Cover Page for SAP

Sponsor name:	Novo Nordisk A/S
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Official title of study:	PIONEER TEENS- Efficacy and safety of oral semaglutide versus placebo both in combination with metformin and/or basal insulin in children and adolescents with type 2 diabetes
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Statistical Analysis Plan

PIONEER TEENS - Efficacy and safety of oral semaglutide versus placebo both in combination with metformin and/or basal insulin in children and adolescents with type 2 diabetes

Substance name: Oral Semaglutide

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Version History

This Statistical Analysis Plan (SAP) for study NN9924-4437 is based on the protocol version 9.0 dated 14MAY2025.

SAP Version	Date	Change	Rationale
1.0		Not Applicable	Original version
2.0	21 May 2025	Section 4.2.2 For the primary analysis of primary estimand, the multiple imputation method using stepwise collapsing of group method to handle the missing data has been replaced with wash-out multiple imputation approach (WO-MI) method. Section 4.2.3 For the sensitivity analyses, the method for the comparator multiple imputation analysis I is replaced with the previous imputation method for primary analysis. The comparator multiple imputation analysis II is removed as it is similar to the WO-MI method. Section 4.3.2 Stratification factors in logistic regression model were added as suggested by the FDA. Section 1.2.3.2 and 4.3.2 The below additional supportive secondary endpoints were added: □ Change in BMI (kg/m2) □ Percent change in BMI (%) □ Change in BMI percentage of the 95th percentile (% points) Section 4.3.2 Under treatment policy estimand, for the time to additional anti diabetic medication endpoint analysis, an additional analysis after censoring the subjects who withdraw or are lost to follow-up has been added. Section 4.6.2 Subgroup analyses has been added to the primary endpoint based on race, sex, region, ethnicity and age group. Throughout the document: The unit for FPG has been changed from mmol/L to mg/dL.	Based on FDA feedback Based on FDA feedback Based on FDA feedback Based on FDA feedback Based on FDA feedback Based on FDA feedback Based on FDA feedback
3.0	10 March 2026	Section 1.2.4 and 6.1 The unit for FPG has been changed from mmol/L to mg/dL. Section 1.2.4, 4.4 and 6.1 The below endpoints are added • BMI (kg/m^2) • BMI (Percent change, %)	Based on previous FDA feedback Based on previous FDA feedback

SAP Version	Date	Change	Rationale
		• BMI percentage of the 95th percentile (% points) • Systolic and diastolic blood pressure (mmHg) Section 4.2.2 Added the seed for imputations Section 4.2.3 Added detailed explanation on tipping point analyses for secondary estimand. Section 4.4 Updated the unit of fasting C-peptide from pmol/L to nmol/L	Specifications for statistical programming To be more specific in the tipping point analysis for secondary estimand To align with the rest of the document

List of abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis covariance
BG	blood glucose
BMI	body mass index
Cavg	average concentration
CHMP	Committee for Medicinal Products for Human Use
CL/F	apparent clearance
DHEAS	dehydroepiandrosterone sulphate
ECG	electrocardiogram
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GLP-1	glucagon-like-peptide-1
HbA_{1c}	glycated haemoglobin
HDL	high density lipoprotein
HMW	high molecular weight
ICH	International Council for Harmonisation
IGF-1	insulin-like growth factor 1
ISPAD	International Society for Paediatric and Adolescent Diabetes
LH	luteinizing hormone
LDL	low-density lipoprotein
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MMRM	Mixed Model for Repeated Measurements
OGTT	oral glucose tolerance test
PIONEER	Peptide InnOvatioN for Early DiabEtes TReatment
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan

SAS	safety analysis set
SDS	standard deviation score
SMPG	self-measured plasma glucose
SNAC	sodium N-[8-(2-hydroxybenzoyl) amino] caprylate
T2D	type 2 diabetes
TSH	thyroid-stimulating hormone
VLDL	very low density lipoprotein
WHO	World Health Organisation

1 Introduction

1.1 Objectives, Endpoints, and Estimands

Objectives and Endpoints

Primary, secondary and exploratory objectives

1.1.1 Primary objective

To confirm superiority of oral semaglutide at the maximum tolerated dose* (3 mg, 7 mg or 14 mg) versus placebo on glycaemic control in children and adolescents (age 10 to <18 years) with type 2 diabetes on a background treatment of metformin or basal insulin or both.

*maximum tolerated dose is defined as maximum dose level defined according to individual glycaemic response and tolerability as assessed by the investigator

1.1.2 Secondary objectives

To assess and compare the efficacy of oral semaglutide at the maximum tolerated dose (3 mg, 7 mg or 14 mg) versus placebo on a background treatment of metformin or basal insulin or both on:

- Other parameters of glycaemic control
- Parameters of body composition
- Growth parameters
- Cardio-metabolic parameters

To assess and compare the safety and tolerability of oral semaglutide at the maximum tolerated dose (3 mg, 7 mg or 14 mg) versus placebo on a background treatment of metformin or basal insulin or both.

