the date the last patient completes the year 1 dedicated study visit.

The primary endpoint is binary, with success represented by an HbA1c <7.0% (53 mmol/mol) at year 1 (yes/no). Confirmatory secondary endpoints include:

- Change in HbA1c (%-point) from baseline to year 1
- HbA1c <7.0% (53 mmol/mol) at year 2 (yes/no)
- Change in HbA1c (%-point) from baseline to year 2

This study is designed to have 90% power to confirm superiority of the primary endpoint and 85% power to also confirm superiority of the first confirmatory secondary endpoint based on an analysis of the primary estimand for each of the endpoints.

The confirmatory endpoints will all be tested under multiplicity control via a hierarchical testing scheme according to the order given in the above bullet list.

The estimand informs choices about data foundation and statistical analysis including possible imputation of missing data, hereby ensuring that randomization is preserved as a sound basis for statistical inference; i.e., estimation of effect size, associated uncertainty, and statistical testing.

The full analysis set (FAS) comprising all randomized patients will be the analysis population for evaluation of both the primary and secondary estimands. For both estimands, the primary endpoint, HbA1c <7.0%, will be analyzed using a logistic regression model with a logit link function and will include treatment and baseline HbA1c as independent variables. Continuous endpoints will be analyzed using analysis of covariance (ANCOVA) and will include the same independent variables. Prior to analysis, missing data will be imputed by multiple imputation on the continuous HbA1c scale and subsequently dichotomized for the primary endpoint.

Supplementary Analyses: Two complete case analyses will complement the analyses for the primary and secondary estimands. The supplementary complete case analyses will be based on the subset of patients without missing endpoint data, i.e., patients that do not have their endpoint imputed in the two analyses used for the primary estimand and the secondary estimand, respectively.

Secondary Analyses: Secondary analyses will compare semaglutide versus SOC treatment groups in terms of change in body weight, SBP, DBP, and PRO and ClinRO measures, based on the similar analysis methods as for the primary and secondary estimands. Similarly, binary endpoints and other secondary endpoints will be compared statistically between treatment groups, including HCRU and adherence/persistence to treatment measures, hypoglycemic events leading to inpatient admission or ER encounter, as well as composite measures of HbA1c, weight loss, and hypoglycemia.

Safety: The principal study physician is responsible for monitoring the safety of participating patients. For the purposes of this study, AEs that do not meet the definition of an SAE will only be collected/recorded in the EDC if they lead to study drug discontinuation. Study physicians are responsible for reporting all SAEs and following the patient until the outcome of the SAE is closed out. All SAEs will be reported from randomization until end of study (EOS) at year 2 or patient study withdrawal. Study physicians are also responsible for recording all pregnancies in female patients from randomization until EOS at year 2 or patient study withdrawal. The patient will be followed for the duration of the pregnancy until one month post-delivery to report the pregnancy outcome and any AEs or SAEs observed in the fetus or newborn until 1 month of age. Safety will be summarized descriptively.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	American Diabetes Association
AE	Adverse Event
ANCOVA	Analysis of Covariance
eCCGs	Electronic Case Report Form Completion Guidelines
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinician Global Impression of Disease Severity
CI	Confidence Interval
ClinRO	Clinician Reported Outcome
eCRF	Electronic Case Report Form
DBP	Diastolic Blood Pressure
DPP-4	Dipeptidyl peptidase 4
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTSQc	Diabetes Treatment Satisfaction Questionnaire, change version
DTSQs	Diabetes Treatment Satisfaction Questionnaire, status version
EASD	European Association for the Study of Diabetes
EDC	Electronic Data Capture
EOS	End of Study
ER	Emergency Room
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonists

HbA1c	Glycosylated Hemoglobin A1c
HCRU	Healthcare Resource Utilization
HEDIS	Healthcare Effectiveness Data and Information Set
HIRD^{SM}	HealthCore Integrated Research Database
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ID	Identifier
IRB	Institutional Review Board
ITT	Intent to Treat
LPLV	Last Patient Last Visit
LTFU	Lost to Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
MCS-12	Mental Summary Component (of the Short Form 12-Item version 2)
MPR	Medication Possession Ratio
OR	Odds Ratio
PCD	Primary Completion Date
PCS-12	Physical Summary Component (of the Short Form 12-Item version 2)
PCT	Pragmatic Clinical Trial
PDC	Proportion Days Covered
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Disease Severity
PRO	Patient Reported Outcome
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation

[redacted]

SF-12v2	Short Form 12-Item version 2
SGLT-2	Sodium-Glucose Co-transporter 2
SM	Service Mark
SOC	Standard of Care
SUSTAIN	Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes
T2DM	Type 2 Diabetes Mellitus
TD	Treatment Difference
US	United States
WPAI-GH	Work Productivity and Activity Impairment, General Health

LIST OF DEFINITIONS

Term	Definition
Administrative Claims Data	Medical, pharmacy, and health plan eligibility data created in the processing of medical and pharmacy claims. The claims data utilized in this study are obtained from the HealthCore Integrated Research Database (HIRD) for [redacted] patients and requested, via patient written authorization, from a set of other health insurers for non-[redacted] patients.
Baseline	Baseline refers to assessments conducted and patient data collected at or prior to randomization. Baseline HbAlc may be ≤ 90 days prior to randomization. Baseline for secondary endpoint assessments may be ≤ 4 weeks prior to randomization.
Baseline Endpoint	For continuous endpoints and endpoints derived from continuous sources, the baseline value is defined as the last assessment taken prior to or at the randomization visit *and* before first use of study drug.
Comparator Treatment	Standard of Care (SOC) (excluding semaglutide); Commercially available oral or injectable antidiabetic medication, excluding semaglutide, prescribed at the discretion of the study physician for antidiabetic treatment intensification following randomization.
Complete the Study	Complete the study at 52 weeks: Patient has year 1 HbA1c data Complete the study at 104 weeks: Patient has year 2 HbA1c data
Dedicated Study Visit	One of three required study visits: randomization, year 1, and year 2.
Enrollment	Randomization
Estimand	The estimate targeted to address the research question posed by the study objective, i.e., "what is to be estimated." [1] The estimand translates the study objective into a precise definition of the effect of treatment.
Healthcare Resource Utilization (HCRU)	Broad term encompassing use of healthcare services, including inpatient admissions, ER encounters, outpatient encounters including office visits, and pharmacy prescription fills.
Index Date	The date corresponding to an event of interest. In this study, index date is the date corresponding to a claims-based proxy for antidiabetic treatment intensification for 2 comparator populations, thus mimicking randomization date in the study population.
Principal Study Physician	Physician at study site who is responsible for the overall conduct and oversight of the study at their site, including: supervision of study personnel, monitoring the safety of all participating patients, ensuring the accurate and complete collection and reporting of study data,

[redacted]

	continued review of the IRB study approval, and maintenance of study records. This term is analogous to "Investigator" in Good Clinical Practice (GCP) requirements.
Randomization	The point at which a patient is assigned by chance to either semaglutide or standard of care (SOC).
Routine Diabetic Care Visit	An office visit or other patient contact during the study period that occurs outside of the dedicated study visits (randomization, year 1, and year 2) according to routine clinical practice.
Study Physician	Physician at study site who participates in the conduct of the study.
Study/Trial	For the purposes of this protocol, study and trial are considered synonyms. Study is used throughout the body of the text as it reflects the post-regulatory approval setting and real world design. Trial is used in the title and in referring to the PCT acronym to maintain consistency with the industry standard Pragmatic Clinical Trial or PCT.
Study Drug	Study drug is the first antidiabetic oral or injectable medication prescribed for treatment intensification following randomization. A patient can start and stop study drug throughout the study. At any time during the duration of the study, if a patient is taking study drug as defined, they will be considered "on study drug" regardless of prior study drug discontinuations. • For the semaglutide treatment group, study drug is defined as semaglutide. • For the SOC treatment group, study drug is defined as the drug class of the first antidiabetic oral or injectable medication prescribed for treatment intensification following randomization. If a fixed dose combination (FDC) product is prescribed, one of the drugs will be chosen by the study physician to be the study drug. A patient randomized to the SOC treatment group will still be considered "on study drug" if they are taking a drug in the same drug class as their first study drug, even if it is not the same individual drug. This also applies to treatment intensification with a FDC product if one of the drugs is in the same drug class as the first study drug.
Study Drug Discontinuations	Study drug discontinuation is termination of the study drug. A patient can start and stop study drug throughout the study; therefore a patient's study drug discontinuation status can change throughout the duration of the study. At any time during the duration of the study, if a patient is not taking study drug as defined, they will be considered "off study drug."

1 INTRODUCTION

1.1 Background and Rationale

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) position statement recommends a patient-centric approach to the selection of pharmacological treatment for type 2 diabetes mellitus (T2DM), including considerations on effectiveness, hypoglycemia risk, impact on body weight, side effects, costs, and patient preferences. [2] Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are recommended for the management of hyperglycemia in T2DM, primarily in combination with other antidiabetic medications. [2] [3]

Semaglutide, a human GLP-1 analogue for once-weekly subcutaneous administration, has been shown to improve glycemic control in adults with T2DM as monotherapy when the use of metformin is considered inappropriate, or as add-on to other glucose lowering therapies including insulin. In the *Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes* (SUSTAIN) clinical development program, semaglutide demonstrated clinically relevant and superior glycemic control, as well as weight loss versus placebo and active comparators, both when used as mono- and combination therapy in inadequately controlled patients with T2DM. In addition, a significant reduction in cardiovascular risk was demonstrated for semaglutide versus placebo in patients with T2DM at high risk of cardiovascular events. The overall safety profile of semaglutide was consistent with the well-established GLP-1 RA safety profile. [4]

Pragmatic clinical trials (PCTs) are designed and conducted to reflect patient outcomes and to investigate how a product is used and performs in routine clinical practice. This type of study compares two or more medical interventions that are directly relevant to clinical care and strives to assess those interventions' effectiveness in real world practice. They use broad eligibility criteria and recruit patients from a variety of practice settings to ensure the inclusion of the type of patients whose care will be influenced by the study´s results. Such studies are increasingly important to generate evidence regarding real world treatment outcomes to inform and support appropriate market access. [5]

The current local US study serves the purpose of evaluating the long term comparative effectiveness of semaglutide with existing commercially available antidiabetic medications in a real world population and in a variety of practice settings, thereby maximizing external validity while balancing the internal validity of a randomized controlled trial. This will generate data to complement the findings from the SUSTAIN clinical development program. Taken together, these findings may provide important evidence for decision making by clinicians, payers, and policy makers in routine clinical practice.

This local US study will enroll adult patients with T2DM who have inadequate glycemic control on up to 2 oral antidiabetic medications, as defined by the need for treatment intensification with an additional antidiabetic oral or injectable medication per the study physician´s discretion. The current study targets patients at this particular treatment point because they represent the

population inadequately controlled on the current ADA recommended first lines of treatment of T2DM. The addition of a GLP-1 RA as second-line treatment is in line with the ADA guidance from 2017. [6] In keeping with the ADA and EASD position statement recommending a patient-centric approach to treatment selection for T2DM patients, in addition to comparative effectiveness, this study will also evaluate hypoglycemia risk, body weight, healthcare resource utilization (HCRU), patient reported outcomes (PROs), and clinician reported outcomes (ClinROs). Adverse events (AEs) leading to study drug discontinuation will also be collected. [2]

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to demonstrate superior long term effects of treatment with semaglutide compared to standard of care (SOC) both added to up to 2 oral antidiabetic medications on glycemic control when used as intensification in routine clinical practice in adult patients with T2DM.

2.2 Secondary Objectives

The secondary objectives are to compare the long term effect of semaglutide versus SOC both added to up to 2 oral antidiabetic medications and used as intensification in routine clinical practice in adult patients with T2DM with regards to:

- Weight loss
- Patient reported outcomes (PROs) and clinician reported outcomes (ClinROs)
- Hypoglycemia
- Healthcare Resource Utilization (HCRU)
- Adherence and persistence to treatment

3 STUDY ENDPOINTS

3.1 Baseline

Baseline is defined as ≤ 90 days prior to randomization visit (week 0) for glycosylated hemoglobin A1c (HbA1c). For secondary endpoint assessments, baseline is defined as ≤ 4 weeks prior to the randomization visit (week 0).

3.2 Primary Endpoint

Primary completion date (PCD) is the date the last patient completes the year 1 dedicated study visit.

[redacted]

The primary endpoint of this study is:

- HbA1c <7.0% (53 mmol/mol) at year 1 (yes/no)

3.3 Secondary Endpoints

3.3.1 Confirmatory Secondary Endpoints

Confirmatory secondary endpoints of this study include:

- Change in HbA1c (%-point) from baseline to year 1
- HbA1c <7.0% (53 mmol/mol) at year 2 (yes/no)
- Change in HbA1c (%-point) from baseline to year 2

3.3.2 Supportive Secondary Endpoints

Supportive secondary endpoints of this study include:

- Individualized HbA1c target attained at year 1 (yes/no)
- HbA1c <7.0% (53mmol/mol) or at least 1% point improvement in HbA1c compared to baseline at year 1 (yes/no)
- HbA1c target attainment per Healthcare Effectiveness Data and Information Set (HEDIS) criteria (<8.0% if age ≥65 years or with defined comorbidities, otherwise <7.0%) at year 1 (yes/no)
- Change in body weight (lb) from baseline to year 1
- Change in body weight (%) from baseline to year 1
- Change in systolic blood pressure (SBP; mm Hg) from baseline to year 1
- Change in diastolic blood pressure (DBP; mm Hg) from baseline to year 1
- Time to first study drug discontinuation during 2 years (day)
- Time to first treatment intensification (add-on) or change (switch) after randomization during 2 years (day)
- Study drug medication adherence for the first year of the study, as measured by medication possession ratio (MPR) (%)
- Number of hypoglycemic episodes leading to an inpatient admission or emergency room (ER) encounter from baseline to year 2
- Diabetes Treatment Satisfaction Questionnaire, change version (DTSQc), Total treatment satisfaction score measured at year 1
- DTSQc, Total treatment satisfaction score measured at year 2

- Change from baseline in Short Form 12-Item Version 2 Survey (SF-12 v2), Physical summary component (PCS-12) score at year 1
- Change from baseline in SF-12 v2, PCS-12 score at year 2
- Change from baseline in SF-12 v2, Mental summary component (MCS-12) score at year 1
- Change from baseline in SF-12 v2, MCS-12 score at year 2
- Change from baseline in Work Productivity and Activity Impairment, General Health questionnaire (WPAI-GH) Absenteeism (work time missed) score at year 1
- Change from baseline in WPAI-GH Absenteeism (work time missed) score at year 2
- Change from baseline in WPAI-GH Presenteeism (impairment at work / reduced on-the-job effectiveness) score at year 1
- Change from baseline in WPAI-GH Presenteeism (impairment at 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
- Change from baseline in WPAI-GH Work productivity loss (overall work impairment / absenteeism plus presenteeism) score at year 2
- Change from baseline in WPAI-GH Activity Impairment score at year 1
- Change from baseline in WPAI-GH Activity Impairment score at year 2

All cause healthcare resource utilization (HCRU) from baseline to year 2:

- Number of inpatient admissions
- Cumulative length of stay for inpatient admissions (days)
- Number of ER encounters
- Number of outpatient encounters
- Number of medications
- Occurrence of inpatient admission (yes/no)
- Occurrence of ER encounter (yes/no)
- Occurrence of outpatient encounter (yes/no)

Diabetes related HCRU from baseline to year 2:

- Number of diabetes related inpatient admissions

[redacted]

- Cumulative length of stay for diabetes related inpatient admissions (days)
- Number of diabetes related ER encounters
- Number of diabetes related outpatient encounters
- Number of diabetes related medications
- Occurrence of diabetes related inpatient admission (yes/no)
- Occurrence of diabetes related ER encounter (yes/no)
- Occurrence of diabetes related outpatient encounter (yes/no)

3.3.3 Exploratory Endpoints

Not applicable.

4 STUDY DESIGN

4.1 Overview

This is a 2-year, multi-center, randomized, open label, parallel group, active comparator PCT comparing semaglutide versus SOC when added to up to 2 oral antidiabetic medications as treatment intensification among adult T2DM patients in the course of routine clinical practice. Patients will be randomized 1:1 to receive either semaglutide or SOC.

The decision that further antidiabetic treatment intensification with an additional oral or injectable antidiabetic medication is indicated is at the discretion of the study physician and will be made prior to and independent of enrollment in this study. The study physician will have determined the patient's suitability for treatment with semaglutide prior to inviting them to participate in the study. However, the determination to initiate semaglutide versus SOC will be made by randomization.

Patients will be followed for 2 years, regardless of changes in antidiabetic treatment over the course of the study. Data collection will continue for the full 2 year study period unless a patient withdraws informed consent. Patients who enroll in the study agree to the release of health information, and to answer questions about their health during the course of the study. Additionally, medical and pharmacy claims data will be extracted for the 2 year study period, as well as up to 12 months prior to randomization as available.

In keeping with the study objectives and pragmatic design to evaluate semaglutide versus SOC in real world, routine clinical practice, inclusion and exclusion criteria are minimally restrictive and there are few study-specific evaluations. Study physicians will follow and treat patients according to their routine clinical practice and judgement. All oral and injectable antidiabetic medications are allowed at the study physicians' discretion, with the exception of semaglutide in the SOC group. It is anticipated that patients will undergo medical evaluation at regular intervals

over the course of the study duration as per standard of care, but the only dedicated study visits are at randomization, at year 1, and at year 2. The study will also capture clinical data collected at the sites during routine diabetic care visits, i.e., office visits and other patient contacts that occur as part of routine clinical practice. Assessments will be conducted according to the study physician's routine clinical practice, with a few study-specific assessments as described in section 5. The data available may differ from site to site and patient to patient. To ensure flexibility, the dedicated year 1 and year 2 study visits have a window of ±6 weeks.

4.2 Practice and Patient Selection

The target population for this study consists of adult T2DM patients on up to 2 oral antidiabetic medications who are in need of treatment intensification with an additional antidiabetic oral or injectable medication. To support study objectives, including claims analysis of HCRU, eligible patients will also be currently insured through a commercial health plan or Medicare with pharmacy benefits.

Study site recruitment will target both primary care practitioners and specialized endocrinologists to reflect diverse treatment settings and patient populations. Potential sites will be evaluated regarding feasibility of their participation in the study, including having a T2DM population to meet enrollment goals. Potential sites will be tiered based on their estimated number of eligible study patients, and outreach will begin with all sites that meet a pre-determined minimum number of potentially eligible patients. Outreach and follow-up will be performed until the requisite number of physician sites is enrolled. Study-specific assessments have been kept to a minimum, thereby decreasing burden on study sites and increasing participation to a wide range of sites.

4.2.1 Physician Practices

Participation of approximately 200 physician sites in the US, including both general practitioners and endocrinologists, is anticipated.

4.2.2 Patient Recruitment and Eligibility

Eligible patients include adult T2DM patients whose physicians determine that they have inadequate glycemic control on 1 or 2 oral antidiabetic medications. Inadequate glycemic control is defined by the need for T2DM treatment intensification with an additional antidiabetic oral or injectable medication, as determined by the study physician. Patients must also meet all of the inclusion criteria (section 4.2.3) and none of the exclusion criteria (section 4.2.4). Inclusion and exclusion criteria are minimally restrictive to ensure a broad population of adult T2DM patients to generate data in a population that reflects the heterogeneity of a real world population treated in general practice, and support the study objectives to evaluate semaglutide versus SOC in real world, routine clinical practice.

4.2.3 Patient Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for the study:

[redacted]

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study.
2. Male or female, age ≥ 18 years at the time of signing informed consent.
3. Type 2 diabetes mellitus diagnosis.
4. Treatment with either 1 or 2 oral antidiabetic medications.
5. Current member of a commercial or Medicare health plan with pharmacy benefits.
6. Recorded HbAlc value within last 90 days prior to randomization.
7. Further intensification with an additional antidiabetic oral or injectable medication is indicated to achieve glycemic target at the discretion of the study physician according to approved labelling.

4.2.4 Patient Exclusion Criteria

Patients presenting with any of the following exclusion criteria will not be eligible for the study:

1. Previous randomization in this study.
2. Treatment with more than 2 oral antidiabetic medications or any injectable antidiabetic medication in a period of 30 days before the day of eligibility assessment. Temporary/emergency use of any type of insulin is allowed, as is prior insulin treatment for gestational diabetes.
3. Contraindications to semaglutide according to the FDA approved label.
4. Female who is pregnant, breastfeeding or intends to become pregnant.
5. Participation in another clinical trial.

4.2.5 Patient Enrollment

Planned number of patients to be randomized: 1387

Expected number of patients to complete the study after 52 weeks: 1040

Expected number of patients to complete the study after 104 weeks: 780

4.2.6 Patient Randomization

Study patients will be randomized to either semaglutide or SOC in a 1:1 ratio. The study design and patient randomization is depicted in Figure 1.

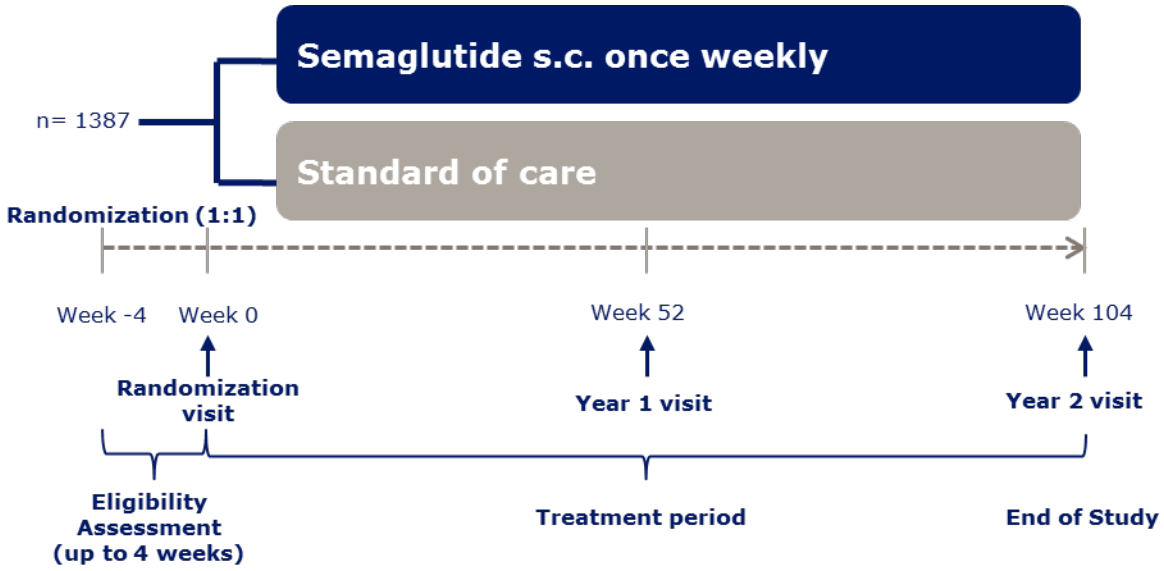

Figure 1 Study design diagram. Patients will be randomized in a 1:1 manner using centralized allocation to receive semaglutide or SOC as add-on to up to 2 oral antidiabetic medications.

5 STUDY PROCEDURES

The study visit schedule is summarized in Appendix 1.

5.1 Enrollment Procedures

The determination that a patient has inadequate glycemic control on up to 2 oral antidiabetic medications, and the subsequent decision to intensify antidiabetic treatment with an additional oral or injectable antidiabetic medication, will be made by the study physician during the course of routine clinical practice. Following the decision to initiate treatment intensification, the study physician will determine the patient's suitability for the study. Suitability for the study will be assessed using the current inclusion and exclusion criteria, including the approved label for semaglutide. Only patients who are eligible for treatment intensification and have been found suitable for treatment with semaglutide, as determined by the study physician, are in scope for randomization. Prior to being randomized, patients must be willing to intensify with an antidiabetic medication, including GLP-1 receptor agonists. Study physicians will set and document an individualized HbA1c target for patients prior to randomization based on their clinical judgement and knowledge of the patient. To preserve the real-world nature of the study, patients will be approached for potential enrollment into the study through their physician if review of their medical history indicates that they may be eligible for the study. Outreach may occur when patients present to their physician as part of their standard care or through proactive contact of potentially eligible patients identified within the study physician's practice.

Informed consent will be obtained prior to any study related activities. The most recent HbA1c completed in the course of routine care up to 90 days prior to and including the date of randomization will be considered a baseline assessment and does not need to be repeated.

[redacted]

Study physicians or site personnel will collect patient characteristics and study data at each study visit as outlined in the Time and Events Schedule (Appendix 1), either directly from the patient or abstracted from the patient's medical records, and enter them into the electronic Case Report Form (eCRF).

5.2 Randomization Visit

Following informed consent and confirmation of inclusion/exclusion criteria, patients will be randomized to either semaglutide or SOC. Data collection at the randomization visit will include inclusion/exclusion criteria as well as the data outlined in the sections below. PRO and ClinRO questionnaires will also be administered (section 5.3).

5.2.1 Patient Characteristics

Baseline assessments at the randomization visit will include: demographic data, medical history, diabetes history including antidiabetic medications and diabetes complications, pre-specified concomitant medications related to cardiovascular risk, and clinical data (weight, height, HbA1c, SBP, DBP). Individualized HbA1c target will be set prior to randomization. The baseline HbA1c will be the patient's most recent HbA1c within 90 days of randomization.

5.2.2 Treatments

To preserve the real-world nature of the study, the patient experience will be as close to routine care as possible. The study physician will be one of the patient's own treating physicians, who may make treatment adjustments according to their clinical judgement. The study physician can make repeat prescriptions of the study drug as usual, which are collected by patients from the pharmacy of their choice. Patients will be randomized to either semaglutide or SOC. Treatment details will be recorded in the eCRF.

Semaglutide Group

Patients randomized to the semaglutide group will be prescribed commercially available semaglutide in a prefilled pen injector and will be instructed to initiate treatment with semaglutide according to the approved label. The study physician will determine the intended maintenance dose of semaglutide, as well as changes to the maintenance dose thereafter. Add-on, discontinuation or dose modification of antidiabetic medication, including semaglutide, during the study is allowed at the discretion of the study physician.

> *Semaglutide Study Drug*: For patients randomized to the semaglutide group, study drug is defined as semaglutide.

SOC Group

SOC is defined as commercially available oral or injectable antidiabetic medication (see current representative list below) other than semaglutide. Patients randomized to SOC will be prescribed and instructed to initiate commercially available antidiabetic medication according to the approved label and, if relevant for the specific antidiabetic medication, adjusted at the discretion

of the study physician. Patients randomized to SOC may discontinue SOC, add-on to the SOC or switch to another antidiabetic medication during the study, with the exception of semaglutide which is not allowed in the SOC group for the duration of the study.

> *SOC Study Drug*: For patients randomized to the SOC group, study drug is defined as the drug class of the first antidiabetic oral or injectable medication prescribed for treatment intensification following randomization. If a fixed dose combination (FDC) product is prescribed, one of the drugs will be chosen by the study physician to be the study drug. A patient randomized to the SOC treatment group will still be considered "on study drug" if they are taking a drug in the same class as their first study drug, even if it is not the same individual drug. This also applies to treatment intensification with a FDC product if one of the drugs is in the same class as the first study drug.

Study Drug: Start/Stop, Discontinuations

Study drug discontinuation is termination of the study drug. A patient can stop or start study drug throughout the study; therefore a patient's study drug discontinuation status can change throughout the duration of the study. At any time during the duration of the study, if a patient is not taking study drug as defined, they will be considered "off study drug." Conversely, at any time during the duration of the study, if a patient is taking study drug as defined, they will be considered "on study drug," regardless of prior study drug discontinuations.

If a participating patient becomes pregnant, the study physician will review the patient's antidiabetic treatment regimen and make any changes necessary according to standard care of patients with T2DM during pregnancy. Semaglutide will be discontinued and will not be restarted unless the patient is no longer pregnant or breast-feeding. All study drug copay assistance will end.

Copay assistance

The study products will be handled and dispensed by the patients' pharmacy(s) per their preference and health plan benefits. In order to minimize the impact of any differential in out-of-pocket costs between the treatment groups, an out-of-pocket maximum will be provided by Novo Nordisk as part of the study. In both treatment groups, the patient's copay will be up to the specified maximum for the study drug (as defined above) and ancillary needles (if required to administer the study drug). Copay assistance will only apply to the study drug as defined above (i.e., not to any subsequent add-on treatment or treatment changes outside the study drug definition). Because patients can start and stop study drug throughout the study, copay assistance may also start and stop throughout the study. For the duration of the study, any time a patient is "on study drug" they will receive copay assistance, and any time a patient is "off study drug" they will not receive copay assistance. The only exceptions are if a patient initiates prescription coverage through Medicaid, at which point all copay assistance will end.

[redacted]

Products

A current representative list of the products used in this study is below. All treatments will be used in accordance with local clinical practice and guidelines. Products with more than one active substance i.e., FDC products, can be used in this study.

Semaglutide: Semaglutide in a prefilled pen (Ozempic®)

Oral antidiabetic drugs: The oral antidiabetic drug classes included in this study are the commercially available options (listed in alphabetic order):

- Alpha-glucosidase inhibitors
- Dipeptidyl peptidase 4 (DPP-4) inhibitors
- Meglitinides
- Metformin
- Sodium-glucose co-transporter 2 (SGLT-2) inhibitors
- Sulfonylureas
- Thiazolidinediones
- Other
    - Bromocriptine
    - Colesevelam

Injectable antidiabetic drugs: The injectable antidiabetic drug classes included in this study are the commercially available options (listed in alphabetic order):

- GLP-1 RAs
- Basal Insulin
    - Long acting insulin
    - Intermediate acting insulin including premix
- Prandial Insulin
    - Short acting insulin
    - Rapid acting insulin
- Other
    - Pramlintide

Background medication: The (up to 2) oral antidiabetic medication(s) taken prior to randomization and treatment intensification is considered background medication. Patients may discontinue background medication at any time during the study. Patients may change the pre-

study dose and frequency of background medication at any time during the study. Background medication will not be provided nor reimbursed by Novo Nordisk.

5.3 Patient Reported Outcomes, Clinician Reported Outcomes, and Diabetes Treatment Satisfaction

Diabetes treatment satisfaction, generic health-related quality of life (HRQoL), work productivity, and patient and clinician global assessments will be assessed by the following instruments at randomization, year 1, and year 2. Patients will self-administer these instruments on paper. Site study personnel will review for completeness and enter responses into the eCRF.

5.3.1 PRO and Treatment Satisfaction questionnaires

5.3.1.1 Diabetes Treatment Satisfaction Questionnaire (DTSQ) [7] [8] [9] [10]

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) evaluates patient satisfaction with treatment. The DTSQ status version (DTSQs) will be completed at the randomization visit and the DTSQ change version (DTSQc) will be completed at the year 1 and year 2 dedicated study visits.

5.3.1.2 Short Form 12-Item version 2 (SF-12 v2) Health Survey [11]

The SF-12 v2 is a generic HRQoL questionnaire that assesses physical and mental functioning and overall HRQoL. The SF-12v2 standard 4-week recall period questionnaire will be completed at the randomization, year 1, and year 2 dedicated study visits.

5.3.1.3 Work Productivity and Activity Impairment: General Health (WPAI-GH) Questionnaire [12]

The WPAI-GH questionnaire assesses both absenteeism (i.e., work time missed) and presenteeism (i.e., impairment at work or reduced on-the-job effectiveness) as well as daily activity impairment (e.g., work around the house, shopping, exercising, childcare, studying) attributable to general health. The WPAI-GH will be administered at the randomization, year 1, and year 2 dedicated study visits.

5.3.1.4 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, i.e., normal, mild, moderate, or severe, whereas 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, i.e., very much better, much better, a little better, no change, a little worse, much worse, or very much worse. The PGI-S will be administered at the randomization visit and the PGI-C will be administered at the year 1 and year 2 dedicated study visits.

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

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 symptoms, i.e., normal, mild, moderate, or severe, whereas 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, i.e., very much better, much better, a little better, no change, a little worse, much worse, or very much worse. The study physician will complete the CGI-S at the randomization visit and the CGI-C at the year 1 and year 2 dedicated study visits.

5.4 Study Period

Patients will be followed from randomization to end of study (EOS) at 2 years, during which study physicians or trained site personnel will collect study data and record it in the eCRF at dedicated study visits (randomization, year 1, year 2) and routine diabetic care visits. Patients will be followed for the full 2 year study period regardless of treatment changes or discontinuation during the study period, other than withdrawal of consent. If a patient leaves their health plan during the 2 year study period, administrative claims data will be collected from randomization through the date they leave the health plan. If the patient switches to another health plan during the 2-year study period, an attempt may be made to collect administrative claims data from that plan as well. In these scenarios, site-based study data collection will continue without change.

On-study data collection at dedicated study visits and routine diabetic care visits (if available per local clinical practice) will include: clinical data (weight, HbA1c, SBP, DBP), treatment details (study drug, other antidiabetic medication, pre-specified concomitant medications related to cardiovascular risk, reasons for treatment discontinuation as applicable), hypoglycemia leading to inpatient admission or ER encounter, AEs leading to study drug discontinuation, pregnancy, and serious adverse events (SAEs). Of note, AEs leading to study drug discontinuation or SAEs will be collected from all interactions with the patient, as well as if discovered when reviewing documents from healthcare encounters with other providers. Additionally, PRO and ClinRO instruments will be completed at randomization, year 1, and year 2.

EOS visit is 2 years (±6 weeks) after randomization.

5.5 Administrative Claims Data

In addition to prospectively collected clinical data and PROs, this study will also utilize claims data from the HealthCore Integrated Research Database (HIRD[SM]) for [redacted] patients or requested, via patient written authorization, from a set of other health insurers for non-[redacted] patients. Data collected will include integrated medical claims, pharmacy claims, and health plan eligibility files for the 2 years after the respective patient's study randomization. Final extraction of this data will take place approximately 3 months after the last patient's last visit (LPLV) to

[redacted]

allow for data lags in the claims. Administrative claims data will also be collected for up to 12 months prior to study randomization, if available. The prospectively collected eCRF study data and claims data will be merged into one dataset via a study-specific patient identifier (ID) for analysis.

5.6 Withdrawals

5.6.1 Physician Practices

Novo Nordisk and/or the Institutional Review Board (IRB) reserve the right to terminate the study any time. In this event, all data collection will end. After the collected data is received, study physicians will be compensated as contractually agreed.

The IRB reserves the right to terminate participation of individual study sites at any time. Individual study sites may also be terminated for cause by Novo Nordisk per contractual agreement. In such cases, all data collection at terminated study sites will end. After the collected data is received, the study physicians will be compensated as contractually agreed.

5.6.2 Patients

Participation in the study is voluntary, and all patients are free to terminate their participation at any time. A patient will only be withdrawn from the study if they withdraw consent. In the event of study withdrawal, the study physician will record the reason for study withdrawal and continue to follow-up with the patient for any unresolved SAEs or pregnancies, if patient agrees. Upon patient withdrawal from the study, all data collection will end, but all study data collected up to withdrawal will be included in the study database. If a patient has not been in contact with the Prescribing Physician by the end of the 2 year study duration period and the site is not able to reach the patient after 3 contact attempts, the patient can be considered Lost To Follow-Up (LTFU). One of the 3 contact attempts should include a certified letter being sent to the patient. If a patient's status is determined to be LTFU, this must be recorded on the End of Study eCRF.

6 STATISTICAL METHODS

6.1 Introduction

Patients are randomized 1:1 to semaglutide or SOC. The data analyses for this study will be outlined in further detail in a Statistical Analysis Plan (SAP) developed prior to database lock at year 1.

For continuous endpoints and categorical endpoints derived from continuous sources, the baseline value is defined as the last assessment taken prior to or at the randomization visit *and* before first use of study drug.

If endpoint data is missing then any routine care data that are collected within ±10 weeks of the dedicated study visit will be used.

[redacted]

The significance level used in all statistical analyses will be 5% (two-sided).

6.1.1 Estimands

Two estimands, each targeting a unique research question, have been defined to adequately describe the effect of semaglutide as compared to SOC (excluding semaglutide).

The primary estimand for all objectives will be the "intention-to-treat" (ITT) estimand evaluating the effectiveness of randomized treatment intervention irrespective of adherence to this randomized intervention or changes to other antidiabetic medication during follow-up. The purpose of this estimand is to quantify the expected effect size in the commercially-insured health plan population upon adoption of semaglutide as compared SOC (excluding semaglutide), and is as such relevant to inform and support appropriate market access and population based treatment guidance.

The secondary estimand for all objectives with the exception of the adherence and persistence to treatment objective, is the "if all patients had adhered" estimand. This estimand evaluates the effect of randomized treatment intervention for all randomized patients if all patients had adhered to randomized treatment, regardless of changes to other (i.e., non-study drug) antidiabetic medication. The purpose of this estimand lies in quantifying the expected effect size for an individual patient in the commercially-insured health plan population who is prescribed, initiates, and continues treatment with semaglutide as compared to SOC (excluding semaglutide). The relevance of this effect measure is to inform decision making for individual patients and prescribing physicians.

6.1.2 Confirmatory Endpoints and Hypotheses

The primary endpoint is HbA1c <7.0% (53 mmol/mol) at year 1 (yes/no). This is a binary endpoint. Confirmatory secondary endpoints include:

- Change in HbA1c (%-point) from baseline to year 1
- HbA1c <7.0% (53 mmol/mol) at year 2 (yes/no)
- Change in HbA1c (%-point) from baseline to year 2

The primary and confirmatory endpoints will all be tested for superiority under multiplicity control via a hierarchical testing scheme according to the order given in the above bullet list. Confirmatory testing will only be performed for the primary estimand with the secondary estimand being supportive. The testing procedure will be stopped the first time an analysis fails to confirm superiority of the endpoint in question using a two-sided significance level of 5%.

Superiority on HbA1c <7.0% will be evaluated with respect to the odds ratio (OR) (odds semaglutide / odds SOC):

$$H_0: OR \leq 1 \text{ against } H_a: OR > 1$$

[redacted]

Superiority on change in HbA1c (year 1 – baseline; year 2 – baseline) will be evaluated with respect to the mean treatment difference (TD) (semaglutide – SOC):

$$H_0: TD \geq 0 \text{ against } H_a: TD < 0$$

6.1.3 Study Populations

The following analysis set will be defined:

Full analysis set (FAS): Includes all randomized patients analyzed according to the treatment group to which they were assigned at randomization.

6.2 Sample Size Determination

6.2.1 Power and Sample Size for Primary Objective

Assumptions for the sample size were based on input from the HIRD claims/laboratory results database. In line with the primary ITT estimand, the assumptions for the proportion of patients with HbA1c < 7.0% at year 1 and year 2, and for the change from baseline in HbA1c, were based on the claims/laboratory results data within the [redacted] population for all patients initiating treatment intensification, regardless of whether patients adhered to this treatment. Specifically, for semaglutide, assumptions were based on data for liraglutide and dulaglutide. For SOC, assumptions were based on all intensifications in the claims database. The study sample size of 1,387 was calculated based on the following assumptions, informed from HIRD data: 10% difference in proportion patients with HbA1c < 7.0% at year 1 and year 2 (60% semaglutide versus 50% SOC), absolute difference in change from baseline HbA1c of 0.5%-point (SD=2.3%) between treatment groups, 90% power for confirming superiority of the primary endpoint, and an overall alpha leve1 of 5%. Sample size calculations, including different sample size scenarios and a summary of the data from the HIRD, will be documented in the SAP.

The proportion of missing data for the confirmatory endpoints was estimated to be 25% after one year and 44% after two years. In the sample size calculation, it was assumed that only non-missing data at year 1 and year 2 would be used for the respective analyses. This is considered conservative, since the use of imputed data in the actual primary analysis (see 6.3) will increase the power. When accounting for missing data, randomizing 1387 patients will contribute 1040 patients for the year 1 analyses and 780 patients for the year 2 analyses, achieving a total power of 85% for confirming the two year 1 confirmatory hypotheses. The joint power for confirming all 4 confirmatory hypotheses is 58%. The corresponding marginal powers for presence of HbA1c < 7.0% at year 1, change in HbA1c to 1 year, presence of HbA1c < 7.0% at year 2, and change in HbA1c to 2 years are 90%, 94%, 80%, and 86% respectively.

6.3 Statistical Analysis for the Primary Estimand

The primary estimand will be estimated based on the FAS using data from all patients with observations at the dedicated study visit (year 1 for the primary endpoint), with the exception of patients who, in violation of the protocol, have initiated semaglutide in the SOC treatment group.

The data collected following initiation of semaglutide from these patients will be censored and imputed together with missing data. The primary endpoint, HbA1c < 7.0%, will be analyzed with a logistic regression model with a logit link function, treatment as a categorical effect, and baseline HbA1c as covariate. From the model, the estimated OR (semaglutide versus SOC) will be presented. The underlying continuous endpoint of change in HbA1c will be analyzed using analysis of covariance (ANCOVA) that will include the same independent variables. From the model, the estimated mean difference in change from baseline to dedicated study visit (semaglutide versus SOC) will be presented. The estimated treatment effect from each of these analyses will be complemented with associated 95% confidence interval (CI) and two-sided p-value for testing the null-hypothesis of no difference.

Prior to analysis, missing data will be imputed by multiple imputation on the continuous HbA1c scale and subsequently dichotomized for the primary endpoint. 500 complete data sets will be generated to adequately account for the uncertainty due to missing data. Missing endpoint data will be imputed separately by treatment group and based on patients who remained in the study according to study drug treatment status, i.e., according to whether these patients are on or off study drug at the dedicated study visit. Data will be imputed based on the assumption that, within treatment groups, patients with missing endpoint data will behave like patients with the same study drug treatment status at endpoint as the missing patients' last registered treatment status prior to the missing endpoint. For example, for patients withdrawing from the study with an "off study drug" treatment status, data will be imputed based on the assumption that the withdrawn patients will behave like patients who remain in the study but are not receiving study drug at the dedicated study visit. Technically, the imputation model will be an ANCOVA for the endpoint data. The ANCOVA will include baseline HbA1c, diabetes duration, age, and sex as independent variables. After this model has been used to predict missing values, each of the now 500 complete data sets will be analyzed as described above. Finally, the multiple analysis results will be combined using Rubin's rule. [13] For the OR the results will be combined on the logarithm scale.

Superiority for the primary endpoint, HbA1c <7.0% at year 1, will be considered established if the OR 95% CI is greater than 1, or similarly if the two-sided p-value is significant on a 5% level and the treatment OR is in favor of semaglutide.

If the hierarchical testing scheme allows, superiority for change from baseline to dedicated study visit in HbA1c will be considered established if the 95% CI for the estimated treatment difference is smaller than 0, or similarly if the two-sided p-value is significant on a 5% level and the treatment difference is in favor of semaglutide.

6.4 Statistical Analysis for the Secondary Estimand

The secondary estimand will be estimated based on the FAS. The analysis is similar to the primary analysis for the primary endpoint, but varies with regards to the data used and the imputation of missing data. Specifically, data will only be used from the subset of patients who

[redacted]

are receiving study drug at the dedicated study visit (year 1 for the primary endpoint), in order to estimate the treatment effect if all patients had continued treatment. Patients who no longer are receiving study drug will be censored and imputed together with missing data. The same will apply to patients who, in violation of the protocol, have initiated semaglutide in the SOC group. Collectively, missing and censored data will be imputed separately by treatment group based on all patients who are on study drug at the dedicated study visit. Data will be imputed based on the assumption that withdrawn or censored patients behave like patients that remain in the study and continue on study drug.

The technical aspects of missing data imputation based on multiple imputation, the statistical analysis of the multiple complete data sets, and combination of the multiple results will be the same as that described for the primary estimand.