1.1.3 Exploratory objectives

To evaluate swallowability of tablet.

To assess and compare the efficacy of oral semaglutide at the maximum tolerated dose (3 mg, 7 mg or 14 mg) versus placebo on a background treatment of metformin or basal insulin or both on:

- Glucose metabolism parameters
- Oral glucose tolerance test (OGTT) parameters
- Adiponectin
- Lipid profile

To explore the beta-cell-preserving effect of oral semaglutide treatment in children and adolescents with type 2 diabetes on parameters derived from OGTT after the 12 weeks off-trial product period.

1.1.4 Estimands

For each efficacy endpoint, a primary (treatment policy) and a secondary estimand (hypothetical) are defined. The estimands are used to address the trial objectives in terms of two different aspects of the treatment effect of oral semaglutide. The purpose of each estimand is introduced below.

The treatment policy estimand evaluates the treatment effect (oral semaglutide vs placebo) including the effect of any additional anti-diabetic medication for all randomised subjects regardless of trial product discontinuation. For the treatment policy estimand, the occurrence of either intercurrent event is irrelevant, i.e. all randomised subjects contribute with baseline and landmark data regardless of whether treatment with trial product was initiated, whether trial product was discontinued or whether additional anti-diabetic medication was initiated (in-trial observation period).

The hypothetical estimand evaluates the treatment effect (oral semaglutide vs placebo) for all randomised subjects assuming that all subjects remained on trial product and did not use additional anti-diabetic medication (on-treatment principle). This assumes that neither intercurrent event will occur; i.e. all randomised subjects contribute with baseline data and with data collected from first dose of trial product until last dose of trial product or initiation of rescue medication (on-treatment without rescue medication observation period). The hypothetical estimand aims at estimating the achievable treatment effect without a confounding effect of rescue medication.

1.2 Primary, secondary and exploratory endpoints

1.2.1 Endpoints

For each assessment, the baseline assessment is defined as the latest available measurement obtained at either the randomisation visit (visit 2) or screening visit (visit 1). Thus, if a visit 2 assessment is missing (whether it was planned or not) then the assessment from visit 1, if available, will be used as the baseline assessment.

1.2.2 Primary endpoint

Change from baseline (week 0) to week 26 in glycosylated haemoglobin (HbA_{1c}) (%-point and mmol/mol)

1.2.3 Secondary endpoints

1.2.3.1 Confirmatory secondary endpoints

Change from baseline (week 0) to week 26 in:

- Fasting plasma glucose (FPG) (mg/dL)
- Body mass index (BMI) standard deviation score (SDS)

1.2.3.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

Change from baseline (week 0) to week 26 and to week 52 in:

- HbA_{1c} (%-point and mmol/mol) (only at week 52)
- FPG (mg/dL) (only at week 52)
- Body weight (kg)
- Body weight (relative change, %)
- Waist circumference (cm)
- BMI SDS (only at week 52)

- BMI percentile (age and gender adjusted) (%)
- BMI (kg/m^2)
- BMI (Percent change, %)
- BMI percentage of the 95th percentile (% points)
- Systolic and diastolic blood pressure (mmHg)

HbA_{1c} targets:
- HbA_{1c} <7.0% (53 mmol/mol) at week 26 (yes/no), American Diabetes Association (ADA) target and International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines from 2018[1]
- HbA_{1c} ≤6.5% (48 mmol/mol) at week 26 (yes/no), American Association of Clinical Endocrinologists (AACE) target
- HbA_{1c} <7.0% (53 mmol/mol) at week 52 (yes/no), ADA target and ISPAD guidelines from 2018[1]
- HbA_{1c} ≤6.5% (48 mmol/mol) at week 52 (yes/no), AACE target

Time to event:
- Time to additional anti-diabetic medication (to support the treatment policy estimand)
- Time to rescue medication (to support the hypothetical estimand)

Supportive secondary safety endpoints

Number of treatment-emergent adverse events (TEAEs) during exposure to trial product, assessed up to approximately 57 weeks

Hypoglycaemic episodes:
- Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes from randomisation to week 26
- Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks
- Treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episode from randomisation to week 26 (yes/no)
- Treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episode during exposure to trial product, assessed up to approximately 57 weeks (yes/no)

Change from baseline (week 0) to week 26 and week 52 in:
- biochemistry
  - amylase (U/L)
  - lipase (U/L)
- biomarkers
  - insulin-like growth factor 1 (IGF-1) (ng/mL)
  - insulin–like growth factor binding protein 3 (IGFBP 3) (ng/mL)
- hormones
  - calcitonin (pmol/L)
  - estradiol (for girls) (pmol/L)
  - testosterone (for boys) (nmol/L)

- prolactin (mIU/L)
- thyroid stimulating hormone (TSH/thyrotropin) (mIU/L)
- follicle stimulating hormone (FSH) (mIU/mL)
- luteinizing hormone (LH) (mIU/mL)
- dehydroepiandrosterone sulfate (DHEAS) (µmol/L)