6.5 Supplementary Analyses

The HbA1c analyses described for the two estimands above will be complemented with two complete case analyses based on the subset of patients without missing endpoint data, i.e., patients that do not have their endpoint imputed in the two analyses used for the primary and secondary estimand.

Complete case analysis

This analysis will be based only on patients with available measurements at the dedicated study visit including measurements irrespective of whether patients discontinued study drug or not. The analysis will use the same analysis model as described under the primary estimand.

Complete case on-study drug analysis

The analysis will be based only on patients with available measurements at the dedicated study visit including only measurements for patients still on study drug. The analysis will use the same analysis model as described under the primary estimand.

6.6 PRO Analysis

PRO and physician assessments will be measured with the instruments described in Section 5.3. Analysis of these measures will address the secondary objective of this study to compare semaglutide versus SOC in the study's patient population as is relates to PRO, i.e., treatment satisfaction, generic health outcomes, work productivity, and patient and physician global assessment measures, over one and two year observation periods. PRO analysis will descriptively summarize these measures at baseline, year 1, and year 2, as well as compare semaglutide versus SOC for change from baseline to year 1 and year 2. The continuous change from baseline endpoints will be analyzed using the same analysis approach as described under the complete case and complete case on-study drug analyses in Section 6.5. Details will be fully described in the SAP.

6.7 Safety Analysis

SAEs and AEs will be collected as described in Section 7. No formal safety analyses are planned for this study. SAEs, AEs leading to study drug discontinuation, and pregnancies will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and descriptively summarized by System Organ Class and Preferred Term (PT).

6.8 Other Analyses

The following analyses are planned to further support the primary objective to compare semaglutide versus SOC in glycemic control. They will also address the secondary objectives of this study to compare semaglutide versus SOC in the study's patient population over one and two year observation periods as is relates to body weight loss, hypoglycemia, HCRU, and adherence and persistence to treatment. The binary and continuous endpoints that include HbA1c, weight, SBP, or DBP data will be analyzed using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections. All other endpoints will be analyzed using the same analysis approach as described under the complete case and complete case on-study drug analyses in Section 6.5. Further details of these analyses and details for analyses of other endpoint types will be fully described in the SAP.

6.8.1 Supportive Analyses of Glycemic Control

The proportion of patients achieving the secondary endpoints related to glycemic control at year 1 as defined in section 3.3.2 (individualized HbA1c target, HbA1c <7.0% (53mmol/mol) or at least 1% point improvement in HbA1c from baseline, HbA1c target attainment per HEDIS criteria) will be compared between semaglutide and SOC treatment groups using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections.

Additionally, derived outcome variables for supportive measures of glycemic control (Appendix 2) will be utilized to support these analyses.

6.8.2 Weight Loss

Change in patient weight from baseline to year one will be calculated in pounds and percentage as defined in section 3.3.2. Mean change in weight will be compared between semaglutide and SOC treatment groups using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections.

Additionally, derived outcome variables for supportive measures of body weight loss (Appendix 2) will be utilized to support these analyses.

6.8.3 Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP)

Change in patient SBP and DBP from baseline to year 1 and baseline to year 2 will be calculated as defined in section 3.3.2 and Appendix 2. Mean change in SBP and DBP will be compared

between semaglutide and SOC treatment groups using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections.

6.8.4 Hypoglycemia

The number of hypoglycemic episodes leading to an inpatient admission or ER encounter will be reported by patients and compared by semaglutide and SOC treatment groups utilizing a negative binomial model.

Additionally, derived outcome variables for supportive measures of hypoglycemia (Appendix 2) will be utilized to support these analyses.

6.8.5 Healthcare Resource Utilization (HCRU)

HCRU analyses will compare all-cause and diabetes-related HCRU (inpatient admissions, ER encounters, outpatient encounters, and pharmacy utilization) as defined in section 3.3.2 from claims data by semaglutide and SOC treatment group from baseline to year 2.

The details of claims data definitions and calculations will be fully described in the SAP.

6.8.6 Adherence and Persistence to Treatment

Adherence and persistence to the study drug will be calculated and compared between semaglutide and SOC treatment groups.

Medication adherence refers to a patient's conformance to the provider's recommendation with respect to timing, dosage, and frequency of medication taken during the prescribed length of time. In claims, adherence is typically measured using either medication possession ratio (MPR) or proportion of days covered (PDC).

Medication persistence refers to whether a patient stays on therapy or the time from initiation to discontinuation of therapy. In claims, persistence is typically defined as the duration of time from initiation of the therapy to discontinuation or switching, whichever comes first.

Adherence and persistence will be further defined in the SAP.

6.8.7 Antidiabetic Treatment Patterns

Antidiabetic treatment patterns will be assessed and compared between semaglutide and SOC treatment groups. This analysis will summarize the number and classification type of antidiabetic medications taken during the study period.

6.8.8 Exploratory Predictive Analysis

An exploratory predictive analysis will be performed within and between the semaglutide and SOC treatment groups to identify predictors of treatment adherence and persistence and glycemic control. The objectives of the exploratory predictive analyses are to identify within and between treatment groups: 1) patients less likely to discontinue treatment and 2) patients more likely to reach clinical target.

[redacted]

6.8.9 Evaluation of the Study Population

To evaluate the generalizability of the study results, an analysis of the study population will be performed. The primary objective of this analysis is to evaluate the external validity of the study and to understand how the study population fits into the larger T2DM populations within study sites and a commercially-insured population as a whole. Two claims-based T2DM patient populations will be described and compared to the study population: (1) commercially-insured and Medicare Advantage [redacted] T2DM patients treated with up to 2 oral antidiabetic medications who undergo an antidiabetic treatment intensification, and (2) within the study sites, commercially-insured and Medicare Advantage [redacted] T2DM patients treated with up to 2 oral antidiabetic medications who are not enrolled in the study, but who undergo an antidiabetic treatment intensification. The analysis will compare the demographics, HCRU, and HbA1c between the study population and the two comparator populations during the 12 month period prior to randomization (for study population) or prior to a claims-based proxy for antidiabetic treatment intensification index date (for comparators). Additionally, treatment patterns of non-enrolled T2DM patients within the practices from which the study patients are recruited will be evaluated to identify any relevant patterns of care suggesting channeling of certain types to patients away from the study. These analyses will help to contextualize study results within the T2DM population broadly.

The details of this analysis will be fully described in the SAP.

7 Adverse Event Collection

The principal study physician is responsible for monitoring the safety of participating patients. All SAEs reported by the patients during the study observational period are required to be documented on the appropriate SAE reporting form. For the purposes of this study, AEs that do not meet the definition of SAE will only be collected if they lead to study drug discontinuation.

7.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product or medical device, which does not necessarily have to have a causal relationship to the product of device. Study physicians will follow AEs that occur in any patient during this study in a manner consistent with routine clinical practice. For the purposes of this study, AEs that do not meet the definition of an SAE (section 7.2) will only be collected in the eCRF if they lead to study drug discontinuation.

7.2 Serious Adverse Events

All AEs meeting the definition of SAE will be collected in the eCRF. SAEs will be reported from the time a patient is randomized until EOS at year 2, or until the patient withdraws from the study. An SAE is defined as any AE which results in at least one of the following outcomes:

- Initial inpatient admission or prolongation of existing inpatient admission
- A life-threatening event, i.e., an event in which the patient was at immediate risk of dying at the time of the event; not an event that hypothetically could have caused death had it been more severe
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect in offspring
- Death
- Is deemed serious for any other reason, i.e., if it is an important medical event based on appropriate medical judgement which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other listed outcomes.

7.2.1 Collection Period of Serious Adverse Events

SAEs will be reported from the time a patient is randomized until EOS at year 2, or until the patient withdraws from the study. The principal study physician is responsible for alerting Novo Nordisk or its designee to any SAE within 24 hours of becoming aware of it via electronic data capture (EDC) entry. The patient should be followed until the outcome of the event is closed out. Follow-up information should be reported within 24 hours of it becoming available. Requests for follow-up information should be resolved within 14 calendar days.

At each visit (both routine diabetic care visits and dedicated study visits), patients will be asked about AEs including hypoglycemic events, e.g. “Have you experienced any problems since the last contact?” Any SAE identified from any patient encounter or notation at any time must be reported.

If an investigator becomes aware of SAEs after EOS at year 2 that are possibly related to the study product, these should be reported as spontaneous events.

7.3 Pregnancy

Any abnormal pregnancy outcome (e.g., spontaneous miscarriage, fetal death, congenital anomaly/birth defect, etc.) is considered an SAE. For the purposes of this study, any pregnancies in participating female patients will be reported, along with pregnancy outcome and any AEs or SAEs observed in the fetus or newborn until 1 month of age.

7.3.1 Reporting Period of Pregnancy

Pregnancies will be reported from the time a patient is randomized until EOS at year 2 or until the patient withdraws from the study. The principal study physician is responsible for alerting Novo Nordisk or its designee to any drug exposure during pregnancy within 14 days of the first knowledge of the pregnancy via the pregnancy reporting form. The study physician will follow the patient for the duration of the pregnancy.

7.4 Technical Complaints

Technical complaints may be reported as per usual practice. However, any SAEs resulting from a technical complaint must be reported via EDC.

8 DATA COLLECTION

8.1 Data Sources

Data sources include primary data collected prospectively by study sites at study visits (demographic and clinical data, patient-completed PRO data, and physician reported global assessments) as well as secondary data collection utilizing administrative claims data from health plans, as available. In order to maintain patient confidentiality, each patient will be assigned a unique patient study ID number upon signing informed consent to use in place of patient name or any other identifying information (e.g., medical record number). Clinical study data, PROs/ClinROs and claims-derived variables will be integrated into one analysis dataset via this confidential patient ID.

8.2 Electronic Case Report Forms (eCRFs)

All clinical study data will be collected at the physician office and entered into eCRF by trained site study personnel through a fully validated, 21 CFR 11 and HIPAA compliant EDC system. Patients will complete PRO questionnaires on paper and the site study personnel will enter the completed forms into the EDC system. Site users will be provided eCRF Completion Guidelines (eCCGs) to assist with study data collection and entry. Study personnel will access the EDC system through a secure study website.

Some clinical assessments utilized in this study may be completed in the course of routine clinical practice by site personnel not affiliated with study (e.g., blood pressure), however any activities completed solely for the study (e.g., data entry, PRO administration) must be done by trained site study personnel. For example, a nurse not affiliated with the study may measure blood pressure as part of routine care. The data from this assessment may be used for this study, but must be extracted from the patient's medical record and entered into the eCRF by trained site study personnel.

The principal study physician has the ultimate responsibility for the collection and reporting of all clinical and patient data through the eCRFs, as well as ensuring that they are accurate and complete to the extent possible.

8.3 Year One Database Lock

The primary analysis for this study is a year 1 analysis. Once data collection for year 1 has completed, a database lock and year 1 analysis will be performed. The year 1 analysis will not be integrated with HCRU and will be limited to year 1 endpoints derived from eCRF data, including PRO data. To maintain study integrity for the remaining study period, data from year 1 will be

used for limited and confidential communications while complying with public disclosure requirements. All other analyses will be conducted following a second database lock once data collection for the entire study is complete.

9 STUDY MANAGEMENT

9.1 Regulatory and Ethical Consideration

All study activities will be conducted in accordance with Good Clinical Practice (GCP) guidelines. Study personnel at physician sites will be provided training on the study protocol, the Informed Consent Form (ICF), data collection, and data entry to ensure both the protection of potential study patients as well as the scientific integrity of the study. Site monitoring will be conducted by [redacted] staff.

9.1.1 Institutional Review Board (IRB)

The principal study physician will have prospective IRB approval of the study protocol, ICF, and any patient information or recruiting materials prior to commencement of any study activities at their site. In the case of a protocol amendment, the study physician must sign the revised protocol and submit the amendment to the IRB for review and approval prior to implementation of any changes specified in the protocol amendment. All changes in research activity and all unanticipated problems involving risk to human patients or others must be reported to the IRB as required.

The principal study physician will obtain continued review of the IRB study approval at intervals not to exceed one year or otherwise specified by the IRB.

9.1.2 Informed Consent

An ICF describing the purpose, procedures, and potential risks and benefits of the study will be developed and approved by the IRB prior to study initiation. The principal study physician must ensure that each study patient is informed of the study and authorizes release of health information prior to study-related activities. The study physician, or study personnel designated by the study physician, will obtain written informed consent from each patient prior to initiation of any study-related procedures. Each patient will be given a copy of the signed ICF. The principal study physician will retain the original signed ICF for each patient.

The IRB must prospectively approve the ICF and any changes to the ICF during the course of the study before use. If a protocol amendment increases the potential risk to the patient, the ICF must be revised and submitted to the IRB for review and approval prior to implementation. The revised ICF must then be used to obtain consent from new patients entering the study as well as from currently enrolled patients if they are affected by the amendment, per IRB guidance.

9.2 Record Retention and Access

This study may be subject to audits or inspections by regulatory authorities or Novo Nordisk (or its designee). To enable such inspections and/or audits, the principal study physician must agree to maintain and allow access to required patient and study records. The principal study physician agrees to keep the identity of all participating patients (sufficient information to link records, e.g., hospital records), all original signed ICFs, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls, reports). The principal study physician should retain records according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

10 PUBLICATION OF STUDY RESULTS

All information related to this study is considered confidential information belonging to Novo Nordisk and [redacted] as consistent with contractual agreement. A final study report will be generated following completion of data collection and analysis. Results and findings will be submitted to conferences and for publication in peer-reviewed scientific journals with authorship following the International Committee of Medical Journal Editors (ICMJE) guidelines.

Information regarding the study will be disclosed at clinicaltrials.gov and novonordisk-trials.com. Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of studies regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this study will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

11 INDEMNIFICATION

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the trial or by persons for whom the said site or investigator are responsible.

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[redacted]

Appendix 1: Time and Events Schedule

Study NN9535-4416	Dedicated Study visit, Randomization	Routine Diabetic Care visits, Year 1	Dedicated Study visit, Year 1	Routine Diabetic 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]					
Informed consent[c]	X				
Specific authorization forms for release of non-[redacted] health plan claims data	X		X		X
Inclusion/Exclusion criteria	X				
Demographics (date of birth, gender, race, ethnicity)	X				
Selected medical history	X				
Diabetes history and diabetes complications	X				
Individualized HbA1c target[d]	X				
Type of glucose-lowering medication including semaglutide[e]	X	X	X	X	X
Concomitant cardiovascular medication[e]	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,[g] pregnancies, and AEs leading to study drug discontinuation		X	X	X	X

[redacted]

Study NN9535-4416	Dedicated Study visit, Randomization	Routine Diabetic Care visits, Year 1	Dedicated Study visit, Year 1	Routine Diabetic Care visits, Year 2	Dedicated Study visit, Year 2
Healthcare resource utilization[h]		X	X	X	X
Hypoglycemia leading to inpatient admission or ER encounter		X	X	X	X
PROs and Physician Completed Assessments					
DTSQs	X				
DTSQc			X		X
SF-12v2	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 mediations 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 patient'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 patient, as well as if discovered when reviewing documents from healthcare encounters with other providers. Additionally, PRO

[redacted]

and ClinRO 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 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 patient randomization through EOS or withdrawal.

[redacted]

Appendix 2: Additional Derived Outcome Variables for Supportive Analyses

Supportive Measures of Glycemic Control

- Individualized HbA1c target attained at year 2 (yes/no)
- HbA1c <7.0% (53 mmol/mol) or at least 1% point improvement in HbA1c compared to baseline at year 2 (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 1 (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 2 (yes/no)
- HbA1c <7.0% (53 mmol/mol) and no further antidiabetic medication intensification after randomization at year 1 (yes/no)
- HbA1c <7.0% (53 mmol/mol) and no further antidiabetic medication intensification after randomization at year 2 (yes/no)
- HbA1c target attainment per HEDIS criteria (<8.0% if age ≥65 years or with defined comorbidities, otherwise <7.0%) at year 2 (yes/no)
- HbA1c <7.0% (53 mmol/mol) at year 1 in patients with HbA1c >9.0% at baseline (yes/no)
- HbA1c <7.0% (53 mmol/mol) at year 2 in patients with HbA1c >9.0% at baseline (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 1 in patients with HbA1c >9.0% at baseline (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 2 in patients with HbA1c >9.0% at baseline (yes/no)

Body Weight Loss

- Change in body weight (%) from baseline to year 2
- Change in body weight (lb) from baseline to year 2

Blood Pressure

- Change in SBP (mm Hg) from baseline to year 2
- Change in DPB (mm Hg) from baseline to year 2

Hypoglycemia

- Reported hypoglycemia leading to inpatient admission or ER encounter during year 1 (yes/no)

- Reported hypoglycemia leading to inpatient admission or ER encounter during year 2 (yes/no)

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 (yes/no)

- 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 (yes/no)

- 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 (yes/no)

- 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 2 (yes/no)

- 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 (yes/no)

- 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 (yes/no)

Adherence to Treatment

- Study drug medication adherence for the two years of the study, as measured by the medication possession ratio (MPR)

[redacted]

Appendix 3: Patient Reported Outcome Additional Information

DTSQc

The DTSQc provides a measure of how satisfied patients are with their current diabetes treatment compared with previous treatment. It consists of 8 questions, which are to be answered on a Likert scale from -3 to +3 (-3 = much less satisfied now to +3 = much more satisfied now), with 0 (midpoint), representing no change. Six questions are summed 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.

SF-12 v2

The SF-12v2 is a 12-item generic health-related quality of life measure that assesses physical and mental functioning. The items will be scored using the scoring software that will be provided with the license. The following two summary scores are used as endpoints: Physical Component Summary (PCS) Score and Mental Component Summary (MCS) Score. The scores are norm-scored such that the scores range from 0-100 with a mean of 50 and standard deviation of 10. A higher score is associated with better quality of life and a lower score, poorer quality of life.

WPAI-GH

The WPAI-GH yields four types of scores: Absenteeism (work time missed), Presenteeism (impairment at work / reduced on-the-job effectiveness), Work productivity loss (overall work impairment / absenteeism plus presenteeism), and Activity Impairment. WPAI outcomes are expressed as percentages, with higher numbers indicating greater impairment and less productivity, i.e., 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).

Summary of Amendments and Updates

Summary of Changes
NN95359-4416 Protocol Version 2.0, dated 27MAR2019

Number	Section/Page	Change	Rationale
1	Global Change, Study Population	Allow enrollment of patients treated with either 1 or 2 oral antidiabetic medications.	Expand study population from patients treated with metformin monotherapy to patients treated with either 1 or 2 oral antidiabetic medications to facilitate enrollment.
2	Global Change	**March ~~13~~27, ~~2018~~2019** Version ~~1~~2.0	Update protocol date and version.
3	Study Approvals, p. 2	**Name:** [redacted] **Title:** [redacted]	Study approval title update.
4	Study Approvals, p. 2	**Name:** [redacted] **Title:** [redacted] Statistician	Update to study statistician.
5	Patient Description, Synopsis, p. 7	Eligible patients include adult T2DM patients on ~~metformin monotherapy~~ up to 2 oral antidiabetic medications whose physician deems that they have inadequate glycemic control and need treatment intensification with an additional antidiabetic oral or injectable medication.	Update patient description to reflect expanded study population.
6	Primary Objective Synopsis, p. 7 Section 2.1, Primary Objective, p. 17	The primary objective is to demonstrate superior long term effects of treatment with semaglutide compared to SOC both added to ~~metformin~~ up to 2 oral antidiabetic medications on	Update primary objective to reflect expanded study population.

		glycemic control when used as intensification in routine clinical practice in adult patients with T2DM.	
7	Secondary Objective Synopsis, p. 7 Section 2.2, Secondary Objectives, p. 17	The secondary objectives are to compare the long term effect of semaglutide versus SOC both added to ~~metformin~~ up to 2 oral antidiabetic medications and used as intensification in routine clinical practice in adult patients with T2DM with regards to:	Update secondary objectives to reflect expanded study population.
8	Study Design Synopsis, p. 7 Section 4.1, Study Design Overview, p. 20	This is a 2-year, multi-center, randomized, open label, parallel group, active comparator pragmatic clinical trial (PCT) comparing semaglutide versus SOC when added to ~~metformin monotherapy~~ up to 2 oral antidiabetic medications as treatment intensification among adult T2DM patients in the course of routine clinical practice.	Update study design to reflect expanded study population.
9	Inclusion Criteria, #4 Synopsis, p. 8 Section 4.2.3, Patient Inclusion Criteria, p. 22	4.) Treatment with ~~metformin as antidiabetic monotherapy~~ either 1 or 2 oral antidiabetic medications.	Expand study population from patient treated with metformin monotherapy to patients treated with either 1 or 2 oral antidiabetic medications to facilitate enrollment.
10	Inclusion Criteria, #5 Synopsis, p. 8 Section 4.2.3, Patient Inclusion Criteria, p. 22	5.) Current member of an [redacted] affiliated commercial health plan with pharmacy benefits.	Clarification of health plan requirements.
11	Exclusion Criteria, #2 Synopsis, p. 8	2.) Treatment with more than 2 oral antidiabetic medications or any injectable antidiabetic medication ~~any medication for the indication of diabetes other~~	Update exclusion criterion #2 to be consistent with inclusion criterion #4.

	Section 4.2.4, Patient Exclusion Criteria, p. 22	~~than metformin~~ in a period of 30 days before the day of eligibility assessment. Temporary/emergency use of any type of insulin is allowed, as is prior insulin treatment for gestational diabetes.	
12	Section 1, Introduction, p. 16	This local US study will enroll adult patients with T2DM who have inadequate glycemic control on ~~metformin as their only~~ up to 2 oral antidiabetic medications, as defined by the need for treatment intensification with an additional antidiabetic oral or injectable medication per the study physician´s discretion.	Update description of study to reflect expanded study population.
13	Section 4.2, Practice and Patient Selection, p. 21	The target population for this study consists of adult, commercially-insured, T2DM patients on ~~metformin mono-therapy~~ up to 2 oral antidiabetic medications who are in need of treatment intensification with an additional antidiabetic oral or injectable medication.	Update target population to reflect expanded study population.
14	Section 4.2, Practice and Patient Selection, p. 21	[redacted] ~~health plans serve a large population of T2DM patients. In feasibility data from the HIRD, the number of patients with T2DM, at least one claim for metformin in the most recent 6 months, and without prior use of other antidiabetic drug classes (per study exclusion criterion #2), amounts to circa 300,000 potential eligible patients distributed across 61,803 unique providers.~~	Delete data based on metformin monotherapy as it is not relevant to updated inclusion criteria.
15	Section 4.2.2, Patient Recruitment and Eligibility, p. 21	Eligible patients include adult T2DM patients whose physicians determine that they have inadequate glycemic control on ~~metformin antidiabetic monotherapy~~1 or 2 oral antidiabetic medications.	Update description of eligible patients to reflect expanded study population.

[redacted]

16	Figure 1, Study design, p. 23	**Figure 1 Study design diagram**. Patients will be randomized in a 1:1 manner using centralized allocation to receive semaglutide or SOC as add-on to ~~metformin~~ up to 2 oral antidiabetic medications.	Update description of study design to reflect expanded study population.
17	Section 5.1, Enrollment Procedures, p. 23	The determination that a patient has inadequate glycemic control on ~~metformin antidiabetic monotherapy~~ up to 2 oral antidiabetic medications, and the subsequent decision to intensify antidiabetic treatment with an additional oral or injectable antidiabetic medication, will be made by the study physician during the course of routine clinical practice.	Update enrollment procedures to reflect expanded study population.
18	Section 5.2.2, Treatments, p. 26	• Metformin	Add metformin to the list of oral antidiabetic drugs included in this study to reflect expanded study population.
19	Section 5.2.2, Treatments, p. 26-27	**Background medication:** The (up to 2) oral antidiabetic medication(s) taken prior to randomization and treatment intensification ~~following treatment~~ is considered background medication~~: metformin~~. Patients may discontinue ~~metformin~~ background medication at any time during the study. Patients may change the pre-study dose and frequency of ~~metformin~~ background medication at any time during the study. Background medication will not be provided nor reimbursed by Novo Nordisk.	Update description of background medication to reflect expanded study population.
20	Section 6.6, PRO Analysis, p. 33	The continuous change from baseline endpoints will be analyzed using the same analysis approach as described under the complete case and complete case on-study drug	Update to planned PRO analyses, with no missing data imputation for PRO endpoints.

[redacted]

		analyses in ~~primary estimand, secondary estimand, and supplementary analysis~~ ~~s~~Section 6.5.	
21	Section 6.8, Other Analyses, p. 34	The binary and continuous endpoints that include HbA1c, weight, SBP, or DBP data will be analyzed using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections. All other endpoints will be analyzed using the same analysis approach as described under the complete case and complete case on-study drug analyses in Section 6.5.	Update to planned analyses, with missing data imputation only for endpoints including HbA1c, weight, SBP, or DBP data.
22	Section 6.8.9, Evaluation of Study Population, p. 35	Two claims-based T2DM patient populations will be described and compared to the study population: (1) commercially-insured [redacted] T2DM patients treated with ~~metformin~~ up to 2 oral antidiabetic medications who undergo an antidiabetic treatment intensification, and (2) within the study sites, commercially-insured [redacted] T2DM patients treated with ~~metformin~~ up to 2 oral antidiabetic medications who are not enrolled in the study, but who undergo an antidiabetic treatment intensification.	Update claims-based comparator population to reflect expanded study population.

Summary of Changes
NN95359-4416 Protocol Version 3.0, dated 21AUG2019

Number	Section/Page	Change	Rationale
1	Global Change, Study Population	Allow enrollment of patients with any commercial or Medicare insurance with pharmacy benefits.	Expand study population to facilitate enrollment.
2	Global Change	~~**March 27**~~**August 21 2019** Version ~~3~~2.0	Update protocol date and version.
3	Study Approvals	[redacted]	Update to project statistician.
4	Study Physician Sites, Synopsis, p. 7 Section 4.2.1, Physician Practice Eligibility, p. 21	Participation of approximately ~~285~~ 200 physician sites	Reduction in number of sites necessary with expanded study population.
5	Study Physician Sites, Synopsis, p. 7	…that have a population of patients with the target indication, type 2 diabetes mellitus (T2DM), actively enrolled in ~~an~~ [redacted] ~~affiliated~~a commercial or Medicare health plan with pharmacy benefits.	Update description to reflect expanded study population.
6	Patients, Synopsis, p. 7	Planned enrollment in this study is ~~2250~~1387.	Reduction in planned enrollment based on updated power assumptions.
7	Global Change	routine diabetic care visits	Clarify data collection between study visits for sites.
8	Study Design, Synopsis, p. 8 Study Procedures, Synopsis, p. 9	Additionally, medical and pharmacy claims data will be captured utilizing the HealthCore Integrated Research Database (HIRD^{SM}) for [redacted] patients or requested, via patient written authorization, from a set of other health insurers for non-[redacted] patients for the 2 year study period. ~~HIRD~~ Claims data for the 12 months prior to randomization will [redacted]	Update to reflect expanded study population and collection of claims data from other health insurers.

		also be collected if available.	
9	Inclusion Criteria, #5 Synopsis, p. 8 Section 4.2.3, Patient Inclusion Criteria, p. 22	5.) Current member of ~~an affiliated~~ a commercial or Medicare health plan with pharmacy benefits.	Expand study population to facilitate enrollment.
10	Study Procedures, Synopsis, p. 9 Appendix, Time and Events Schedule, Note 1, p. 43	Of note, AEs leading to study drug discontinuation or SAEs will be collected from all interactions with the patient, as well as if discovered when reviewing documents from healthcare encounters with other providers.	Clarification of AE leading to study drug discontinuation and SAE identification outside of routine diabetic care or dedicated study visits.
11	Statistical Analysis, Synopsis, p. 10	This study is designed to have 90% power to ~~jointly~~ confirm superiority of the primary endpoint and 85% power to also confirm superiority of the ~~above three~~ first confirmatory secondary endpoint~~s~~ based on an analysis of the primary estimand for each of the endpoints.	Update to power calculations.
12	List of Definitions, Administrative Claims Data, p. 14	Medical, pharmacy, and health plan eligibility data created in the processing of medical and pharmacy claims. The claims data utilized in this study are obtained from the HealthCore Integrated Research Database (HIRD) for [redacted] patients and requested, via patient written authorization, from a set of other health insurers for non-[redacted] patients.	Updated definition to reflect expanded study population and collection of claims data.
13	Section 4.2, Practice and Patient Selection, p. 21	The target population for this study consists of adult~~, commercially insured,~~ T2DM patients on up to 2 oral antidiabetic medications who are in need of treatment intensification with an additional antidiabetic oral or injectable medication. To support study objectives, including claims	Update to reflect expanded study population.

		analysis of HCRU, eligible patients will also be currently insured through a commercial health plan or Medicare with pharmacy benefits.	
14	Section 4.2, Practice and Patient Selection, p. 21	~~Physician practice and participant eligibility criteria were guided by feasibility data from the HealthCore Integrated Research Database (HIRD℠) prior to protocol development.~~ ~~Physician sites recruited for the study will be those who provide care for members of [redacted] health plans, one of the largest healthcare insurance providers in the US. [redacted] provides medical coverage for roughly 1 in 8 Americans, and although this is mostly concentrated in the employer-supported, commercially-insured market, the data in the HIRD are overall representative of the entire US population.~~ [14]	Update to reflect expanded study population and site selection.
15	Section 4.2, Practice and Patient Selection, p. 21	Potential sites will be evaluated regarding feasibility of their participation in the study, including having a T2DM population ~~of~~ [redacted] ~~members~~ to meet enrollment goals~~, based on the initial data analysis from the HIRD~~.	Update to reflect expanded study population and site selection.
16	Section 4.2.1, Physician Practices, p. 21	**4.2.1 Physician Practices** ~~**Eligibility**~~ Participation of approximately ~~285~~200 physician sites in the US, including both general practitioners and endocrinologists ~~that have a T2DM population~~, is anticipated. ~~Physician sites will be limited to those that participate in the care of patients who are actively enrolled in an~~ [redacted] ~~health plan (hence forth referred to as~~ [redacted]	Update to reflect expanded study population and site selection.

[redacted]

		~~health plans).~~	
17	Section 4.2.5, Patient Enrollment, p. 22	Planned number of patients to be randomized: ~~2250~~1387 Expected number of patients to complete the study after 52 weeks: ~~1687~~1040 Expected number of patients to complete the study after 104 weeks: ~~1260~~780	Reduction in planned enrollment based on updated power assumptions.
18	Section 4.2.6, Patient Randomization, Figure 1, p. 23	n=~~2250~~1387	Reduction in planned enrollment based on updated power assumptions.
19	Section 5.1, Enrollment Procedures, p. 23-24	To preserve the real-world nature of the study, patients will be approached for potential enrollment into the study through their physician if review of their medical history indicates that they may be eligible for the study. Outreach may occur when ~~they~~ patients present to their physician as part of their standard care or through proactive contact of potentially eligible patients identified within the study physician's practice.	Clarification of patient recruitment and enrollment procedures.
20	Section 5.2.2, Treatments, Copay assistance, p. 26	The only exceptions are if a patient initiates prescription coverage through ~~Medicare or~~ Medicaid, at which point all copay assistance will end.	Update to reflect expanded study population and copay coverage for Medicare patients.
21	Section 5.4, Study Period, p. 28	If a patient leaves their [redacted] health plan ~~network~~ during the 2 year study period, administrative claims data will be collected from randomization through the date they leave the health plan. If a patient switches to another health plan during the 2-year study period, an attempt may be made to collect administrative claims data from that plan as well. In ~~this~~ these scenarios,	Update to reflect expanded study population and collection of claims data.

		site-based study data collection will continue without change.	
22	Section 5.5, Administrative Claims Data, p. 28	**5.1 Administrative Claims Data ~~HIRD℠~~** In addition to prospectively collected clinical data and PROs, this study will also utilize claims data from the HealthCore Integrated Research Database (HIRD℠) ~~HIRD~~ for ~~all study~~ [redacted] patients or requested, via patient written authorization, from a set of other health insurers for non-[redacted] patients.	Update to reflect expanded study population and collection of claims data.
23	Section 5.5, Administrative Claims Data, p. 28	Final ~~E~~extraction of this data will take place approximately 3 months after the last patient's last visit (LPLV) to allow for data lags in the claims.	Update to reflect expanded collection of claims data.
24	Section 5.6.2, Patients, p. 28	If a patient has not been in contact with the Prescribing Physician by the end of the 2 year study duration period and the site is not able to reach the patient after 3 contact attempts, the patient can be considered Lost To Follow-Up (LTFU). One of the 3 contact attempts should include a certified letter being sent to the patient. If a patient's status is determined to be LTFU, this must be recorded on the End of Study eCRF.	Added new language to clarify patients lost to follow-up.
25	Section 6.2.1, Power and Sample Size for the Primary Objective, p. 31	The study sample size of ~~2,250~~ 1,387 was calculated based on the following assumptions,… 90% power for confirming superiority of the primary endpoint, and an overall alpha leve1 of 5%.	Update to planned enrollment and power calculations.
26	Section 6.2.1, Power and Sample Size for the Primary Objective, p. 31	When accounting for missing data, randomizing ~~2250~~ 1387 patients will contribute ~~1687~~ 1040 patients for the year 1 analyses and ~~1260~~ 780 patients for the year 2 analyses, achieving a total power of ~~90%~~	Update to planned enrollment and power calculations.

		85% for confirming the two year 1 confirmatory hypotheses. The joint power for confirming all 4 confirmatory hypotheses is 58%. The corresponding marginal powers for presence of HbA1c < 7.0% at year 1, change in HbA1c to 1 year, presence of HbA1c < 7.0% at year 2, and change in HbA1c to 2 years are ~~99%~~90%, ~~99%~~94%, ~~95%~~80%, and ~~97%~~86% respectively.	
27	Section 6.8.5, Healthcare Resource Utilization (HCRU), p. 35	HCRU analyses will compare all-cause and diabetes-related HCRU (inpatient admissions, ER encounters, outpatient encounters, and pharmacy utilization) as defined in section 3.3.2 from ~~the HIRD~~ claims data by semaglutide and SOC treatment group from baseline to year 2.	Update to reflect expanded study population and collection of claims data.
28	Section 6.8.9, Evaluation of Study Population, p. 36	The primary objective of this analysis is to evaluate the external validity of the study and to understand how the study population fits into the larger T2DM populations within study sites and [redacted] a commercially-insured population as a whole. Two claims-based T2DM patient populations will be described and compared to the study population: (1) commercially-insured and Medicare Advantage [redacted] T2DM patients treated with up to 2 oral antidiabetic medications who undergo an antidiabetic treatment intensification, and (2) within the study sites, commercially-insured and Medicare Advantage T2DM patients treated with up to 2 oral antidiabetic medications who are not enrolled in the study, but who undergo an antidiabetic treatment intensification.	Update to reflect expanded study population.
29	Section 7.2.1, Collection Period of Serious Adverse	Any SAE identified from any patient encounter or notation at any time must be reported.	Clarification of SAE identification outside of routine diabetic care or

	Events, p. 37 Appendix 1: Time and Events Schedule, Footnote g, p. 44		dedicated study visits.
30	Section 8.1, Data Sources, p. 38	Data sources include primary data collected prospectively by study sites at study visits (demographic and clinical data, patient-completed PRO data, and physician reported global assessments) as well as secondary data collection utilizing administrative claims data from ~~the HIRD~~ health plans, as available.	Update to reflect expanded study population and collection of claims data.
31	References	~~[7] T. Wasser, J. Yeas and O. Tunceli, "Applying Weighting Methodologies to a Commercial Database to Project US Census Demographic Data," *The American Journal of Accountable Care,* 2015.~~	Reference no longer relevant with expanded study population.
32	Appendix 1: Time and Events Schedule, p. 42	Specific authorization forms for release of non-[redacted] health plan claims data	Addition of claims release for non-[redacted] patients to reflect expanded study population and collection of claims data.
33	Appendix 1: Time and Events Schedule, Note 2, p. 43	2) Healthcare resource utilization and pharmacy prescription data will be extracted from health plan medical and pharmacy claims ~~the HIRD~~ and will not be entered into the eCRF.	Update to reflect expanded study population and collection of claims data.
34	Appendix 1: Time and Events Schedule, Medication Footnote, p. 44	[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.	Footnote clarifying time frame for medication data collected.
35	Appendix 1: Time and Events Schedule, Footnote f, p. 44	~~[f]~~ Data from health plan medical and pharmacy claims ~~the HIRD~~. Data will be extracted ~~from the HIRD~~ at the end of the study, but will include data from patient randomization through EOS or withdrawal.	Update to reflect expanded study population and collection of claims data.

[redacted]

Long term comparative effectiveness of once weekly semaglutide versus standard of care in a real world adult US population with type 2 diabetes - a randomized pragmatic clinical trial

Trial ID NN9535-4416

Novo Nordisk

December 5, 2019

Version 4.0

Trial Phase: 4
Investigational Substance: Semaglutide

[redacted]

[redacted]

STUDY APPROVALS
Protocol No: NN9535-4416
05-DEC-2019

Sponsor Approval:

Name: [redacted]
Title:
Novo Nordisk

Signature: [redacted]

Date: [redacted]

Name: [redacted]
Title:
Novo Nordisk

Signature: [redacted]

Date: [redacted]

[redacted]

Principal Study Physician Agreement:

I have read the protocol "Long term comparative effectiveness of once weekly semaglutide versus standard of care in a real world adult US population with type 2 diabetes - a randomized pragmatic clinical trial" and agree to ensure that all staff members involved in the conduct of this study are informed of their obligations and that they meet the commitments of the protocol in accordance with Good Clinical Practice (GCP) requirements. I have familiarized myself with the prescribing information corresponding with the study drugs associated with this study.

I acknowledge that I am responsible for overall study conduct. I understand GCP requirements and agree to personally conduct or supervise the described pragmatic study in accordance with GCP.

Signature: _____

Print Name: _____

Date: _____

[redacted]

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[redacted]

[redacted]

[redacted]

SYNOPSIS

Title: Long term comparative effectiveness of once weekly semaglutide versus standard of care in a real world US adult population with type 2 diabetes – a randomized pragmatic clinical trial

Sponsor: Novo Nordisk

Study Treatment: Semaglutide in a prefilled pen (Ozempic®)

Active Ingredient: Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA)

Comparator Treatment: Standard of Care (SOC) (excluding semaglutide)

Trial ID: NN9535-4416

Study Physician Sites: Participation of approximately 200 physician sites, including both primary care practitioners and endocrinologists, that have a population of patients with the target indication, type 2 diabetes mellitus (T2DM), actively enrolled in a commercial or Medicare health plan with pharmacy benefits.

Country: United States (US)

Patients: Eligible patients include adult T2DM patients on up to 2 oral antidiabetic medications, excluding oral semaglutide, whose physician deems that they have inadequate glycemic control and need treatment intensification with an additional antidiabetic oral or injectable medication.

Planned enrollment in this study is 1387. Patients will be randomized 1:1 to receive either semaglutide s.c. or SOC.

Study Objectives: The objectives of this study are as follows:

1.) The primary objective is to demonstrate superior long term effects of treatment with semaglutide s.c. compared to SOC both added to up to 2 oral antidiabetic medications on glycemic control when used as intensification in routine clinical practice in adult patients with T2DM.

2.) The secondary objectives are to compare the long term effect of semaglutide s.c. versus SOC both added to up to 2 oral antidiabetic medications and used as intensification in routine clinical practice in adult patients with T2DM with regards to:
   a. Weight loss
   b. Patient reported outcomes (PROs) and clinician reported outcomes (ClinROs)
   c. Hypoglycemia
   d. Healthcare Resource Utilization (HCRU)
   e. Adherence and persistence to treatment

Study Design: This is a 2-year, multi-center, randomized, open label, parallel group, active comparator pragmatic clinical trial (PCT) comparing semaglutide s.c. versus SOC when added to up to 2 oral antidiabetic medications as treatment intensification among adult T2DM patients in the course of routine clinical practice. Patients will be randomized 1:1 to receive either semaglutide s.c. or SOC. The decision that further antidiabetic treatment intensification with oral or injectable antidiabetic medication is indicated is at the discretion of the study physician and will be made prior to and independent of enrollment in this study. The study physician will have determined the patient's suitability for treatment with semaglutide s.c. prior to signing informed consent, but the determination to initiate semaglutide s.c. versus SOC will be made by randomization.

[redacted]

In keeping with the study objectives and pragmatic design to evaluate semaglutide s.c. versus SOC in real world, routine clinical practice, inclusion and exclusion criteria are minimally restrictive and there are few study-specific evaluations. Study physicians will follow and treat patients according to their routine clinical practice and judgement. All oral and injectable antidiabetic medications are allowed at the study physicians' discretion, with the exception of any formulation of semaglutide in the SOC group and oral semaglutide in the semaglutide group. Patients will be followed for 2 years, regardless of changes in antidiabetic treatment over the course of the study.

It is anticipated that patients will undergo medical evaluation at regular intervals over the course of the study duration as per standard of care, but the only dedicated study visits are at randomization, at year 1, and at year 2. The study will also capture clinical data collected at the sites during routine diabetic care visits, i.e., office visits and other patient contacts that occur as part of routine clinical practice. Assessments will be conducted according to the study physician's routine clinical practice, with a few study-specific assessments as outlined in Study Procedures. Additionally, medical and pharmacy claims data will be captured utilizing the HealthCore Integrated Research Database (HIRD^{SM}) for [redacted] patients or requested, via patient written authorization, from a set of other health insurers for non-[redacted] patients for the 2 year study period. Claims data for the 12 months prior to randomization will also be collected if available.

Participant Selection:
Inclusion Criteria:

Patients must meet all of the following inclusion criteria to be eligible for the study:

1.) Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study.
2.) Male or female, age ≥ 18 years at the time of signing informed consent.
3.) Type 2 diabetes mellitus diagnosis.
4.) Treatment with either 1 or 2 oral antidiabetic medications.
5.) Current member of a commercial or Medicare health plan with pharmacy benefits.
6.) Recorded glycosylated hemoglobin A1c (HbAlc) value within the last 90 days prior to randomization.
7.) Further intensification with an additional antidiabetic oral or injectable medication is indicated to achieve glycemic target at the discretion of the study physician according to approved labelling.

Exclusion Criteria:

Patients presenting with any of the following exclusion criteria will not be eligible for the study:

1.) Previous randomization in this study.
2.) Treatment with more than 2 oral antidiabetic medications, oral semaglutide, or any injectable medication in a period of 30 days before the day of eligibility assessment. Temporary/emergency use of any type of insulin is allowed, as is prior insulin treatment for gestational diabetes.
3.) Contraindications to semaglutide according to the FDA approved label.
4.) Female who is pregnant, breastfeeding or intends to become pregnant.
5.) Participation in another clinical trial.

Study Procedures:

- Study physicians will identify eligible patients for participation.

[redacted]

- Study physicians will obtain written informed consent from patients and if eligible, patients will be randomized to either semaglutide s.c. or SOC.
- Study data will be collected on electronic Case Report Forms (eCRFs) via an electronic data capture (EDC) system.
- Study physicians or site personnel will collect demographic, clinical (i.e., height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP)), medical and T2DM specific history, antidiabetic medications, and pre-specified concomitant medications related to cardiovascular risk data prior to or at randomization. Individualized HbA1c target will be set prior to randomization.
- Baseline HbA1c will be collected from physician sites during eligibility assessment and will be the value closest to the date of randomization, within 90 days. All post-randomization HbA1c values will be recorded as available per routine clinical practice during the 2 year study period. Post-randomization HbA1c values are required for the year 1 and year 2 dedicated study visits.
- PROs and ClinROs will be completed at randomization, year 1, and year 2.
- Study physicians will collect patient data (HbA1c, study and antidiabetic medication changes, pre-specified concomitant medications related to cardiovascular risk, weight, SBP, DBP, hypoglycemic events leading to inpatient admission or emergency room (ER) encounter, adverse events (AEs) leading to study drug discontinuation, serious adverse events (SAEs), and pregnancies at the dedicated year 1 and year 2 study visits, as well as at any routine diabetic care visits during the 2 year study period. Of note, AEs leading to study drug discontinuation or SAEs will be collected from all interactions with the patient, as well as if discovered when reviewing documents from healthcare encounters with other providers.
- Administrative medical claims, pharmacy claims and health plan eligibility data will be captured from the HIRD for [redacted] patients or requested, via patient written authorization, from a set of other health insurers for the duration of the 2 year study period. Claims data for the 12 months prior to study randomization will also be collected if available. This data will be used for HCRU measures, as well as adherence and persistence to treatment.