Anti-semaglutide antibodies endpoints during 57 weeks:
- Anti-semaglutide antibody status.
- Anti-semaglutide antibody titer.
- Anti-semaglutide antibodies with *in vitro* neutralising effect to semaglutide
- Anti-semaglutide antibodies cross reacting with endogenous GLP-1
- Cross reacting antibodies with in vitro neutralising effect to endogenous GLP-1

Other supportive safety endpoints

The following will be assessed at week 26 and week 52:
- Height velocity (cm/year)

Safety assessments

The safety assessments are change from baseline (week 0) to week 26 and week 52 in:
- Height SDS
- Bone age assessment, X-ray (only at week 52) (years)
- Pubertal assessment (Tanner staging) (stage 1-5 where 5 is full sexual maturity)
- Pulse rate (beats/minute)

Change from pre-dose to post-dose (25 and 40 min) at week 12 and week 26 in:
- Lactate (mmol/L)

Supportive secondary pharmacokinetic endpoints

Pharmacokinetic (PK) sampling of semaglutide from eight visits over the treatment period of 52 weeks with three samples performed during the dose escalation period will be included in an analysis comparing the following PK properties to historical adult data, at steady state:
- Apparent clearance (CL/F) (L/h)
- Average concentration (C_{avg}) (nmol/L)

SNAC PK samples collected in this trial will be evaluated using relevant summary statistics and compared to historical adult data:
- SNAC plasma concentrations (ng/mL)

1.2.4 Exploratory endpoints

Exploratory efficacy endpoints

Evaluated after intake of first tablet (week 0) and after 26 weeks:
- Swallowability of semaglutide tablet (questionnaire)

Change from baseline (week 0) to week 26 and week 52 in:

- fasting lipid profile
  - cholesterol, low density lipoprotein (LDL), very low density lipoprotein (VLDL), high density lipoprotein (HDL) and triglycerides (mmol/L)

Change from baseline (week 0) to week 26, week 52 and week 64 in:

- adiponectin
  - total (ng/mL)
  - high molecular weight (HMW) (ng/mL)

Change from baseline (week 0) to week 26, week 52, week 57, and week 64 in:

- glucose metabolism
  - fasting insulin (pmol/L)
  - fasting pro-insulin (pmol/L)
  - pro-insulin to insulin ratio (%)
  - fasting glucagon (pg/mL)
  - fasting C-peptide (nmol/L)
  - homeostasis model assessment (HOMA-B and HOMA-IR) (ratio to baseline)

Change from baseline (week 0) to week 57 and to week 64 in:

- HbA_{1c} (%-point and mmol/mol)
- FPG (mg/dL)
- Body weight (kg)
- Body weight (relative change, %)
- Waist circumference (cm)
- BMI SDS
- BMI percentile (age and gender adjusted) (%)
- BMI (kg/m^2)
- BMI (Percent change, %)
- BMI percentage of the 95th percentile (% points)
- Systolic and diastolic blood pressure (mmHg)

The following endpoints are evaluated as change from baseline (week 0) to week 52 and to week 64 in:

- OGTT-derived endpoints
  - Incremental C-peptide ($iAUC_{cp,0\text{-}120\ min}$) (nmol/L)
  - Incremental insulin ($iAUC_{ins,0\text{-}120\ min}$) (pmol/L)
  - Incremental glucose ($iAUC_{g,0\text{-}120\ min}$) (mmol/L)
  - 2-hour glucose value (mmol/L)
  - C-peptide index: Δ C-peptide from 0-30 minutes/Δ glucose from 0-30 minutes [$\Delta C_{30}/\Delta G_{30}$]) (nmol/mmol)
  - Insulinogenic index: Δ insulin from 0-30 minutes/Δ glucose from 0-30 minutes [$\Delta I_{30}/\Delta G_{30}$]) (pmol/mmol)
  - C-peptide derived oral disposition index (DIo; C-peptide index adjusted for insulin sensitivity [$\Delta C_{30}/\Delta G_{30}$]) x $1/I_F$) (1/nM)

- Insulin derived oral disposition index (DIo; insulinogenic index adjusted for insulin sensitivity [$\Delta I_{30}/\Delta G_{30}$]) x $1/I_F$) (1/nM)
- Incremental glucagon relative to glucose ($iAUC_{glucagon,0\text{-}120\ min}$) (pg/mL)
- Early phase glucagon response relative to glucose after oral glucose ingestion (Δ glucagon from 0-30 minutes x Δ glucose from 0-30 minutes [$\Delta Glucagon_{30}$ x ΔG_{30}]) (pg/mL x mmol)