Study Duration: Planned patient time on study will be 2 years. Administrative claims data will also be captured during this time period. Patients will be followed for the full 2 year study period regardless of changes in or discontinuation of antidiabetic treatment, other than withdrawal of consent.

Questionnaires: Diabetes treatment satisfaction, generic health-related quality of life (HRQoL), work productivity, and patient and clinician global assessments will be measured at the randomization, year 1, and year 2 dedicated study visits.

Statistical Analysis: Two estimands, each targeting a unique research question, have been defined to adequately describe the effect of semaglutide s.c. as compared to SOC (excluding semaglutide).

The primary estimand for all objectives will be the "intention-to-treat" estimand evaluating the effectiveness of randomized treatment intervention, irrespective of adherence to this randomized intervention or changes to other antidiabetic medication.

The secondary estimand for all objectives, with the exception of the adherence and persistence to treatment objective, is the "if all patients had adhered" estimand. This estimand evaluates the effect of randomized treatment intervention for all randomized patients if all patients had adhered to randomized treatment, regardless of changes to other antidiabetic medication.

[redacted]

Baseline is defined as ≤ 90 days prior to randomization visit (week 0) for HbA1c. For secondary endpoint assessments, baseline is defined as ≤ 4 weeks prior to the randomization visit (week 0).

Primary completion date (PCD) is the date the last patient completes the year 1 dedicated study visit.

The primary endpoint is binary, with success represented by an HbA1c <7.0% (53 mmol/mol) at year 1 (yes/no). Confirmatory secondary endpoints include:

- Change in HbA1c (%-point) from baseline to year 1
- HbA1c <7.0% (53 mmol/mol) at year 2 (yes/no)
- Change in HbA1c (%-point) from baseline to year 2

This study is designed to have 90% power to confirm superiority of the primary endpoint and 85% power to also confirm superiority of the first confirmatory secondary endpoint based on an analysis of the primary estimand for each of the endpoints.

The confirmatory endpoints will all be tested under multiplicity control via a hierarchical testing scheme according to the order given in the above bullet list.

The estimand informs choices about data foundation and statistical analysis including possible imputation of missing data, hereby ensuring that randomization is preserved as a sound basis for statistical inference; i.e., estimation of effect size, associated uncertainty, and statistical testing.

The full analysis set (FAS) comprising all randomized patients will be the analysis population for evaluation of both the primary and secondary estimands. For both estimands, the primary endpoint, HbA1c <7.0%, will be analyzed using a logistic regression model with a logit link function and will include treatment and baseline HbA1c as independent variables. Continuous endpoints will be analyzed using analysis of covariance (ANCOVA) and will include the same independent variables. Prior to analysis, missing data will be imputed by multiple imputation on the continuous HbA1c scale and subsequently dichotomized for the primary endpoint.

Supplementary Analyses: Two complete case analyses will complement the analyses for the primary and secondary estimands. The supplementary complete case analyses will be based on the subset of patients without missing endpoint data, i.e., patients that do not have their endpoint imputed in the two analyses used for the primary estimand and the secondary estimand, respectively.

Secondary Analyses: Secondary analyses will compare semaglutide versus SOC treatment groups in terms of change in body weight, SBP, DBP, and PRO and ClinRO measures, based on the similar analysis methods as for the primary and secondary estimands. Similarly, binary endpoints and other secondary endpoints will be compared statistically between treatment groups, including HCRU and adherence/persistence to treatment measures, hypoglycemic events leading to inpatient admission or ER encounter, as well as composite measures of HbA1c, weight loss, and hypoglycemia.

Safety: The principal study physician is responsible for monitoring the safety of participating patients. For the purposes of this study, AEs that do not meet the definition of an SAE will only be collected/recorded in the EDC if they lead to study drug discontinuation. Study physicians are responsible for reporting all SAEs and following the patient until the outcome of the SAE is closed out. All SAEs will be reported from randomization until end of study (EOS) at year 2 or patient study withdrawal. Study physicians are also responsible for recording all pregnancies in female patients from randomization until EOS at year 2 or patient study withdrawal. The patient will be followed for the duration of the pregnancy until one month post-delivery to report the pregnancy outcome and any AEs or SAEs observed in the fetus or newborn until 1 month of age. Safety will be summarized descriptively.

[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	American Diabetes Association
AE	Adverse Event
ANCOVA	Analysis of Covariance
eCCGs	Electronic Case Report Form Completion Guidelines
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinician Global Impression of Disease Severity
CI	Confidence Interval
ClinRO	Clinician Reported Outcome
eCRF	Electronic Case Report Form
DBP	Diastolic Blood Pressure
DPP-4	Dipeptidyl peptidase 4
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTSQc	Diabetes Treatment Satisfaction Questionnaire, change version
DTSQs	Diabetes Treatment Satisfaction Questionnaire, status version
EASD	European Association for the Study of Diabetes
EDC	Electronic Data Capture
EOS	End of Study
ER	Emergency Room
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonists
HbA1c	Glycosylated Hemoglobin A1c

[redacted]

HCRU	Healthcare Resource Utilization
HEDIS	Healthcare Effectiveness Data and Information Set
HIRD[SM]	HealthCore Integrated Research Database
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ID	Identifier
IRB	Institutional Review Board
ITT	Intent to Treat
LPLV	Last Patient Last Visit
LTFU	Lost to Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
MCS-12	Mental Summary Component (of the Short Form 12-Item version 2)
MPR	Medication Possession Ratio
OR	Odds Ratio
PCD	Primary Completion Date
PCS-12	Physical Summary Component (of the Short Form 12-Item version 2)
PCT	Pragmatic Clinical Trial
PDC	Proportion Days Covered
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Disease Severity
PRO	Patient Reported Outcome
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
s.c.	Subcutaneous
SD	Standard Deviation

[redacted]

SF-12v2	Short Form 12-Item version 2
SGLT-2	Sodium-Glucose Co-transporter 2
SM	Service Mark
SOC	Standard of Care
SUSTAIN	Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes
T2DM	Type 2 Diabetes Mellitus
TD	Treatment Difference
US	United States
WPAI-GH	Work Productivity and Activity Impairment, General Health

LIST OF DEFINITIONS

Term	Definition
Administrative Claims Data	Medical, pharmacy, and health plan eligibility data created in the processing of medical and pharmacy claims. The claims data utilized in this study are obtained from the HealthCore Integrated Research Database (HIRD) for [redacted] patients and requested, via patient written authorization, from a set of other health insurers for non-[redacted] patients.
Baseline	Baseline refers to assessments conducted and patient data collected at or prior to randomization. Baseline HbAlc may be ≤ 90 days prior to randomization. Baseline for secondary endpoint assessments may be ≤ 4 weeks prior to randomization.
Baseline Endpoint	For continuous endpoints and endpoints derived from continuous sources, the baseline value is defined as the last assessment taken prior to or at the randomization visit *and* before first use of study drug.
Comparator Treatment	Standard of Care (SOC) (excluding semaglutide); Commercially available oral or injectable antidiabetic medication, excluding semaglutide, prescribed at the discretion of the study physician for antidiabetic treatment intensification following randomization.
Complete the Study	Complete the study at 52 weeks: Patient has year 1 HbA1c data Complete the study at 104 weeks: Patient has year 2 HbA1c data
Dedicated Study Visit	One of three required study visits: randomization, year 1, and year 2.
Enrollment	Randomization
Estimand	The estimate targeted to address the research question posed by the study objective, i.e., "what is to be estimated." [1] The estimand translates the study objective into a precise definition of the effect of treatment.
Healthcare Resource Utilization (HCRU)	Broad term encompassing use of healthcare services, including inpatient admissions, ER encounters, outpatient encounters including office visits, and pharmacy prescription fills.
Index Date	The date corresponding to an event of interest. In this study, index date is the date corresponding to a claims-based proxy for antidiabetic treatment intensification for 2 comparator populations, thus mimicking randomization date in the study population.
Principal Study Physician	Physician at study site who is responsible for the overall conduct and oversight of the study at their site, including: supervision of study personnel, monitoring the safety of all participating patients, ensuring the accurate and complete collection and reporting of study data,

[redacted]

	continued review of the IRB study approval, and maintenance of study records. This term is analogous to "Investigator" in Good Clinical Practice (GCP) requirements.
Randomization	The point at which a patient is assigned by chance to either semaglutide s.c. or standard of care (SOC).
Routine Diabetic Care Visit	An office visit or other patient contact during the study period that occurs outside of the dedicated study visits (randomization, year 1, and year 2) according to routine clinical practice.
Study Physician	Physician at study site who participates in the conduct of the study.
Study/Trial	For the purposes of this protocol, study and trial are considered synonyms. Study is used throughout the body of the text as it reflects the post-regulatory approval setting and real world design. Trial is used in the title and in referring to the PCT acronym to maintain consistency with the industry standard Pragmatic Clinical Trial or PCT.
Study Drug	Study drug is the first antidiabetic oral or injectable medication prescribed for treatment intensification following randomization. A patient can start and stop study drug throughout the study. At any time during the duration of the study, if a patient is taking study drug as defined, they will be considered "on study drug" regardless of prior study drug discontinuations. • For the semaglutide treatment group, study drug is defined as semaglutide s.c. • For the SOC treatment group, study drug is defined as the drug class of the first antidiabetic oral or injectable medication prescribed for treatment intensification following randomization. If a fixed dose combination (FDC) product is prescribed, one of the drugs will be chosen by the study physician to be the study drug. A patient randomized to the SOC treatment group will still be considered "on study drug" if they are taking a drug in the same drug class as their first study drug, even if it is not the same individual drug. This also applies to treatment intensification with a FDC product if one of the drugs is in the same drug class as the first study drug.
Study Drug Discontinuations	Study drug discontinuation is termination of the study drug. A patient can start and stop study drug throughout the study; therefore a patient's study drug discontinuation status can change throughout the duration of the study. At any time during the duration of the study, if a patient is not taking study drug as defined, they will be considered "off study drug."

[redacted]

1 INTRODUCTION

1.1 Background and Rationale

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) position statement recommends a patient-centric approach to the selection of pharmacological treatment for type 2 diabetes mellitus (T2DM), including considerations on effectiveness, hypoglycemia risk, impact on body weight, side effects, costs, and patient preferences. [2] Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are recommended for the management of hyperglycemia in T2DM, primarily in combination with other antidiabetic medications. [2] [3]

Semaglutide, a human GLP-1 analogue for once-weekly administration, has been shown to improve glycemic control in adults with T2DM as monotherapy when the use of metformin is considered inappropriate, or as add-on to other glucose lowering therapies including insulin. In the *Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes* (SUSTAIN) clinical development program, semaglutide demonstrated clinically relevant and superior glycemic control, as well as weight loss versus placebo and active comparators, both when used as mono- and combination therapy in inadequately controlled patients with T2DM. In addition, a significant reduction in cardiovascular risk was demonstrated for semaglutide versus placebo in patients with T2DM at high risk of cardiovascular events. The overall safety profile of semaglutide was consistent with the well-established GLP-1 RA safety profile. [4]

Pragmatic clinical trials (PCTs) are designed and conducted to reflect patient outcomes and to investigate how a product is used and performs in routine clinical practice. This type of study compares two or more medical interventions that are directly relevant to clinical care and strives to assess those interventions' effectiveness in real world practice. They use broad eligibility criteria and recruit patients from a variety of practice settings to ensure the inclusion of the type of patients whose care will be influenced by the study´s results. Such studies are increasingly important to generate evidence regarding real world treatment outcomes to inform and support appropriate market access. [5]

The current local US study serves the purpose of evaluating the long term comparative effectiveness of semaglutide s.c. with existing commercially available antidiabetic medications in a real world population and in a variety of practice settings, thereby maximizing external validity while balancing the internal validity of a randomized controlled trial. This will generate data to complement the findings from the SUSTAIN clinical development program. Taken together, these findings may provide important evidence for decision making by clinicians, payers, and policy makers in routine clinical practice.

This local US study will enroll adult patients with T2DM who have inadequate glycemic control on up to 2 oral antidiabetic medications (excluding oral semaglutide), as defined by the need for treatment intensification with an additional antidiabetic oral or injectable medication per the study physician´s discretion. The current study targets patients at this particular treatment point

[redacted]

because they represent the population inadequately controlled on the current ADA recommended first lines of treatment of T2DM. The addition of a GLP-1 RA as second-line treatment is in line with the ADA guidance from 2017. [6] In keeping with the ADA and EASD position statement recommending a patient-centric approach to treatment selection for T2DM patients, in addition to comparative effectiveness, this study will also evaluate hypoglycemia risk, body weight, healthcare resource utilization (HCRU), patient reported outcomes (PROs), and clinician reported outcomes (ClinROs). Adverse events (AEs) leading to study drug discontinuation will also be collected. [2]

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to demonstrate superior long term effects of treatment with semaglutide s.c. compared to standard of care (SOC) both added to up to 2 oral antidiabetic medications on glycemic control when used as intensification in routine clinical practice in adult patients with T2DM.

2.2 Secondary Objectives

The secondary objectives are to compare the long term effect of semaglutide s.c. versus SOC both added to up to 2 oral antidiabetic medications and used as intensification in routine clinical practice in adult patients with T2DM with regards to:

- Weight loss
- Patient reported outcomes (PROs) and clinician reported outcomes (ClinROs)
- Hypoglycemia
- Healthcare Resource Utilization (HCRU)
- Adherence and persistence to treatment

3 STUDY ENDPOINTS

3.1 Baseline

Baseline is defined as ≤ 90 days prior to randomization visit (week 0) for glycosylated hemoglobin A1c (HbA1c). For secondary endpoint assessments, baseline is defined as ≤ 4 weeks prior to the randomization visit (week 0).

3.2 Primary Endpoint

Primary completion date (PCD) is the date the last patient completes the year 1 dedicated study visit.

[redacted]

The primary endpoint of this study is:

- HbA1c <7.0% (53 mmol/mol) at year 1 (yes/no)

3.3 Secondary Endpoints

3.3.1 Confirmatory Secondary Endpoints

Confirmatory secondary endpoints of this study include:

- Change in HbA1c (%-point) from baseline to year 1
- HbA1c <7.0% (53 mmol/mol) at year 2 (yes/no)
- Change in HbA1c (%-point) from baseline to year 2

3.3.2 Supportive Secondary Endpoints

Supportive secondary endpoints of this study include:

- Individualized HbA1c target attained at year 1 (yes/no)
- HbA1c <7.0% (53mmol/mol) or at least 1% point improvement in HbA1c compared to baseline at year 1 (yes/no)
- HbA1c target attainment per Healthcare Effectiveness Data and Information Set (HEDIS) criteria (<8.0% if age ≥65 years or with defined comorbidities, otherwise <7.0%) at year 1 (yes/no)
- Change in body weight (lb) from baseline to year 1
- Change in body weight (%) from baseline to year 1
- Change in systolic blood pressure (SBP; mm Hg) from baseline to year 1
- Change in diastolic blood pressure (DBP; mm Hg) from baseline to year 1
- Time to first study drug discontinuation during 2 years (day)
- Time to first treatment intensification (add-on) or change (switch) after randomization during 2 years (day)
- Study drug medication adherence for the first year of the study, as measured by medication possession ratio (MPR) (%)
- Number of hypoglycemic episodes leading to an inpatient admission or emergency room (ER) encounter from baseline to year 2
- Diabetes Treatment Satisfaction Questionnaire, change version (DTSQc), Total treatment satisfaction score measured at year 1
- DTSQc, Total treatment satisfaction score measured at year 2

- Change from baseline in Short Form 12-Item Version 2 Survey (SF-12 v2), Physical summary component (PCS-12) score at year 1
- Change from baseline in SF-12 v2, PCS-12 score at year 2
- Change from baseline in SF-12 v2, Mental summary component (MCS-12) score at year 1
- Change from baseline in SF-12 v2, MCS-12 score at year 2
- Change from baseline in Work Productivity and Activity Impairment, General Health questionnaire (WPAI-GH) Absenteeism (work time missed) score at year 1
- Change from baseline in WPAI-GH Absenteeism (work time missed) score at year 2
- Change from baseline in WPAI-GH Presenteeism (impairment at work / reduced on-the-job effectiveness) score at year 1
- Change from baseline in WPAI-GH Presenteeism (impairment at 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
- Change from baseline in WPAI-GH Work productivity loss (overall work impairment / absenteeism plus presenteeism) score at year 2
- Change from baseline in WPAI-GH Activity Impairment score at year 1
- Change from baseline in WPAI-GH Activity Impairment score at year 2

All cause healthcare resource utilization (HCRU) from baseline to year 2:

- Number of inpatient admissions
- Cumulative length of stay for inpatient admissions (days)
- Number of ER encounters
- Number of outpatient encounters
- Number of medications
- Occurrence of inpatient admission (yes/no)
- Occurrence of ER encounter (yes/no)
- Occurrence of outpatient encounter (yes/no)

Diabetes related HCRU from baseline to year 2:

- Number of diabetes related inpatient admissions

[redacted]

- Cumulative length of stay for diabetes related inpatient admissions (days)
- Number of diabetes related ER encounters
- Number of diabetes related outpatient encounters
- Number of diabetes related medications
- Occurrence of diabetes related inpatient admission (yes/no)
- Occurrence of diabetes related ER encounter (yes/no)
- Occurrence of diabetes related outpatient encounter (yes/no)

3.3.3 Exploratory Endpoints

Not applicable.

4 STUDY DESIGN

4.1 Overview

This is a 2-year, multi-center, randomized, open label, parallel group, active comparator PCT comparing semaglutide s.c. versus SOC when added to up to 2 oral antidiabetic medications as treatment intensification among adult T2DM patients in the course of routine clinical practice. Patients will be randomized 1:1 to receive either semaglutide s.c. or SOC.

The decision that further antidiabetic treatment intensification with an additional oral or injectable antidiabetic medication is indicated is at the discretion of the study physician and will be made prior to and independent of enrollment in this study. The study physician will have determined the patient's suitability for treatment with semaglutide s.c. prior to inviting them to participate in the study. However, the determination to initiate semaglutide s.c. versus SOC will be made by randomization.

Patients will be followed for 2 years, regardless of changes in antidiabetic treatment over the course of the study. Data collection will continue for the full 2 year study period unless a patient withdraws informed consent. Patients who enroll in the study agree to the release of health information, and to answer questions about their health during the course of the study. Additionally, medical and pharmacy claims data will be extracted for the 2 year study period, as well as up to 12 months prior to randomization as available.

In keeping with the study objectives and pragmatic design to evaluate semaglutide s.c. versus SOC in real world, routine clinical practice, inclusion and exclusion criteria are minimally restrictive and there are few study-specific evaluations. Study physicians will follow and treat patients according to their routine clinical practice and judgement. All oral and injectable antidiabetic medications are allowed at the study physicians' discretion, with the exception of any formulation of semaglutide in the SOC group and oral semaglutide in the semaglutide group.

[redacted]

It is anticipated that patients will undergo medical evaluation at regular intervals over the course of the study duration as per standard of care, but the only dedicated study visits are at randomization, at year 1, and at year 2. The study will also capture clinical data collected at the sites during routine diabetic care visits, i.e., office visits and other patient contacts that occur as part of routine clinical practice. Assessments will be conducted according to the study physician's routine clinical practice, with a few study-specific assessments as described in section 5. The data available may differ from site to site and patient to patient. To ensure flexibility, the dedicated year 1 and year 2 study visits have a window of ±6 weeks.

4.2 Practice and Patient Selection

The target population for this study consists of adult T2DM patients on up to 2 oral antidiabetic medications, excluding oral semaglutide, who are in need of treatment intensification with an additional antidiabetic oral or injectable medication. To support study objectives, including claims analysis of HCRU, eligible patients will also be currently insured through a commercial health plan or Medicare with pharmacy benefits.

Study site recruitment will target both primary care practitioners and specialized endocrinologists to reflect diverse treatment settings and patient populations. Potential sites will be evaluated regarding feasibility of their participation in the study, including having a T2DM population to meet enrollment goals. Potential sites will be tiered based on their estimated number of eligible study patients, and outreach will begin with all sites that meet a pre-determined minimum number of potentially eligible patients. Outreach and follow-up will be performed until the requisite number of physician sites is enrolled. Study-specific assessments have been kept to a minimum, thereby decreasing burden on study sites and increasing participation to a wide range of sites.

4.2.1 Physician Practices

Participation of approximately 200 physician sites in the US, including both general practitioners and endocrinologists, is anticipated.

4.2.2 Patient Recruitment and Eligibility

Eligible patients include adult T2DM patients whose physicians determine that they have inadequate glycemic control on 1 or 2 oral antidiabetic medications, excluding oral semaglutide. Inadequate glycemic control is defined by the need for T2DM treatment intensification with an additional antidiabetic oral or injectable medication, as determined by the study physician. Patients must also meet all of the inclusion criteria (section 4.2.3) and none of the exclusion criteria (section 4.2.4). Inclusion and exclusion criteria are minimally restrictive to ensure a broad population of adult T2DM patients to generate data in a population that reflects the heterogeneity of a real world population treated in general practice, and support the study objectives to evaluate semaglutide s.c. versus SOC in real world, routine clinical practice.

4.2.3 Patient Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for the study:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study.
2. Male or female, age ≥ 18 years at the time of signing informed consent.
3. Type 2 diabetes mellitus diagnosis.
4. Treatment with either 1 or 2 oral antidiabetic medications.
5. Current member of a commercial or Medicare health plan with pharmacy benefits.
6. Recorded HbAlc value within last 90 days prior to randomization.
7. Further intensification with an additional antidiabetic oral or injectable medication is indicated to achieve glycemic target at the discretion of the study physician according to approved labelling.

4.2.4 Patient Exclusion Criteria

Patients presenting with any of the following exclusion criteria will not be eligible for the study:

1. Previous randomization in this study.
2. Treatment with more than 2 oral antidiabetic medications, oral semaglutide, or any injectable antidiabetic medication in a period of 30 days before the day of eligibility assessment. Temporary/emergency use of any type of insulin is allowed, as is prior insulin treatment for gestational diabetes.
3. Contraindications to semaglutide according to the FDA approved label.
4. Female who is pregnant, breastfeeding or intends to become pregnant.
5. Participation in another clinical trial.

4.2.5 Patient Enrollment

Planned number of patients to be randomized: 1387

Expected number of patients to complete the study after 52 weeks: 1040

Expected number of patients to complete the study after 104 weeks: 780

4.2.6 Patient Randomization

Study patients will be randomized to either semaglutide s.c. or SOC in a 1:1 ratio. The study design and patient randomization is depicted in Figure 1.

[redacted]

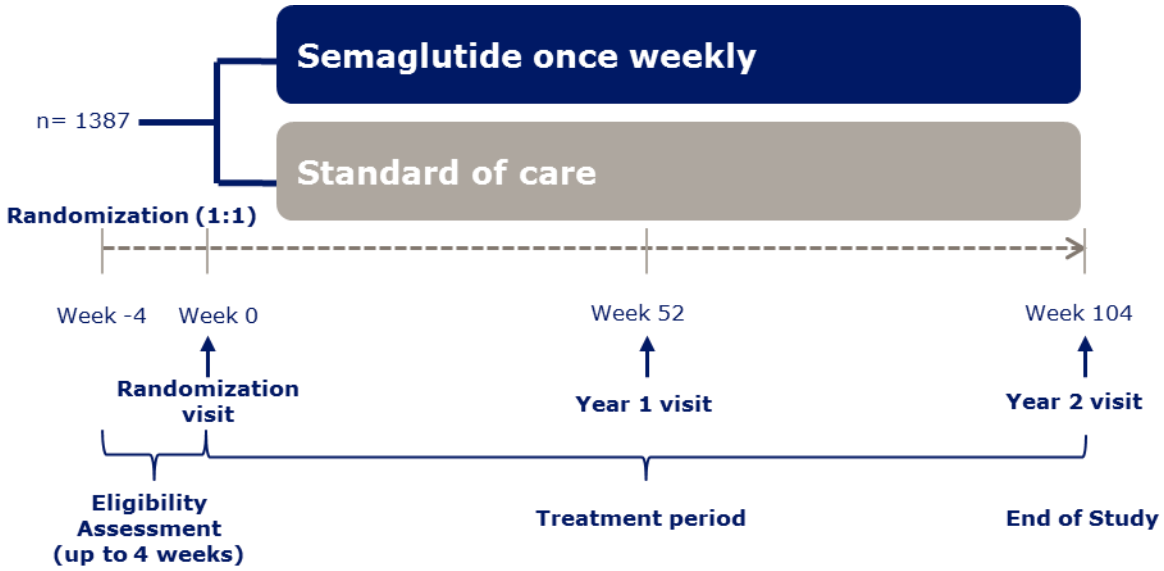

Figure 1 Study design diagram. Patients will be randomized in a 1:1 manner using centralized allocation to receive semaglutide s.c. or SOC as add-on to up to 2 oral antidiabetic medications.

5 STUDY PROCEDURES

The study visit schedule is summarized in Appendix 1.

5.1 Enrollment Procedures

The determination that a patient has inadequate glycemic control on up to 2 oral antidiabetic medications, excluding oral semaglutide, and the subsequent decision to intensify antidiabetic treatment with an additional oral or injectable antidiabetic medication, will be made by the study physician during the course of routine clinical practice. Following the decision to initiate treatment intensification, the study physician will determine the patient's suitability for the study. Suitability for the study will be assessed using the current inclusion and exclusion criteria, including the approved label for semaglutide s.c. Only patients who are eligible for treatment intensification and have been found suitable for treatment with semaglutide s.c., as determined by the study physician, are in scope for randomization. Prior to being randomized, patients must be willing to intensify with an antidiabetic medication, including GLP-1 receptor agonists. Study physicians will set and document an individualized HbA1c target for patients prior to randomization based on their clinical judgement and knowledge of the patient. To preserve the real-world nature of the study, patients will be approached for potential enrollment into the study through their physician if review of their medical history indicates that they may be eligible for the study. Outreach may occur when patients present to their physician as part of their standard care or through proactive contact of potentially eligible patients identified within the study physician's practice.

[redacted]

Informed consent will be obtained prior to any study related activities. The most recent HbA1c completed in the course of routine care up to 90 days prior to and including the date of randomization will be considered a baseline assessment and does not need to be repeated.

Study physicians or site personnel will collect patient characteristics and study data at each study visit as outlined in the Time and Events Schedule (Appendix 1), either directly from the patient or abstracted from the patient's medical records, and enter them into the electronic Case Report Form (eCRF).

5.2 Randomization Visit

Following informed consent and confirmation of inclusion/exclusion criteria, patients will be randomized to either semaglutide s.c. or SOC. Data collection at the randomization visit will include inclusion/exclusion criteria as well as the data outlined in the sections below. PRO and ClinRO questionnaires will also be administered (section 5.3).

5.2.1 Patient Characteristics

Baseline assessments at the randomization visit will include: demographic data, medical history, diabetes history including antidiabetic medications and diabetes complications, pre-specified concomitant medications related to cardiovascular risk, and clinical data (weight, height, HbA1c, SBP, DBP). Individualized HbA1c target will be set prior to randomization. The baseline HbA1c will be the patient's most recent HbA1c within 90 days of randomization.

5.2.2 Treatments

To preserve the real-world nature of the study, the patient experience will be as close to routine care as possible. The study physician will be one of the patient's own treating physicians, who may make treatment adjustments according to their clinical judgement. The study physician can make repeat prescriptions of the study drug as usual, which are collected by patients from the pharmacy of their choice. Patients will be randomized to either semaglutide s.c. or SOC. Treatment details will be recorded in the eCRF.

Semaglutide Group

Patients randomized to the semaglutide group will be prescribed commercially available semaglutide in a prefilled pen injector and will be instructed to initiate treatment with semaglutide s.c. according to the approved label. The study physician will determine the intended maintenance dose of semaglutide s.c., as well as changes to the maintenance dose thereafter. Add-on, discontinuation or dose modification of antidiabetic medication, including semaglutide s.c., during the study is allowed at the discretion of the study physician, with the exception of oral semaglutide, which is not allowed during the study period.

Semaglutide Study Drug: For patients randomized to the semaglutide group, study drug is defined as semaglutide s.c.

[redacted]

SOC Group

SOC is defined as commercially available oral or injectable antidiabetic medication (see current representative list below) other than semaglutide. Patients randomized to SOC will be prescribed and instructed to initiate commercially available antidiabetic medication according to the approved label and, if relevant for the specific antidiabetic medication, adjusted at the discretion of the study physician. Patients randomized to SOC may discontinue SOC, add-on to the SOC or switch to another antidiabetic medication during the study, with the exception of semaglutide which is not allowed in the SOC group for the duration of the study.

> *SOC Study Drug*: For patients randomized to the SOC group, study drug is defined as the drug class of the first antidiabetic oral or injectable medication prescribed for treatment intensification following randomization. If a fixed dose combination (FDC) product is prescribed, one of the drugs will be chosen by the study physician to be the study drug. A patient randomized to the SOC treatment group will still be considered "on study drug" if they are taking a drug in the same class as their first study drug, even if it is not the same individual drug. This also applies to treatment intensification with a FDC product if one of the drugs is in the same class as the first study drug.

Study Drug: Start/Stop, Discontinuations

Study drug discontinuation is termination of the study drug. A patient can stop or start study drug throughout the study; therefore a patient's study drug discontinuation status can change throughout the duration of the study. At any time during the duration of the study, if a patient is not taking study drug as defined, they will be considered "off study drug." Conversely, at any time during the duration of the study, if a patient is taking study drug as defined, they will be considered "on study drug," regardless of prior study drug discontinuations.

If a participating patient becomes pregnant, the study physician will review the patient's antidiabetic treatment regimen and make any changes necessary according to standard care of patients with T2DM during pregnancy. Semaglutide will be discontinued and will not be restarted unless the patient is no longer pregnant or breast-feeding. All study drug copay assistance will end.

Copay assistance

The study products will be handled and dispensed by the patients' pharmacy(s) per their preference and health plan benefits. In order to minimize the impact of any differential in out-of-pocket costs between the treatment groups, an out-of-pocket maximum will be provided by Novo Nordisk as part of the study. In both treatment groups, the patient's copay will be up to the specified maximum for the study drug (as defined above) and ancillary needles (if required to administer the study drug). Copay assistance will only apply to the study drug as defined above (i.e., not to any subsequent add-on treatment or treatment changes outside the study drug definition). Because patients can start and stop study drug throughout the study, copay assistance

may also start and stop throughout the study. For the duration of the study, any time a patient is "on study drug" they will receive copay assistance, and any time a patient is "off study drug" they will not receive copay assistance. The only exceptions are if a patient initiates prescription coverage through Medicaid or if a patient loses pharmacy coverage, at which point all copay assistance will end.

Products

A current representative list of the products used in this study is below. All treatments will be used in accordance with local clinical practice and guidelines. Products with more than one active substance i.e., FDC products, can be used in this study.

Semaglutide: Semaglutide in a prefilled pen (Ozempic®)

Oral antidiabetic drugs: The oral antidiabetic drug classes included in this study are the commercially available options (listed in alphabetic order):

- Alpha-glucosidase inhibitors
- Dipeptidyl peptidase 4 (DPP-4) inhibitors
- Meglitinides
- Metformin
- Sodium-glucose co-transporter 2 (SGLT-2) inhibitors
- Sulfonylureas
- Thiazolidinediones
- Other
    - Bromocriptine
    - Colesevelam

Injectable antidiabetic drugs: The injectable antidiabetic drug classes included in this study are the commercially available options (listed in alphabetic order):

- GLP-1 RAs
- Basal Insulin
    - Long acting insulin
    - Intermediate acting insulin including premix
- Prandial Insulin
    - Short acting insulin
    - Rapid acting insulin
- Other

[redacted]

- Pramlintide

Background medication: The (up to 2) oral antidiabetic medication(s) taken prior to randomization and treatment intensification is considered background medication. Patients may discontinue background medication at any time during the study. Patients may change the pre-study dose and frequency of background medication at any time during the study. Background medication will not be provided nor reimbursed by Novo Nordisk.

5.3 Patient Reported Outcomes, Clinician Reported Outcomes, and Diabetes Treatment Satisfaction

Diabetes treatment satisfaction, generic health-related quality of life (HRQoL), work productivity, and patient and clinician global assessments will be assessed by the following instruments at randomization, year 1, and year 2. Patients will self-administer these instruments on paper. Site study personnel will review for completeness and enter responses into the eCRF.

5.3.1 PRO and Treatment Satisfaction questionnaires

5.3.1.1 Diabetes Treatment Satisfaction Questionnaire (DTSQ) [7] [8] [9] [10]

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) evaluates patient satisfaction with treatment. The DTSQ status version (DTSQs) will be completed at the randomization visit and the DTSQ change version (DTSQc) will be completed at the year 1 and year 2 dedicated study visits.

5.3.1.2 Short Form 12-Item version 2 (SF-12 v2) Health Survey [11]

The SF-12 v2 is a generic HRQoL questionnaire that assesses physical and mental functioning and overall HRQoL. The SF-12v2 standard 4-week recall period questionnaire will be completed at the randomization, year 1, and year 2 dedicated study visits.

5.3.1.3 Work Productivity and Activity Impairment: General Health (WPAI-GH) Questionnaire [12]

The WPAI-GH questionnaire assesses both absenteeism (i.e., work time missed) and presenteeism (i.e., impairment at work or reduced on-the-job effectiveness) as well as daily activity impairment (e.g., work around the house, shopping, exercising, childcare, studying) attributable to general health. The WPAI-GH will be administered at the randomization, year 1, and year 2 dedicated study visits.

5.3.1.4 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, i.e., normal, mild, moderate, or severe, whereas 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, i.e., very

much better, much better, a little better, no change, a little worse, much worse, or very much worse. The PGI-S will be administered at the randomization visit and the PGI-C will be administered at the year 1 and year 2 dedicated study visits.

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

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 symptoms, i.e., normal, mild, moderate, or severe, whereas 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, i.e., very much better, much better, a little better, no change, a little worse, much worse, or very much worse. The study physician will complete the CGI-S at the randomization visit and the CGI-C at the year 1 and year 2 dedicated study visits.

5.4 Study Period

Patients will be followed from randomization to end of study (EOS) at 2 years, during which study physicians or trained site personnel will collect study data and record it in the eCRF at dedicated study visits (randomization, year 1, year 2) and routine diabetic care visits. Patients will be followed for the full 2 year study period regardless of treatment changes or discontinuation during the study period, other than withdrawal of consent. If a patient leaves their health plan during the 2 year study period, administrative claims data will be collected from randomization through the date they leave the health plan. If the patient switches to another health plan during the 2-year study period, an attempt may be made to collect administrative claims data from that plan as well. In these scenarios, site-based study data collection will continue without change.

On-study data collection at dedicated study visits and routine diabetic care visits (if available per local clinical practice) will include: clinical data (weight, HbA1c, SBP, DBP), treatment details (study drug, other antidiabetic medication, pre-specified concomitant medications related to cardiovascular risk, reasons for treatment discontinuation as applicable), hypoglycemia leading to inpatient admission or ER encounter, AEs leading to study drug discontinuation, pregnancy, and serious adverse events (SAEs). Of note, AEs leading to study drug discontinuation or SAEs will be collected from all interactions with the patient, as well as if discovered when reviewing documents from healthcare encounters with other providers. Additionally, PRO and ClinRO instruments will be completed at randomization, year 1, and year 2.

EOS visit is 2 years (±6 weeks) after randomization.

5.5 Administrative Claims Data

In addition to prospectively collected clinical data and PROs, this study will also utilize claims data from the HealthCore Integrated Research Database (HIRD[SM]) for [redacted] patients or requested, via patient written authorization, from a set of other health insurers for non-[redacted]

[redacted]

patients. Data collected will include integrated medical claims, pharmacy claims, and health plan eligibility files for the 2 years after the respective patient's study randomization. Final extraction of this data will take place approximately 3 months after the last patient's last visit (LPLV) to allow for data lags in the claims. Administrative claims data will also be collected for up to 12 months prior to study randomization, if available. The prospectively collected eCRF study data and claims data will be merged into one dataset via a study-specific patient identifier (ID) for analysis.

5.6 Withdrawals

5.6.1 Physician Practices

Novo Nordisk and/or the Institutional Review Board (IRB) reserve the right to terminate the study any time. In this event, all data collection will end. After the collected data is received, study physicians will be compensated as contractually agreed.

The IRB reserves the right to terminate participation of individual study sites at any time. Individual study sites may also be terminated for cause by Novo Nordisk per contractual agreement. In such cases, all data collection at terminated study sites will end. After the collected data is received, the study physicians will be compensated as contractually agreed.

5.6.2 Patients

Participation in the study is voluntary, and all patients are free to terminate their participation at any time. A patient will only be withdrawn from the study if they withdraw consent. In the event of study withdrawal, the study physician will record the reason for study withdrawal and continue to follow-up with the patient for any unresolved SAEs or pregnancies, if patient agrees. Upon patient withdrawal from the study, all data collection will end, but all study data collected up to withdrawal will be included in the study database. If a patient has not been in contact with the Prescribing Physician by the end of the 2 year study duration period and the site is not able to reach the patient after 3 contact attempts, the patient can be considered Lost To Follow-Up (LTFU). One of the 3 contact attempts should include a certified letter being sent to the patient. If a patient's status is determined to be LTFU, this must be recorded on the End of Study eCRF.

6 STATISTICAL METHODS

6.1 Introduction

Patients are randomized 1:1 to semaglutide s.c. or SOC. The data analyses for this study will be outlined in further detail in a Statistical Analysis Plan (SAP) developed prior to database lock at year 1.

For continuous endpoints and categorical endpoints derived from continuous sources, the baseline value is defined as the last assessment taken prior to or at the randomization visit *and* before first use of study drug.

[redacted]

If endpoint data is missing then any routine care data that are collected within ±10 weeks of the dedicated study visit will be used.

The significance level used in all statistical analyses will be 5% (two-sided).

6.1.1 Estimands

Two estimands, each targeting a unique research question, have been defined to adequately describe the effect of semaglutide s.c. as compared to SOC (excluding semaglutide).

The primary estimand for all objectives will be the "intention-to-treat" (ITT) estimand evaluating the effectiveness of randomized treatment intervention irrespective of adherence to this randomized intervention or changes to other antidiabetic medication during follow-up. The purpose of this estimand is to quantify the expected effect size in the commercially-insured health plan population upon adoption of semaglutide s.c. as compared SOC (excluding semaglutide), and is as such relevant to inform and support appropriate market access and population based treatment guidance.

The secondary estimand for all objectives with the exception of the adherence and persistence to treatment objective, is the "if all patients had adhered" estimand. This estimand evaluates the effect of randomized treatment intervention for all randomized patients if all patients had adhered to randomized treatment, regardless of changes to other (i.e., non-study drug) antidiabetic medication. The purpose of this estimand lies in quantifying the expected effect size for an individual patient in the commercially-insured health plan population who is prescribed, initiates, and continues treatment with semaglutide s.c. as compared to SOC (excluding semaglutide). The relevance of this effect measure is to inform decision making for individual patients and prescribing physicians.

6.1.2 Confirmatory Endpoints and Hypotheses

The primary endpoint is HbA1c <7.0% (53 mmol/mol) at year 1 (yes/no). This is a binary endpoint. Confirmatory secondary endpoints include:

- Change in HbA1c (%-point) from baseline to year 1
- HbA1c <7.0% (53 mmol/mol) at year 2 (yes/no)
- Change in HbA1c (%-point) from baseline to year 2

The primary and confirmatory endpoints will all be tested for superiority under multiplicity control via a hierarchical testing scheme according to the order given in the above bullet list. Confirmatory testing will only be performed for the primary estimand with the secondary estimand being supportive. The testing procedure will be stopped the first time an analysis fails to confirm superiority of the endpoint in question using a two-sided significance level of 5%.

Superiority on HbA1c <7.0% will be evaluated with respect to the odds ratio (OR) (odds semaglutide / odds SOC):

[redacted]

H_0: OR≤1 against H_a: OR>1

Superiority on change in HbA1c (year 1 – baseline; year 2 – baseline) will be evaluated with respect to the mean treatment difference (TD) (semaglutide – SOC):

H_0: TD≥0 against H_a: TD<0

6.1.3 Study Populations

The following analysis set will be defined:

Full analysis set (FAS): Includes all randomized patients analyzed according to the treatment group to which they were assigned at randomization.

6.2 Sample Size Determination

6.2.1 Power and Sample Size for Primary Objective

Assumptions for the sample size were based on input from the HIRD claims/laboratory results database. In line with the primary ITT estimand, the assumptions for the proportion of patients with HbA1c < 7.0% at year 1 and year 2, and for the change from baseline in HbA1c, were based on the claims/laboratory results data within the [redacted] population for all patients initiating treatment intensification, regardless of whether patients adhered to this treatment. Specifically, for semaglutide, assumptions were based on data for liraglutide and dulaglutide. For SOC, assumptions were based on all intensifications in the claims database. The study sample size of 1,387 was calculated based on the following assumptions, informed from HIRD data: 10% difference in proportion patients with HbA1c < 7.0% at year 1 and year 2 (60% semaglutide versus 50% SOC), absolute difference in change from baseline HbA1c of 0.5%-point (SD=2.3%) between treatment groups, 90% power for confirming superiority of the primary endpoint, and an overall alpha leve1 of 5%. Sample size calculations, including different sample size scenarios and a summary of the data from the HIRD, will be documented in the SAP.

The proportion of missing data for the confirmatory endpoints was estimated to be 25% after one year and 44% after two years. In the sample size calculation, it was assumed that only non-missing data at year 1 and year 2 would be used for the respective analyses. This is considered conservative, since the use of imputed data in the actual primary analysis (see 6.3) will increase the power. When accounting for missing data, randomizing 1387 patients will contribute 1040 patients for the year 1 analyses and 780 patients for the year 2 analyses, achieving a total power of 85% for confirming the two year 1 confirmatory hypotheses. The joint power for confirming all 4 confirmatory hypotheses is 58%. The corresponding marginal powers for presence of HbA1c < 7.0% at year 1, change in HbA1c to 1 year, presence of HbA1c < 7.0% at year 2, and change in HbA1c to 2 years are 90%, 94%, 80%, and 86% respectively.

6.3 Statistical Analysis for the Primary Estimand

The primary estimand will be estimated based on the FAS using data from all patients with observations at the dedicated study visit (year 1 for the primary endpoint), with the exception of

[redacted]

patients who, in violation of the protocol, have initiated semaglutide in the SOC treatment group. The data collected following initiation of semaglutide from these patients will be censored and imputed together with missing data. The primary endpoint, HbA1c < 7.0%, will be analyzed with a logistic regression model with a logit link function, treatment as a categorical effect, and baseline HbA1c as covariate. From the model, the estimated OR (semaglutide versus SOC) will be presented. The underlying continuous endpoint of change in HbA1c will be analyzed using analysis of covariance (ANCOVA) that will include the same independent variables. From the model, the estimated mean difference in change from baseline to dedicated study visit (semaglutide versus SOC) will be presented. The estimated treatment effect from each of these analyses will be complemented with associated 95% confidence interval (CI) and two-sided p-value for testing the null-hypothesis of no difference.