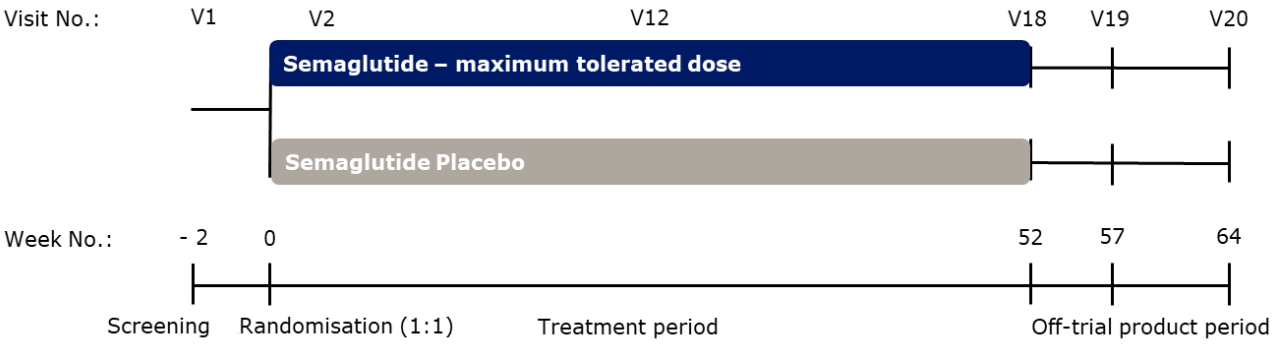
1.3 Study Design

This is a randomised, double-blind, placebo-controlled, parallel-group, multi-national, and multi-centre clinical trial that includes a 52-week treatment period followed by a 12-week off-trial product follow-up period in subjects aged 10 to <18 years (at randomisation) with T2D diagnosed according to the most recent ADA criteria[2]. Subjects will be randomised in a 1:1 manner to receive either oral semaglutide or oral semaglutide placebo (hereafter referred to as placebo) once daily in addition to background treatment with metformin or basal insulin or both, in addition to diet and exercise for 52 weeks. Randomisation will be stratified by sex (male or female) and by age (<14 years of age or ≥14 years of age). The stratification is done to ensure an even distribution of males vs. females and age groups across treatment groups.

The trial consists of a 2-week screening period during which time all screening parameters must be assessed. If eligible according to the inclusion and exclusion criteria, subjects are to be randomised to either oral semaglutide or placebo treatment for 52 weeks. All subjects will be dose-escalated to an individual maximum tolerated dose. For the duration of the trial, subjects should be on stable background treatment with either metformin, basal insulin or a combination of both, all in addition to diet and exercise. After the 52-week treatment period, all subjects will continue in a 12-week follow-up period with visits at week 57 and week 64 (end-of-trial visit). The maximum duration of the trial including the 2-week screening and the 12-week follow-up period will be up to 66 weeks (2+52+12 weeks), with an additional 2 weeks if the visit window is fully used. The follow-up period is 12 weeks plus a 7-day visit window.

No interim analyses will be performed during the trial.

Figure 1 Trial design



2 Statistical Hypotheses

Three confirmatory hypotheses will be evaluated based on the primary. For the primary endpoint, change in HbA1c from baseline to week 26, the following confirmatory one-sided hypothesis of superiority will be tested. Let the mean treatment difference (oral semaglutide at the maximum tolerated dose (3 mg, 7 mg or 14 mg) – placebo) be defined as μ.

The null (H0) and alternative (HA) hypotheses to be tested are:

$$H0: \mu \geq 0 \text{ \%-point against } HA: \mu < 0 \text{ \%-point}$$

For the confirmatory secondary endpoint, change in FPG from baseline to week 26, the following confirmatory one-sided hypothesis of superiority will be tested.

$$H0: \mu \geq 0 \text{ mmol/L against } HA: \mu < 0 \text{ mmol/L}$$

For the other confirmatory secondary endpoint, change in BMI SDS from baseline to week 26, the following confirmatory one-sided hypothesis of superiority will be tested.

$$H0: \mu \geq 0 \text{ against } HA: \mu < 0$$

Operationally, the hypotheses will be evaluated by two-sided tests.

2.1 Hierarchical testing

The confirmatory secondary endpoints will be analysed in a hierarchical manner in the following order:

- Change from baseline (week 0) to week 26 in HbA1c (primary efficacy endpoint)
- Change from baseline (week 0) to week 26 in FPG
- Change from baseline (week 0) to week 26 in BMI SDS

In order to confirm superiority for an endpoint in the hierarchical list above, the test for that endpoint and the tests for the endpoints higher up in the hierarchy must all be concluded significant with a difference favouring oral semaglutide.

3 Analysis Sets

The same definitions of analysis set as used for adults in the oral semaglutide phase 3a program will be used for the paediatric trial. The following analysis sets are defined in accordance with ICH E9[3].

- The full analysis set (FAS) comprises all randomised subjects. Subjects contribute to a treatment group based on the trial product they were randomised to receive.
- The safety analysis set (SAS) comprises all randomised subjects who received at least one dose of trial product. Subjects contribute to a treatment group based on the trial product they actually received for the majority of the on-treatment observation period.

The FAS will primarily be used in the evaluation of the efficacy endpoints; the SAS will be used for the evaluation of the safety endpoints, exclusively.

Observation periods

For the efficacy and safety evaluations, five different observation periods will be defined:

- The **in-trial** observation period – the time period from when a subject is randomised up to and including the 5-week follow-up visit, including any period after initiation of rescue medication or premature discontinuation of trial product. This observation period includes the 52-week treatment period and the 5-week follow-up visit (week 0 – week 57).
- The **extended in-trial** observation period – the time period from when a subject is randomised until the final scheduled visit, including any period after initiation of rescue medication or premature discontinuation of trial product. This observation period includes the 52-week treatment period and the 12-week follow-up visit (week 0 – week 64).
- The **on-treatment** observation period – the time period when a subject is on treatment with trial product, including any period after initiation of rescue medication.
- The **on-treatment without rescue medication** observation period – the time period when a subject is on treatment with trial product, excluding any period after initiation of rescue medication.
- The **12-week follow-up** observation period – the time period from when a subject has completed the 52-week treatment period until the final scheduled visit.

The **in-trial** observation period begins at the date of randomisation and ends at the first of the following time points:

- the 5-week follow-up visit (visit 19)
- the last contact for subjects who premature discontinue trial product, or who withdraw from trial, are lost to follow-up or die prior to the 5-week follow-up visit.

The **extended in-trial** observation period begins at the date of randomisation and ends at the final scheduled visit, which can be one of the below:

- the end-of-trial (visit 20)
- the last contact for subjects who premature discontinue trial product, withdraw from trial, are lost to follow-up or die

The **on-treatment** observation period begins at the date of first dose of trial product; the end date depends on the assessment being evaluated:

- For all efficacy assessments and certain safety assessments (laboratory assessments, physical examination and vital signs), a plus-3-day window (i.e. the 3-day visit window) is used and the period ends at the first of the following time points:
    - last dose of trial product plus a 3-day window
    - end of the in-trial observation period

- For the remaining safety assessments (ECGs, eye examination categories, AEs, and hypoglycaemic episodes), a plus-38-day window (i.e. the 5-week follow-up period plus the 3-day visit window) is used and the period ends at the first of the following time points:
    - 5-week follow-up visit (visit 19)
    - last dose of trial product plus 38 days
    - end of the in-trial observation period.

The **on-treatment without rescue medication** observation period begins at the date of the first dose of trial product and ends at the first of the following time points:

- end of the on-treatment observation period
- initiation of rescue medication (if any)

The **12-week follow-up** observation period begins at the date of the end-of-treatment visit (visit 18) and ends at the last scheduled visit, which can be one of the below:

- the end-of-trial visit (visit 20)
- the last contact for subjects who withdraw from trial, are lost to follow-up or die

For the efficacy endpoints, the treatment policy estimand will be evaluated based on data from the in-trial observation period and the hypothetical estimand will be evaluated based on data from the on-treatment without rescue medication observation period. The safety evaluation will primarily be based on the on-treatment observation period, except for deaths and AE types with potentially long latency between onset and diagnosis, for which the in-trial observation period will be used. The observation period determines what data subjects contributes with to a specific analysis. Baseline values are by definition included in all observation periods; other data points collected outside the observation period used for an analysis will be considered missing.

4 Statistical Analyses

4.1 General Considerations

Data from all sites will be analysed and reported together.

The latest available measurement, at or prior to the randomisation visit, will be used as the baseline measurement. If no measurement(s) have been obtained, at or prior to randomisation, the baseline value will be left missing.

Results from a statistical analysis will as a minimum be presented by the estimated treatment contrasts with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference with no multiplicity adjustments.

If no statistical analysis is specified, data will be presented using relevant summary statistics.

4.2 Primary Endpoint Analysis

4.2.1 Definition of Endpoint

The primary endpoint is change from baseline to week 26 in HbA_{1c} (%-point and mmol/mol).

4.2.2 Main Analytical Approach

Primary analysis for the primary estimand

The primary estimand will be estimated based on the FAS using week 26 measurements from the in-trial observation period. The primary statistical analysis will be a pattern mixture model using multiple imputations to impute missing week 26 data, assuming that such data were missing at random (MAR).
Wash-out multiple imputation approach (WO-MI): Missing values of HbA_{1c} at week 26 will be imputed using the Imputation, Analysis, Pooling framework.

Imputation: Defines an imputation step procedure utilising different imputation models depending on randomised treatment group and end of treatment status as describe in the following steps:

1. For on-treatment participants in the treatment group, missing HbA_{1c} values for week 26 will be imputed based on observed data from the on-treatment participants. An analysis of covariance model (ANCOVA) with baseline HbA_{1c} will be used to impute 1000 values for each participant with missing data. This will result in 1000 complete data sets for on-treatment participants in the treatment groups.