Prior to analysis, missing data will be imputed by multiple imputation on the continuous HbA1c scale and subsequently dichotomized for the primary endpoint. 500 complete data sets will be generated to adequately account for the uncertainty due to missing data. Missing endpoint data will be imputed separately by treatment group and based on patients who remained in the study according to study drug treatment status, i.e., according to whether these patients are on or off study drug at the dedicated study visit. Data will be imputed based on the assumption that, within treatment groups, patients with missing endpoint data will behave like patients with the same study drug treatment status at endpoint as the missing patients' last registered treatment status prior to the missing endpoint. For example, for patients withdrawing from the study with an "off study drug" treatment status, data will be imputed based on the assumption that the withdrawn patients will behave like patients who remain in the study but are not receiving study drug at the dedicated study visit. Technically, the imputation model will be an ANCOVA for the endpoint data. The ANCOVA will include baseline HbA1c, diabetes duration, age, and sex as independent variables. After this model has been used to predict missing values, each of the now 500 complete data sets will be analyzed as described above. Finally, the multiple analysis results will be combined using Rubin's rule. [13] For the OR the results will be combined on the logarithm scale.

Superiority for the primary endpoint, HbA1c <7.0% at year 1, will be considered established if the OR 95% CI is greater than 1, or similarly if the two-sided p-value is significant on a 5% level and the treatment OR is in favor of semaglutide.

If the hierarchical testing scheme allows, superiority for change from baseline to dedicated study visit in HbA1c will be considered established if the 95% CI for the estimated treatment difference is smaller than 0, or similarly if the two-sided p-value is significant on a 5% level and the treatment difference is in favor of semaglutide.

6.4 Statistical Analysis for the Secondary Estimand

The secondary estimand will be estimated based on the FAS. The analysis is similar to the primary analysis for the primary endpoint, but varies with regards to the data used and the

imputation of missing data. Specifically, data will only be used from the subset of patients who are receiving study drug at the dedicated study visit (year 1 for the primary endpoint), in order to estimate the treatment effect if all patients had continued treatment. Patients who no longer are receiving study drug will be censored and imputed together with missing data. The same will apply to patients who, in violation of the protocol, have initiated semaglutide in the SOC group. Collectively, missing and censored data will be imputed separately by treatment group based on all patients who are on study drug at the dedicated study visit. Data will be imputed based on the assumption that withdrawn or censored patients behave like patients that remain in the study and continue on study drug.

The technical aspects of missing data imputation based on multiple imputation, the statistical analysis of the multiple complete data sets, and combination of the multiple results will be the same as that described for the primary estimand.

6.5 Supplementary Analyses

The HbA1c analyses described for the two estimands above will be complemented with two complete case analyses based on the subset of patients without missing endpoint data, i.e., patients that do not have their endpoint imputed in the two analyses used for the primary and secondary estimand.

Complete case analysis

This analysis will be based only on patients with available measurements at the dedicated study visit including measurements irrespective of whether patients discontinued study drug or not. The analysis will use the same analysis model as described under the primary estimand.

Complete case on-study drug analysis

The analysis will be based only on patients with available measurements at the dedicated study visit including only measurements for patients still on study drug. The analysis will use the same analysis model as described under the primary estimand.

6.6 PRO Analysis

PRO and physician assessments will be measured with the instruments described in Section 5.3. Analysis of these measures will address the secondary objective of this study to compare semaglutide versus SOC in the study's patient population as is relates to PRO, i.e., treatment satisfaction, generic health outcomes, work productivity, and patient and physician global assessment measures, over one and two year observation periods. PRO analysis will descriptively summarize these measures at baseline, year 1, and year 2, as well as compare semaglutide versus SOC for change from baseline to year 1 and year 2. The continuous change from baseline endpoints will be analyzed using the same analysis approach as described under the complete case and complete case on-study drug analyses in Section 6.5. Details will be fully described in the SAP.

[redacted]

6.7 Safety Analysis

SAEs and AEs will be collected as described in Section 7. No formal safety analyses are planned for this study. SAEs, AEs leading to study drug discontinuation, and pregnancies will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and descriptively summarized by System Organ Class and Preferred Term (PT).

6.8 Other Analyses

The following analyses are planned to further support the primary objective to compare semaglutide versus SOC in glycemic control. They will also address the secondary objectives of this study to compare semaglutide versus SOC in the study's patient population over one and two year observation periods as is relates to body weight loss, hypoglycemia, HCRU, and adherence and persistence to treatment. The binary and continuous endpoints that include HbA1c, weight, SBP, or DBP data will be analyzed using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections. All other endpoints will be analyzed using the same analysis approach as described under the complete case and complete case on-study drug analyses in Section 6.5. Further details of these analyses and details for analyses of other endpoint types will be fully described in the SAP.

6.8.1 Supportive Analyses of Glycemic Control

The proportion of patients achieving the secondary endpoints related to glycemic control at year 1 as defined in section 3.3.2 (individualized HbA1c target, HbA1c <7.0% (53mmol/mol) or at least 1% point improvement in HbA1c from baseline, HbA1c target attainment per HEDIS criteria) will be compared between semaglutide and SOC treatment groups using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections.

Additionally, derived outcome variables for supportive measures of glycemic control (Appendix 2) will be utilized to support these analyses.

6.8.2 Weight Loss

Change in patient weight from baseline to year one will be calculated in pounds and percentage as defined in section 3.3.2. Mean change in weight will be compared between semaglutide and SOC treatment groups using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections.

Additionally, derived outcome variables for supportive measures of body weight loss (Appendix 2) will be utilized to support these analyses.

6.8.3 Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP)

Change in patient SBP and DBP from baseline to year 1 and baseline to year 2 will be calculated as defined in section 3.3.2 and Appendix 2. Mean change in SBP and DBP will be compared

between semaglutide and SOC treatment groups using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections.

6.8.4 Hypoglycemia

The number of hypoglycemic episodes leading to an inpatient admission or ER encounter will be reported by patients and compared by semaglutide and SOC treatment groups utilizing a negative binomial model.

Additionally, derived outcome variables for supportive measures of hypoglycemia (Appendix 2) will be utilized to support these analyses.

6.8.5 Healthcare Resource Utilization (HCRU)

HCRU analyses will compare all-cause and diabetes-related HCRU (inpatient admissions, ER encounters, outpatient encounters, and pharmacy utilization) as defined in section 3.3.2 from claims data by semaglutide and SOC treatment group from baseline to year 2.

The details of claims data definitions and calculations will be fully described in the SAP.

6.8.6 Adherence and Persistence to Treatment

Adherence and persistence to the study drug will be calculated and compared between semaglutide and SOC treatment groups.

Medication adherence refers to a patient's conformance to the provider's recommendation with respect to timing, dosage, and frequency of medication taken during the prescribed length of time. In claims, adherence is typically measured using either medication possession ratio (MPR) or proportion of days covered (PDC).

Medication persistence refers to whether a patient stays on therapy or the time from initiation to discontinuation of therapy. In claims, persistence is typically defined as the duration of time from initiation of the therapy to discontinuation or switching, whichever comes first.

Adherence and persistence will be further defined in the SAP.

6.8.7 Antidiabetic Treatment Patterns

Antidiabetic treatment patterns will be assessed and compared between semaglutide and SOC treatment groups. This analysis will summarize the number and classification type of antidiabetic medications taken during the study period.

6.8.8 Exploratory Predictive Analysis

An exploratory predictive analysis will be performed within and between the semaglutide and SOC treatment groups to identify predictors of treatment adherence and persistence and glycemic control. The objectives of the exploratory predictive analyses are to identify within and between treatment groups: 1) patients less likely to discontinue treatment and 2) patients more likely to reach clinical target.

[redacted]

6.8.9 Evaluation of the Study Population

To evaluate the generalizability of the study results, an analysis of the study population will be performed. The primary objective of this analysis is to evaluate the external validity of the study and to understand how the study population fits into the larger T2DM populations within study sites and a commercially-insured population as a whole. Two claims-based T2DM patient populations will be described and compared to the study population: (1) commercially-insured and Medicare Advantage [redacted] T2DM patients treated with up to 2 oral antidiabetic medications, excluding oral semaglutide, who undergo an antidiabetic treatment intensification, and (2) within the study sites, commercially-insured and Medicare Advantage [redacted] T2DM patients treated with up to 2 oral antidiabetic medications, excluding oral semaglutide, who are not enrolled in the study, but who undergo an antidiabetic treatment intensification. The analysis will compare the demographics, HCRU, and HbA1c between the study population and the two comparator populations during the 12 month period prior to randomization (for study population) or prior to a claims-based proxy for antidiabetic treatment intensification index date (for comparators). Additionally, treatment patterns of non-enrolled T2DM patients within the practices from which the study patients are recruited will be evaluated to identify any relevant patterns of care suggesting channeling of certain types to patients away from the study. These analyses will help to contextualize study results within the T2DM population broadly.

The details of this analysis will be fully described in the SAP.

7 ADVERSE EVENT COLLECTION

The principal study physician is responsible for monitoring the safety of participating patients. All SAEs reported by the patients during the study observational period are required to be documented on the appropriate SAE reporting form. For the purposes of this study, AEs that do not meet the definition of SAE will only be collected if they lead to study drug discontinuation.

7.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product or medical device, which does not necessarily have to have a causal relationship to the product of device. Study physicians will follow AEs that occur in any patient during this study in a manner consistent with routine clinical practice. For the purposes of this study, AEs that do not meet the definition of an SAE (section 7.2) will only be collected in the eCRF if they lead to study drug discontinuation.

7.2 Serious Adverse Events

All AEs meeting the definition of SAE will be collected in the eCRF. SAEs will be reported from the time a patient is randomized until EOS at year 2, or until the patient withdraws from the study. An SAE is defined as any AE which results in at least one of the following outcomes:

[redacted]

- Initial inpatient admission or prolongation of existing inpatient admission
- A life-threatening event, i.e., an event in which the patient was at immediate risk of dying at the time of the event; not an event that hypothetically could have caused death had it been more severe
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect in offspring
- Death
- Is deemed serious for any other reason, i.e., if it is an important medical event based on appropriate medical judgement which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other listed outcomes.

7.2.1 Collection Period of Serious Adverse Events

SAEs will be reported from the time a patient is randomized until EOS at year 2, or until the patient withdraws from the study. The principal study physician is responsible for alerting Novo Nordisk or its designee to any SAE within 24 hours of becoming aware of it via electronic data capture (EDC) entry. The patient should be followed until the outcome of the event is closed out. Follow-up information should be reported within 24 hours of it becoming available. Requests for follow-up information should be resolved within 14 calendar days.

At each visit (both routine diabetic care visits and dedicated study visits), patients will be asked about AEs including hypoglycemic events, e.g. “Have you experienced any problems since the last contact?” Any SAE identified from any patient encounter or notation at any time must be reported.

If an investigator becomes aware of SAEs after EOS at year 2 that are possibly related to the study product, these should be reported as spontaneous events.

7.3 Pregnancy

Any abnormal pregnancy outcome (e.g., spontaneous miscarriage, fetal death, congenital anomaly/birth defect, etc.) is considered an SAE. For the purposes of this study, any pregnancies in participating female patients will be reported, along with pregnancy outcome and any AEs or SAEs observed in the fetus or newborn until 1 month of age.

7.3.1 Reporting Period of Pregnancy

Pregnancies will be reported from the time a patient is randomized until EOS at year 2 or until the patient withdraws from the study. The principal study physician is responsible for alerting Novo Nordisk or its designee to any drug exposure during pregnancy within 14 days of the first knowledge of the pregnancy via the pregnancy reporting form. The study physician will follow the patient for the duration of the pregnancy.

7.4 Technical Complaints

Technical complaints may be reported as per usual practice. However, any SAEs resulting from a technical complaint must be reported via EDC.

8 DATA COLLECTION

8.1 Data Sources

Data sources include primary data collected prospectively by study sites at study visits (demographic and clinical data, patient-completed PRO data, and physician reported global assessments) as well as secondary data collection utilizing administrative claims data from health plans, as available. In order to maintain patient confidentiality, each patient will be assigned a unique patient study ID number upon signing informed consent to use in place of patient name or any other identifying information (e.g., medical record number). Clinical study data, PROs/ClinROs and claims-derived variables will be integrated into one analysis dataset via this confidential patient ID.

8.2 Electronic Case Report Forms (eCRFs)

All clinical study data will be collected at the physician office and entered into eCRF by trained site study personnel through a fully validated, 21 CFR 11 and HIPAA compliant EDC system. Patients will complete PRO questionnaires on paper and the site study personnel will enter the completed forms into the EDC system. Site users will be provided eCRF Completion Guidelines (eCCGs) to assist with study data collection and entry. Study personnel will access the EDC system through a secure study website.

Some clinical assessments utilized in this study may be completed in the course of routine clinical practice by site personnel not affiliated with study (e.g., blood pressure), however any activities completed solely for the study (e.g., data entry, PRO administration) must be done by trained site study personnel. For example, a nurse not affiliated with the study may measure blood pressure as part of routine care. The data from this assessment may be used for this study, but must be extracted from the patient's medical record and entered into the eCRF by trained site study personnel.

The principal study physician has the ultimate responsibility for the collection and reporting of all clinical and patient data through the eCRFs, as well as ensuring that they are accurate and complete to the extent possible.

8.3 Year One Database Lock

The primary analysis for this study is a year 1 analysis. Once data collection for year 1 has completed, a database lock and year 1 analysis will be performed. The year 1 analysis will not be integrated with HCRU and will be limited to year 1 endpoints derived from eCRF data, including PRO data. To maintain study integrity for the remaining study period, data from year 1 will be

[redacted]

used for limited and confidential communications while complying with public disclosure requirements. All other analyses will be conducted following a second database lock once data collection for the entire study is complete.

9 STUDY MANAGEMENT

9.1 Regulatory and Ethical Consideration

All study activities will be conducted in accordance with Good Clinical Practice (GCP) guidelines. Study personnel at physician sites will be provided training on the study protocol, the Informed Consent Form (ICF), data collection, and data entry to ensure both the protection of potential study patients as well as the scientific integrity of the study. Site monitoring will be conducted by [redacted] staff.

9.1.1 Institutional Review Board (IRB)

The principal study physician will have prospective IRB approval of the study protocol, ICF, and any patient information or recruiting materials prior to commencement of any study activities at their site. In the case of a protocol amendment, the study physician must sign the revised protocol and submit the amendment to the IRB for review and approval prior to implementation of any changes specified in the protocol amendment. All changes in research activity and all unanticipated problems involving risk to human patients or others must be reported to the IRB as required.

The principal study physician will obtain continued review of the IRB study approval at intervals not to exceed one year or otherwise specified by the IRB.

9.1.2 Informed Consent

An ICF describing the purpose, procedures, and potential risks and benefits of the study will be developed and approved by the IRB prior to study initiation. The principal study physician must ensure that each study patient is informed of the study and authorizes release of health information prior to study-related activities. The study physician, or study personnel designated by the study physician, will obtain written informed consent from each patient prior to initiation of any study-related procedures. Each patient will be given a copy of the signed ICF. The principal study physician will retain the original signed ICF for each patient.

The IRB must prospectively approve the ICF and any changes to the ICF during the course of the study before use. If a protocol amendment increases the potential risk to the patient, the ICF must be revised and submitted to the IRB for review and approval prior to implementation. The revised ICF must then be used to obtain consent from new patients entering the study as well as from currently enrolled patients if they are affected by the amendment, per IRB guidance.

9.2 Record Retention and Access

This study may be subject to audits or inspections by regulatory authorities or Novo Nordisk (or its designee). To enable such inspections and/or audits, the principal study physician must agree to maintain and allow access to required patient and study records. The principal study physician agrees to keep the identity of all participating patients (sufficient information to link records, e.g., hospital records), all original signed ICFs, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls, reports). The principal study physician should retain records according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

10 PUBLICATION OF STUDY RESULTS

All information related to this study is considered confidential information belonging to Novo Nordisk and [redacted] as consistent with contractual agreement. A final study report will be generated following completion of data collection and analysis. Results and findings will be submitted to conferences and for publication in peer-reviewed scientific journals with authorship following the International Committee of Medical Journal Editors (ICMJE) guidelines.

Information regarding the study will be disclosed at clinicaltrials.gov and novonordisk-trials.com. Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of studies regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this study will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

11 INDEMNIFICATION

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the trial or by persons for whom the said site or investigator are responsible.

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[redacted]

Appendix 1: Time and Events Schedule

Study NN9535-4416	Dedicated Study visit, Randomization	Routine Diabetic Care visits, Year 1	Dedicated Study visit, Year 1	Routine Diabetic 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]					
Informed consent[c]	X				
Specific authorization forms for release of non-[redacted] health plan claims data	X		X		X
Inclusion/Exclusion criteria	X				
Demographics (date of birth, gender, race, ethnicity)	X				
Selected medical history	X				
Diabetes history and diabetes complications	X				
Individualized HbA1c target[d]	X				
Type of glucose-lowering medication including semaglutide s.c.[e]	X	X	X	X	X
Concomitant cardiovascular medication[e]	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,[g] pregnancies, and AEs leading to study drug discontinuation		X	X	X	X

[redacted]

Study NN9535-4416	Dedicated Study visit, Randomization	Routine Diabetic Care visits, Year 1	Dedicated Study visit, Year 1	Routine Diabetic Care visits, Year 2	Dedicated Study visit, Year 2
Healthcare resource utilization[h]		X	X	X	X
Hypoglycemia leading to inpatient admission or ER encounter		X	X	X	X
PROs and Physician Completed Assessments					
DTSQs	X				
DTSQc			X		X
SF-12v2	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 mediations 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 patient'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 patient, as well as if discovered when reviewing documents from healthcare encounters with other providers. Additionally, PRO

[redacted]

and ClinRO 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 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 patient randomization through EOS or withdrawal.

[redacted]

Appendix 2: Additional Derived Outcome Variables for Supportive Analyses

Supportive Measures of Glycemic Control

- Individualized HbA1c target attained at year 2 (yes/no)
- HbA1c <7.0% (53 mmol/mol) or at least 1% point improvement in HbA1c compared to baseline at year 2 (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 1 (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 2 (yes/no)
- HbA1c <7.0% (53 mmol/mol) and no further antidiabetic medication intensification after randomization at year 1 (yes/no)
- HbA1c <7.0% (53 mmol/mol) and no further antidiabetic medication intensification after randomization at year 2 (yes/no)
- HbA1c target attainment per HEDIS criteria (<8.0% if age ≥65 years or with defined comorbidities, otherwise <7.0%) at year 2 (yes/no)
- HbA1c <7.0% (53 mmol/mol) at year 1 in patients with HbA1c >9.0% at baseline (yes/no)
- HbA1c <7.0% (53 mmol/mol) at year 2 in patients with HbA1c >9.0% at baseline (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 1 in patients with HbA1c >9.0% at baseline (yes/no)
- HbA1c <8.0% (64 mmol/mol) at year 2 in patients with HbA1c >9.0% at baseline (yes/no)

Body Weight Loss

- Change in body weight (%) from baseline to year 2
- Change in body weight (lb) from baseline to year 2

Blood Pressure

- Change in SBP (mm Hg) from baseline to year 2
- Change in DPB (mm Hg) from baseline to year 2

Hypoglycemia

- Reported hypoglycemia leading to inpatient admission or ER encounter during year 1 (yes/no)

[redacted]

- Reported hypoglycemia leading to inpatient admission or ER encounter during year 2 (yes/no)

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 (yes/no)

- 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 (yes/no)

- 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 (yes/no)

- 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 2 (yes/no)

- 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 (yes/no)

- 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 (yes/no)

Adherence to Treatment

- Study drug medication adherence for the two years of the study, as measured by the medication possession ratio (MPR)

Appendix 3: Patient Reported Outcome Additional Information

DTSQc

The DTSQc provides a measure of how satisfied patients are with their current diabetes treatment compared with previous treatment. It consists of 8 questions, which are to be answered on a Likert scale from -3 to +3 (-3 = much less satisfied now to +3 = much more satisfied now), with 0 (midpoint), representing no change. Six questions are summed 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.

SF-12 v2

The SF-12v2 is a 12-item generic health-related quality of life measure that assesses physical and mental functioning. The items will be scored using the scoring software that will be provided with the license. The following two summary scores are used as endpoints: Physical Component Summary (PCS) Score and Mental Component Summary (MCS) Score. The scores are norm-scored such that the scores range from 0-100 with a mean of 50 and standard deviation of 10. A higher score is associated with better quality of life and a lower score, poorer quality of life.

WPAI-GH

The WPAI-GH yields four types of scores: Absenteeism (work time missed), Presenteeism (impairment at work / reduced on-the-job effectiveness), Work productivity loss (overall work impairment / absenteeism plus presenteeism), and Activity Impairment. WPAI outcomes are expressed as percentages, with higher numbers indicating greater impairment and less productivity, i.e., 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).