2. For the participants in placebo, missing HbA_{1c} values for week 26 will be imputed based on all observed data at all time points in the placebo group and using an MMRM model with study arm as factor and baseline HbA1c as a covariate – both nested within visit. An unstructured covariance matrix for measurements within the same participant will be employed. If necessary for convergence, a toeplitz or compound symmetry structure will be assumed instead of the unstructured covariance matrix. Each missing value of HbA_{1c} at week 26 is imputed 1000 times by random

sampling from normal distribution with the MMRM-predicted value at week 26 as mean and variance as a sum of prediction variance and residual variance.

3. For off-drug participants in the treatment group, missing HbA_{1c} values for week 26 will be imputed from the placebo group assuming that all drug effect will be washed out and gone before the landmark visit. The imputation procedure will be similar to jump to reference multiple imputation. An imputation model will be fitted to each of 1000 complete data sets resulting from MMRM imputation for the placebo in the previous step. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation model from each of 1000 fits will then be used to impute missing week 26 HbA_{1c} values once, ultimately resulting in 1000 complete data sets for off-drug participants in the treatment group.

The multiple imputations will be generated using Novo Nordisk trial number 99244437 as seed number.

Analysis model: For each of the 1000 (now complete) imputed datasets the change in HbA_{1c} from baseline to week 26 will be analysed using an ANCOVA with treatment, sex, age group and the interaction between sex and age group as categorical fixed effects and baseline HbA_{1c} as covariate.

Pooling: The results obtained from analysing the datasets will be combined using Rubin's rule to draw inference. Superiority in change in HbA_{1c} will be claimed if the upper limit of the 2-sided 95% confidence interval for the estimated treatment difference at week 26 obtained from the primary analysis is below 0%.

Primary analysis for the secondary estimand

The secondary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 26 from the on-treatment without rescue observation period. The primary analysis for the secondary estimand is based on a Mixed Model for Repeated Measurements (MMRM) that accounts for the uncertainty pertaining to missing data. The MMRM approach assumes that data are MAR.

As dependent variables, the MMRM model will include all post baseline values collected at scheduled visits up to and including week 26. The independent effects will be trial product, sex, age group and the interaction between sex and age group as categorical fixed effects and the baseline value as a covariate, all nested within visit. An unstructured covariance matrix is employed for HbA_{1c} values of each subject, assuming that measurements from different subjects are independent. A restricted maximum likelihood will be used.

4.2.3 Sensitivity Analysis

To investigate the sensitivity of the primary analysis results, sensitivity analyses will be performed for both estimands. In line with draft ICH E9 (R1) these analyses will primarily evaluate the sensitivity of the results due to the impact of missing data. **The estimation of the primary estimand** will be repeated based on FAS using the in-trial observation period using the following sensitivity analyses:

- **Comparator multiple imputation analysis I**: Missing week 26 data will be imputed for 4 groups of subjects depending on the treatment arm and whether subjects at week 26 (i) have discontinued trial product or initiated rescue medication or (ii) are still on trial product and have not initiated rescue medication. For this imputation approach, it is assumed that the distribution of missing data for subjects in a specific treatment arm resembled the distribution of available data for other subjects in the same treatment arm with similar trial product and rescue medication statuses at week 26.
  Missing values for each group will be imputed as follows:
  An analysis of covariance (ANCOVA) with baseline HbA_{1c} measurement as a covariate will be fitted to observed values of the change from baseline in HbA_{1c} at week 26.
  The estimated parameters for location and dispersion will be used to impute 1000 values for each subject with missing week 26 data based on baseline HbA_{1c}. Thus, 1000 complete data sets will be generated including observed and imputed values.
  If data is too sparse to fit the described imputation model the groups will be collapsed in below order until the imputation model can be fitted:
    - Subjects who have discontinued trial product or initiated rescue medication will be collapsed regardless of randomised treatment.
    - Subjects who have discontinued trial product or initiated rescue medication regardless of randomised treatment and subjects who are still on trial product, who have not initiated rescue medication and who are randomised to placebo will be collapsed.
- **Two-way tipping-point multiple imputation analysis**: Missing data will be imputed as for the primary analysis. Then, for each confirmed hypothesis, penalties which are required to turn the result of the primary analysis from statistically significant to non-significant will be added to the imputed week 26 values for both the oral semaglutide arm and for the placebo arm simultaneously.

The estimation of the secondary estimand will be repeated based on FAS using the on-treatment without rescue medication observation period and a two-way tipping-point analysis.
In this sensitivity analysis, missing data will first be imputed using a sequential multiple imputation approach assuming MAR. The imputation will be done as described below:

- Intermittent missing values in the on-treatment without rescue medication observation period will be imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each treatment group separately and a 1000 copies of the data set will be generated.

- A sequential regression approach for imputing monotone missing values at planned visits will be implemented starting with the first visit after baseline and sequentially continuing to the planned end of treatment visit. For each treatment group an analysis of covariance model will be used to impute missing values at each planned visit. The model will include region as categorical effect and baseline and post-baseline values prior to the visit in question as covariates.