Summary of Amendments and Updates

Summary of Changes
NN95359-4416 Protocol Version 2.0, dated 27MAR2019

Number	Section/Page	Change	Rationale
1	Global Change, Study Population	Allow enrollment of patients treated with either 1 or 2 oral antidiabetic medications.	Expand study population from patients treated with metformin monotherapy to patients treated with either 1 or 2 oral antidiabetic medications to facilitate enrollment.
2	Global Change	**March ~~13~~27, ~~2018~~2019** Version ~~1~~2.0	Update protocol date and version.
3	Study Approvals, p. 2	**Name:** [redacted] **Title:** [redacted]	Study approval title update.
4	Study Approvals, p. 2	**Name:** [redacted] **Title:** [redacted] Statistician	Update to study statistician.
5	Patient Description, Synopsis, p. 7	Eligible patients include adult T2DM patients on ~~metformin monotherapy~~ up to 2 oral antidiabetic medications whose physician deems that they have inadequate glycemic control and need treatment intensification with an additional antidiabetic oral or injectable medication.	Update patient description to reflect expanded study population.
6	Primary Objective Synopsis, p. 7 Section 2.1, Primary Objective, p. 17	The primary objective is to demonstrate superior long term effects of treatment with semaglutide compared to SOC both added to ~~metformin~~ up to 2 oral antidiabetic medications on	Update primary objective to reflect expanded study population.

		glycemic control when used as intensification in routine clinical practice in adult patients with T2DM.	
7	Secondary Objective Synopsis, p. 7 Section 2.2, Secondary Objectives, p. 17	The secondary objectives are to compare the long term effect of semaglutide versus SOC both added to ~~metformin~~ up to 2 oral antidiabetic medications and used as intensification in routine clinical practice in adult patients with T2DM with regards to:	Update secondary objectives to reflect expanded study population.
8	Study Design Synopsis, p. 7 Section 4.1, Study Design Overview, p. 20	This is a 2-year, multi-center, randomized, open label, parallel group, active comparator pragmatic clinical trial (PCT) comparing semaglutide versus SOC when added to ~~metformin monotherapy~~ up to 2 oral antidiabetic medications as treatment intensification among adult T2DM patients in the course of routine clinical practice.	Update study design to reflect expanded study population.
9	Inclusion Criteria, #4 Synopsis, p. 8 Section 4.2.3, Patient Inclusion Criteria, p. 22	4.) Treatment with ~~metformin as antidiabetic monotherapy~~ either 1 or 2 oral antidiabetic medications.	Expand study population from patient treated with metformin monotherapy to patients treated with either 1 or 2 oral antidiabetic medications to facilitate enrollment.
10	Inclusion Criteria, #5 Synopsis, p. 8 Section 4.2.3, Patient Inclusion Criteria, p. 22	5.) Current member of an [redacted] affiliated commercial health plan with pharmacy benefits.	Clarification of health plan requirements.
11	Exclusion Criteria, #2 Synopsis, p. 8	2.) Treatment with more than 2 oral antidiabetic medications or any injectable antidiabetic medication ~~any medication for the indication of diabetes other~~	Update exclusion criterion #2 to be consistent with inclusion criterion #4.

	Section 4.2.4, Patient Exclusion Criteria, p. 22	~~than metformin~~ in a period of 30 days before the day of eligibility assessment. Temporary/emergency use of any type of insulin is allowed, as is prior insulin treatment for gestational diabetes.	
12	Section 1, Introduction, p. 16	This local US study will enroll adult patients with T2DM who have inadequate glycemic control on ~~metformin as their only~~ up to 2 oral antidiabetic medications, as defined by the need for treatment intensification with an additional antidiabetic oral or injectable medication per the study physician´s discretion.	Update description of study to reflect expanded study population.
13	Section 4.2, Practice and Patient Selection, p. 21	The target population for this study consists of adult, commercially-insured, T2DM patients on ~~metformin mono-therapy~~ up to 2 oral antidiabetic medications who are in need of treatment intensification with an additional antidiabetic oral or injectable medication.	Update target population to reflect expanded study population.
14	Section 4.2, Practice and Patient Selection, p. 21	[redacted] ~~health plans serve a large population of T2DM patients. In feasibility data from the HIRD, the number of patients with T2DM, at least one claim for metformin in the most recent 6 months, and without prior use of other antidiabetic drug classes (per study exclusion criterion #2), amounts to circa 300,000 potential eligible patients distributed across 61,803 unique providers.~~	Delete data based on metformin monotherapy as it is not relevant to updated inclusion criteria.
15	Section 4.2.2, Patient Recruitment and Eligibility, p. 21	Eligible patients include adult T2DM patients whose physicians determine that they have inadequate glycemic control on ~~metformin antidiabetic monotherapy~~1 or 2 oral antidiabetic medications.	Update description of eligible patients to reflect expanded study population.

[redacted]

16	Figure 1, Study design, p. 23	**Figure 1 Study design diagram**. Patients will be randomized in a 1:1 manner using centralized allocation to receive semaglutide or SOC as add-on to ~~metformin~~ up to 2 oral antidiabetic medications.	Update description of study design to reflect expanded study population.
17	Section 5.1, Enrollment Procedures, p. 23	The determination that a patient has inadequate glycemic control on ~~metformin antidiabetic monotherapy~~ up to 2 oral antidiabetic medications, and the subsequent decision to intensify antidiabetic treatment with an additional oral or injectable antidiabetic medication, will be made by the study physician during the course of routine clinical practice.	Update enrollment procedures to reflect expanded study population.
18	Section 5.2.2, Treatments, p. 26	• Metformin	Add metformin to the list of oral antidiabetic drugs included in this study to reflect expanded study population.
19	Section 5.2.2, Treatments, p. 26-27	**Background medication:** The (up to 2) oral antidiabetic medication(s) taken prior to randomization and treatment intensification ~~following treatment~~ is considered background medication~~: metformin~~. Patients may discontinue ~~metformin~~ background medication at any time during the study. Patients may change the pre-study dose and frequency of ~~metformin~~ background medication at any time during the study. Background medication will not be provided nor reimbursed by Novo Nordisk.	Update description of background medication to reflect expanded study population.
20	Section 6.6, PRO Analysis, p. 33	The continuous change from baseline endpoints will be analyzed using the same analysis approach as described under the complete case and complete case on-study drug	Update to planned PRO analyses, with no missing data imputation for PRO endpoints.

[redacted]

		analyses in ~~primary estimand, secondary estimand, and supplementary analysis~~ ~~s~~Section 6.5.	
21	Section 6.8, Other Analyses, p. 34	The binary and continuous endpoints that include HbA1c, weight, SBP, or DBP data will be analyzed using the same analysis approach as described under the primary estimand, secondary estimand, and supplementary analysis sections. All other endpoints will be analyzed using the same analysis approach as described under the complete case and complete case on-study drug analyses in Section 6.5.	Update to planned analyses, with missing data imputation only for endpoints including HbA1c, weight, SBP, or DBP data.
22	Section 6.8.9, Evaluation of Study Population, p. 35	Two claims-based T2DM patient populations will be described and compared to the study population: (1) commercially-insured [redacted] T2DM patients treated with ~~metformin~~ up to 2 oral antidiabetic medications who undergo an antidiabetic treatment intensification, and (2) within the study sites, commercially-insured [redacted] T2DM patients treated with ~~metformin~~ up to 2 oral antidiabetic medications who are not enrolled in the study, but who undergo an antidiabetic treatment intensification.	Update claims-based comparator population to reflect expanded study population.

Summary of Changes
NN95359-4416 Protocol Version 3.0, dated 21AUG2019

Number	Section/Page	Change	Rationale
1	Global Change, Study Population	Allow enrollment of patients with any commercial or Medicare insurance with pharmacy benefits.	Expand study population to facilitate enrollment.
2	Global Change	~~**March 27**~~**August 21 2019** Version ~~3~~2.0	Update protocol date and version.
3	Study Approvals	[redacted]	Update to project statistician.
4	Study Physician Sites, Synopsis, p. 7 Section 4.2.1, Physician Practice Eligibility, p. 21	Participation of approximately ~~285~~ 200 physician sites	Reduction in number of sites necessary with expanded study population.
5	Study Physician Sites, Synopsis, p. 7	…that have a population of patients with the target indication, type 2 diabetes mellitus (T2DM), actively enrolled in ~~an~~ [redacted] ~~affiliated~~a commercial or Medicare health plan with pharmacy benefits.	Update description to reflect expanded study population.
6	Patients, Synopsis, p. 7	Planned enrollment in this study is ~~2250~~1387.	Reduction in planned enrollment based on updated power assumptions.
7	Global Change	routine diabetic care visits	Clarify data collection between study visits for sites.
8	Study Design, Synopsis, p. 8 Study Procedures, Synopsis, p. 9	Additionally, medical and pharmacy claims data will be captured utilizing the HealthCore Integrated Research Database (HIRD^{SM}) for [redacted] patients or requested, via patient written authorization, from a set of other health insurers for non-[redacted] patients for the 2 year study period. ~~HIRD~~ Claims data for the 12	Update to reflect expanded study population and collection of claims data from other health insurers.

[redacted]

		months prior to randomization will also be collected if available.	
9	Inclusion Criteria, #5 Synopsis, p. 8 Section 4.2.3, Patient Inclusion Criteria, p. 22	5.) Current member of ~~an~~ [redacted] ~~affiliated~~ a commercial or Medicare health plan with pharmacy benefits.	Expand study population to facilitate enrollment.
10	Study Procedures, Synopsis, p. 9 Appendix, Time and Events Schedule, Note 1, p. 43	Of note, AEs leading to study drug discontinuation or SAEs will be collected from all interactions with the patient, as well as if discovered when reviewing documents from healthcare encounters with other providers.	Clarification of AE leading to study drug discontinuation and SAE identification outside of routine diabetic care or dedicated study visits.
11	Statistical Analysis, Synopsis, p. 10	This study is designed to have 90% power to ~~jointly~~ confirm superiority of the primary endpoint and 85% power to also confirm superiority of the ~~above three~~ first confirmatory secondary endpoint~~s~~ based on an analysis of the primary estimand for each of the endpoints.	Update to power calculations.
12	List of Definitions, Administrative Claims Data, p. 14	Medical, pharmacy, and health plan eligibility data created in the processing of medical and pharmacy claims. The claims data utilized in this study are obtained from the HealthCore Integrated Research Database (HIRD) for [redacted] patients and requested, via patient written authorization, from a set of other health insurers for non-[redacted] patients.	Updated definition to reflect expanded study population and collection of claims data.
13	Section 4.2, Practice and Patient Selection, p. 21	The target population for this study consists of adult~~, commercially insured,~~ T2DM patients on up to 2 oral antidiabetic medications who are in need of treatment intensification with an additional antidiabetic oral or injectable medication. To support study	Update to reflect expanded study population.

[redacted]

		objectives, including claims analysis of HCRU, eligible patients will also be currently insured through a commercial health plan or Medicare with pharmacy benefits.	
14	Section 4.2, Practice and Patient Selection, p. 21	~~Physician practice and participant eligibility criteria were guided by feasibility data from the HealthCore Integrated Research Database (HIRD℠) prior to protocol development.~~ ~~Physician sites recruited for the study will be those who provide care for members of [redacted] health plans, one of the largest healthcare insurance providers in the US. [redacted] provides medical coverage for roughly 1 in 8 Americans, and although this is mostly concentrated in the employer-supported, commercially-insured market, the data in the HIRD are overall representative of the entire US population.~~ [14]	Update to reflect expanded study population and site selection.
15	Section 4.2, Practice and Patient Selection, p. 21	Potential sites will be evaluated regarding feasibility of their participation in the study, including having a T2DM population ~~of~~ [redacted] ~~members~~ to meet enrollment goals~~, based on the initial data analysis from the HIRD~~.	Update to reflect expanded study population and site selection.
16	Section 4.2.1, Physician Practices, p. 21	**4.2.1 Physician Practices** ~~**Eligibility**~~ Participation of approximately ~~285~~200 physician sites in the US, including both general practitioners and endocrinologists ~~that have a T2DM population~~, is anticipated. ~~Physician sites will be limited to those that participate in the care of patients who are actively enrolled in an~~ [redacted] ~~health plan~~	Update to reflect expanded study population and site selection.

[redacted]

		~~(hence forth referred to as [redacted] health plans).~~	
17	Section 4.2.5, Patient Enrollment, p. 22	Planned number of patients to be randomized: ~~2250~~1387 Expected number of patients to complete the study after 52 weeks: ~~1687~~1040 Expected number of patients to complete the study after 104 weeks: ~~1260~~780	Reduction in planned enrollment based on updated power assumptions.
18	Section 4.2.6, Patient Randomization, Figure 1, p. 23	n=~~2250~~1387	Reduction in planned enrollment based on updated power assumptions.
19	Section 5.1, Enrollment Procedures, p. 23-24	To preserve the real-world nature of the study, patients will be approached for potential enrollment into the study through their physician if review of their medical history indicates that they may be eligible for the study. Outreach may occur when ~~they~~ patients present to their physician as part of their standard care or through proactive contact of potentially eligible patients identified within the study physician's practice.	Clarification of patient recruitment and enrollment procedures.
20	Section 5.2.2, Treatments, Copay assistance, p. 26	The only exceptions are if a patient initiates prescription coverage through ~~Medicare or~~ Medicaid, at which point all copay assistance will end.	Update to reflect expanded study population and copay coverage for Medicare patients.
21	Section 5.4, Study Period, p. 28	If a patient leaves their [redacted] health plan ~~network~~ during the 2 year study period, administrative claims data will be collected from randomization through the date they leave the health plan. If a patient switches to another health plan during the 2-year study period, an attempt may be made to collect administrative claims data from that	Update to reflect expanded study population and collection of claims data.

		plan as well. In ~~this~~ these scenarios, site-based study data collection will continue without change.	
22	Section 5.5, Administrative Claims Data, p. 28	**5.1 Administrative Claims Data ~~HIRD℠~~** In addition to prospectively collected clinical data and PROs, this study will also utilize claims data from the HealthCore Integrated Research Database (HIRD℠) ~~HIRD~~ for ~~all study~~ [redacted] patients or requested, via patient written authorization, from a set of other health insurers for non-[redacted] patients.	Update to reflect expanded study population and collection of claims data.
23	Section 5.5, Administrative Claims Data, p. 28	Final ~~E~~extraction of this data will take place approximately 3 months after the last patient's last visit (LPLV) to allow for data lags in the claims.	Update to reflect expanded collection of claims data.
24	Section 5.6.2, Patients, p. 28	If a patient has not been in contact with the Prescribing Physician by the end of the 2 year study duration period and the site is not able to reach the patient after 3 contact attempts, the patient can be considered Lost To Follow-Up (LTFU). One of the 3 contact attempts should include a certified letter being sent to the patient. If a patient's status is determined to be LTFU, this must be recorded on the End of Study eCRF.	Added new language to clarify patients lost to follow-up.
25	Section 6.2.1, Power and Sample Size for the Primary Objective, p. 31	The study sample size of ~~2,250~~ 1,387 was calculated based on the following assumptions,… 90% power for confirming superiority of the primary endpoint, and an overall alpha leve1 of 5%.	Update to planned enrollment and power calculations.
26	Section 6.2.1, Power and Sample Size for the Primary Objective, p. 31	When accounting for missing data, randomizing ~~2250~~ 1387 patients will contribute ~~1687~~ 1040 patients for the year 1 analyses and ~~1260~~ 780 patients for the year 2 analyses,	Update to planned enrollment and power calculations.

		achieving a total power of ~~90%~~ 85% for confirming the two year 1 confirmatory hypotheses. The joint power for confirming all 4 confirmatory hypotheses is 58%. The corresponding marginal powers for presence of HbA1c < 7.0% at year 1, change in HbA1c to 1 year, presence of HbA1c < 7.0% at year 2, and change in HbA1c to 2 years are ~~99%~~90%, ~~99%~~94%, ~~95%~~80%, and ~~97%~~86% respectively.	
27	Section 6.8.5, Healthcare Resource Utilization (HCRU), p. 35	HCRU analyses will compare all-cause and diabetes-related HCRU (inpatient admissions, ER encounters, outpatient encounters, and pharmacy utilization) as defined in section 3.3.2 from ~~the HIRD~~ claims data by semaglutide and SOC treatment group from baseline to year 2.	Update to reflect expanded study population and collection of claims data.
28	Section 6.8.9, Evaluation of Study Population, p. 36	The primary objective of this analysis is to evaluate the external validity of the study and to understand how the study population fits into the larger T2DM populations within study sites and [redacted] a commercially-insured population as a whole. Two claims-based T2DM patient populations will be described and compared to the study population: (1) commercially-insured and Medicare Advantage [redacted] T2DM patients treated with up to 2 oral antidiabetic medications who undergo an antidiabetic treatment intensification, and (2) within the study sites, commercially-insured and Medicare Advantage T2DM patients treated with up to 2 oral antidiabetic medications who are not enrolled in the study, but who undergo an antidiabetic treatment intensification.	Update to reflect expanded study population.

29	Section 7.2.1, Collection Period of Serious Adverse Events, p. 37 Appendix 1: Time and Events Schedule, Footnote g, p. 44	Any SAE identified from any patient encounter or notation at any time must be reported.	Clarification of SAE identification outside of routine diabetic care or dedicated study visits.
30	Section 8.1, Data Sources, p. 38	Data sources include primary data collected prospectively by study sites at study visits (demographic and clinical data, patient-completed PRO data, and physician reported global assessments) as well as secondary data collection utilizing administrative claims data from ~~the HIRD~~ health plans, as available.	Update to reflect expanded study population and collection of claims data.
31	References	~~[7] T. Wasser, J. Ycas and O. Tunceli, "Applying Weighting Methodologies to a Commercial Database to Project US Census Demographic Data," *The American Journal of Accountable Care,* 2015.~~	Reference no longer relevant with expanded study population.
32	Appendix 1: Time and Events Schedule, p. 42	Specific authorization forms for release of non-[redacted] health plan claims data	Addition of claims release for non-[redacted] patients to reflect expanded study population and collection of claims data.
33	Appendix 1: Time and Events Schedule, Note 2, p. 43	2) Healthcare resource utilization and pharmacy prescription data will be extracted from health plan medical and pharmacy claims ~~the HIRD~~ and will not be entered into the eCRF.	Update to reflect expanded study population and collection of claims data.
34	Appendix 1: Time and Events Schedule, Medication Footnote, p. 44	[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.	Footnote clarifying time frame for medication data collected.
35	Appendix 1: Time and Events Schedule, Footnote f, p. 44	~~[f]~~ Data from health plan medical and pharmacy claims ~~the HIRD~~. Data will be extracted ~~from the HIRD~~ at the end of the study, but [redacted]	Update to reflect expanded study population and collection of claims data.

		will include data from patient randomization through EOS or withdrawal.	

Summary of Changes
NN95359-4416 Protocol Version 4.0, dated 05DEC2019

Number	Section/Page	Change	Rationale
1	Global Change, Patient Eligibility	Oral semaglutide is not allowed as one of the 1-2 oral antidiabetic medications in patient eligibility criteria.	Protocol update following approval oral formulation of semaglutide.
2	Global Change, Study Treatments	Formulation of semaglutide for study is subcutaneous only. • Oral semaglutide is not allowed in either treatment group during the study period.	Protocol update following approval oral formulation of semaglutide.
3	Global Change	~~August 21~~December 5, 2019 Version ~~4~~3.0	Update protocol date and version.
4	Global Change, Study Treatments	semaglutide s.c.	Clarify formulation of semaglutide allowed for study treatment is subcutaneous only.
5	Study Approvals, p. 2	**Name:** [redacted] **Title:** [redacted] ~~Statistician~~ [redacted]	Update to study statistician.
6	Patients, Synopsis, p. 7 Section 4.2, Practice and Patient Selection, p. 21	….adult T2DM patients on up to 2 oral antidiabetic medications, excluding oral semaglutide, ….	Update description of study population to reflect exclusion of oral semaglutide as one of the eligible antidiabetic medications patients can be on prior to eligibility assessment.
7	Study Design, Synopsis, p. 8 Section 4.1, Study Design, p. 20	All oral and injectable antidiabetic medications are allowed at the study physicians' discretion, with the exception of any formulation of semaglutide in the SOC group and oral semaglutide in the semaglutide group.	Oral semaglutide is not allowed in either treatment group during the study period.
8	Exclusion Criteria, #2	6.) Treatment with more than 2 oral antidiabetic medications, [redacted]	Treatment with oral semaglutide is not allowed

	Synopsis, p. 8 Section 4.2.4, Patient Exclusion Criteria, p. 22	oral semaglutide, or any injectable medication in a period of 30 days before the day of eligibility assessment. Temporary/emergency use of any type of insulin is allowed, as is prior insulin treatment for gestational diabetes	prior to patient eligibility assessment.
9	Abbreviations, p. 12	s.c. Subcutaneous	Additional abbreviation.
10	Section 1.1, Background and Rationale, p. 16	This local US study will enroll adult patients with T2DM who have inadequate glycemic control on up to 2 oral antidiabetic medications (excluding oral semaglutide), as defined by the need for treatment intensification with an additional antidiabetic oral or injectable medication per the study physician´s discretion.	Update description of study population to reflect exclusion of oral semaglutide as one of the eligible antidiabetic medications patients can be on prior to eligibility assessment.
11	Section 4.2.2, Patient Recruitment and Eligibility, p. 21	Eligible patients include adult T2DM patients whose physicians determine that they have inadequate glycemic control on 1 or 2 oral antidiabetic medications, excluding oral semaglutide.	Update description of study population to reflect exclusion of oral semaglutide as one of the eligible antidiabetic medications patients can be on prior to eligibility assessment.
12	Section 4.2.6, Patient Randomization, Figure 1, p. 23	Semaglutide ~~s.c.~~ once weekly	Remove redundancy in treatment group label in Figure 1.
13	Section 5.1, Enrollment Procedures, p. 23	The determination that a patient has inadequate glycemic control on up to 2 oral antidiabetic medications, excluding oral semaglutide, and the subsequent decision to intensify antidiabetic treatment	Oral semaglutide is not allowed as one of the 1-2 oral antidiabetic medications in patient eligibility criteria.
14	Section 5.2.2, Treatments, Semaglutide Group, p. 24	Add-on, discontinuation or dose modification of antidiabetic medication, including semaglutide s.c., during the study is allowed at the discretion of the study physician, with the exception of	Oral semaglutide is not allowed during the study period.

[redacted]

		oral semaglutide, which is not allowed during the study period.	
15	Section 5.2.2, Treatments, Copay assistance, p. 26	The only exceptions are if a patient initiates prescription coverage through Medicaid or if a patient loses pharmacy coverage, at which point all copay assistance will end.	Clarification of copay assistance.
16	Section 6.8.9, Evaluation of Study Population, p. 36	Two claims-based T2DM patient populations will be described and compared to the study population: (1) commercially-insured and Medicare Advantage [redacted] T2DM patients treated with up to 2 oral antidiabetic medications, excluding oral semaglutide, who undergo an antidiabetic treatment intensification, and (2) within the study sites, commercially-insured and Medicare Advantage [redacted] T2DM patients treated with up to 2 oral antidiabetic medications, excluding oral semaglutide, who are not enrolled in the study, but who undergo an antidiabetic treatment intensification.	Update to claims-based comparator populations for evaluation of study population to exclude oral semaglutide use.