Secondly, for all oral semaglutide treatment arms a penalty will be added to the imputed values at week 26. The approach is to gradually increase this penalty until all confirmed conclusions from the

secondary analysis are reversed. For each hypothesis tested the specific value of the penalty that reverses the conclusion will be used to evaluate the robustness of the primary analysis results.

4.2.4 Supplementary Analysis

4.3 Secondary Endpoints Analysis

4.3.1 Confirmatory Secondary Endpoints

4.3.1.1 Definition of Endpoints

- Change from baseline (week 0) to week 26 in FPG (mg/dL)
- Change from baseline (week 0) to week 26 in BMI SDS

4.3.1.2 Main Analytical Approach

The change from baseline to week 26 in FPG will be analysed using same model approaches as for change from baseline to week 26 in HbA_{1c} with baseline FPG included in the model instead of baseline HbA_{1c}.

The change from baseline to week 26 in BMI SDS will be analysed using same model approaches as for change from baseline to week 26 in HbA_{1c} with baseline BMI SDS included in the model instead of baseline HbA_{1c}.

4.3.1.3 Sensitivity Analysis

Not applicable.

4.3.1.4 Supplementary Analysis

Not applicable.

4.3.2 Supportive Secondary Endpoints

Continuous efficacy endpoints

The continuous efficacy endpoints are change from baseline (week 0) to week 52 in:

- HbA_{1c} (%-point and mmol/mol)
- FPG (mg/dL)
- BMI SDS

and change from baseline (week 0) to week 26 and to week 52 in:

- Body weight (kg)
- Body weight (relative change, %)
- Waist circumference (cm)
- BMI percentile (age and gender adjusted) (%)
- BMI (kg/m^2)
- BMI (Percent change, %)
- BMI percentage of the 95th percentile (% points)
- Systolic and diastolic blood pressure (mmHg)

The above continuous endpoints will be analysed separately using similar model approaches as for change from baseline to week 26 in HbA_{1c} with the associated baseline response as a covariate. The BMI SDS will be calculated using the LMS[4] method using the WHO 2007[5, 6]. The BMI percentile related endpoints will be calculated using the CDC Growth Charts 2012[7].

For evaluation of the primary estimand the analysis will be performed separately for week 26 and 52. For evaluation of the secondary estimand the MMRM will include all scheduled post-baseline measurement up to and including week 52. From this model the estimated treatment differences (ratios) will be presented at week 26 and week 52 with 95% confidence intervals and two-sided p values for test of no difference. For endpoints where the first planned visit falls later than 8 weeks after randomisation, the baseline will not be carried forward.

Binary efficacy endpoints

The binary HbA_{1c} endpoints are:

- HbA_{1c} <7.0% (53 mmol/mol) at week 26 (yes/no), ADA target and ISPAD guidelines from 2018[1]
- HbA_{1c} ≤6.5% (48 mmol/mol) at week 26 (yes/no), AACE target
- HbA_{1c} <7.0% (53 mmol/mol) at week 52 (yes/no), ADA target and ISPAD guidelines from 2018[1]
- HbA_{1c} ≤6.5% (48 mmol/mol) at week 52 (yes/no), AACE target

Handling of missing data for binary endpoints

HbA_{1c}

Missing data for the above four binary endpoints will be accounted for using multiple imputation techniques. For the primary estimand the binary endpoints will be calculated as dichotomisations of the 1000 multiple imputations underlying the primary MI analysis. For the secondary estimand the model will be implemented using a sequential imputation approach assuming MAR. The imputation will be done as described below:

Intermittent missing values in the on-treatment without rescue observation period will be imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each treatment group separately and 1000 copies of the data set will be generated.

A sequential regression approach for imputing monotone missing values at planned visits will be implemented starting with the first visit after baseline and sequentially continuing to the planned end of treatment visit. For each treatment group an analysis of covariance model will be used to impute missing values at each planned visit. The model will include the baseline and post-baseline values prior to the visit in question as covariates.

The binary endpoints will be derived as dichotomisations of the 1000 multiple imputations from the sequential imputation.

For both estimands, each of the 1000 complete data sets will be analysed using a logistic regression model with treatment, sex, age group as categorical fixed effects and baseline HbA1c as covariate.

The results from this model will be used to predict the probability of achieving the efficacy endpoint for all participants had they (counterfactually) been assigned to each specific treatment. Average treatment difference in probability will be estimated by subtracting the average predicted probabilities and the corresponding standard errors will be calculated using the delta-method.

The results obtained from analysing the individual datasets will be combined using Rubin's rule to draw inference.

In addition to these endpoints the following will be explored:

- HbA_{1c} <7.0% (53 mmol/mol) without severe or BG confirmed symptomatic hypoglycaemia episodes at week 26 (yes/no)
- HbA_{1c} <7.0% (53 mmol/mol) without severe or BG confirmed symptomatic hypoglycaemia episodes at week 52 (yes/no)

Time to event:

- Time to additional anti-diabetic medication (to support the treatment policy estimand)
- Time to rescue medication (to support the hypothetical estimand)

Definition of additional anti-diabetic medication: New anti-diabetic medication and/or intensification of anti-diabetic medication initiated at or after randomisation and before (planned) end-of-treatment.

Definition of rescue medication: New anti-diabetic medication and/or intensification of anti-diabetic medication initiated at or after randomisation and before last date on trial product. This is a subset of the additional anti-diabetic medication.

The following rules will be applied based on the concomitant medication data reported by the investigator, to determine whether or not the recorded anti-diabetic medication is: 1) New anti-diabetic medication or 2) Intensification of anti-diabetic medication.

- ***New anti-diabetic medication***: Anti-diabetic medication (4th-level ATC code) that is initiated at or after randomisation and is new compared to the anti-diabetic background medication used at randomisation (see above) and with a dosing duration of more than 21 days
- ***Intensification of anti-diabetic medication***: A more than 20% increase in the dose of anti-diabetic medication at or after randomisation as compared to the anti-diabetic medication dose at randomisation (5th-level ATC code not changed) and with a dosing duration of more than 21 days.

More than 21 days is chosen as a minimum duration for the medication to be considered as 'anti diabetic medication'. This threshold is set to ensure that the short-term durations (i.e. ≤ 21 days) of anti-diabetic medication (e.g. in connection with concurrent illnesses) are not included because such intensifications are not likely to affect the efficacy endpoints.

Treatment policy estimand: Time to additional anti-diabetic medication

The treatment policy estimand is addressed for the FAS using the in-trial observation period and additional anti-diabetic medication will be considered an event regardless of whether or not subjects

have discontinued treatment. Time from randomisation to additional anti-diabetic medication will be analysed using a Cox proportional hazards model with treatment and sex, age group and the interaction between sex and age group as categorical fixed effects as categorical fixed effects and baseline HbA_{1c} as a covariate. From this analysis the estimated Hazard ratios between each of the oral semaglutide dose levels and placebo together with associated two-sided 95% CIs and unadjusted two-sided p-values will be presented. The analysis aims to address the need of additional anti-diabetic medication regardless of whether this is due to lack of effect or tolerability. Switch to other anti-diabetic treatment is therefore also considered an event and withdrawn subjects or subject lost to follow-up will be considered as having an event on the day of withdrawal. Subjects will be censored on the day before planned end of treatment visit.

An additional analysis, censoring the subjects who withdraw or are lost to follow-up, will be performed. The analysis will be performed as mentioned above. Subjects withdrawn or lost to follow up will be censored on the day of last available visit.

Hypothetical estimand: Time to rescue medication

The hypothetical estimand is addressed for the FAS using the on-treatment without rescue medication observation period. Time from first dose of trial product to initiation of rescue medication will be analysed using the same model as described above. The analysis aims to address lack of effect and only initiation of rescue medication as add-on to randomised treatment is considered an event. Switch to other anti-diabetic treatment is not considered an event and as a consequence subjects will be censored on the day before date of last trial product. Potential events occurring between randomisation and first date on trial product will be included in the analysis as events at day 0, in order to count all events of rescue medication.

Safety endpoints and assessments

The safety endpoints will be evaluated based on SAS using the on-treatment observation period unless otherwise stated. The following endpoints are used to support the safety objectives:

- Adverse events
- Number of treatment-emergent AEs (TEAEs) during exposure to trial product, assessed up to approximately 57 weeks

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding. A treatment-emergent AE is defined as an AE with onset in the on-treatment observation period.

TEAEs will be summarised in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 patient years of observation time (R) for the on-treatment observation period. Supportive summaries of AEs will be made for the in-trial observation period.

Furthermore, AEs with onset in the 12-week follow-up observation period will be summarised similarly.

Hypoglycaemic episodes

- Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes from randomisation to week 26
- Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks
- Treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episode from randomisation to week 26 (yes/no)
- Treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episode during exposure to trial product, assessed up to approximately 57 weeks (yes/no)

Hypoglycaemic episodes will be summarised for the SAS and the on-treatment observation period only. Data on treatment-emergent hypoglycaemic episodes will be presented in terms of the number of subjects with at least one episode, the percentage of subjects with at least one episode (%), the total number of episodes and the episode rate per 100 patient years of observation time.

Analysis of severe or BG-confirmed symptomatic hypoglycaemic endpoints

The number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes will be evaluated for the on-treatment period using a negative binomial regression model with a log-link function and the logarithm of the duration of the subject's on-treatment observation period as offset. The model will include treatment and sex, age group and the interaction between sex and age group as categorical fixed effects and baseline HbA_{1c} as covariate. The binary endpoint showing whether a subject has at least one treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episode will be analysed using a logistic regression model with treatment, sex, age group as categorical fixed effects and baseline HbA1c as covariate.

Other safety endpoints

Change from baseline (week 0) to week 26 and to week 52 in:

- Biochemistry
  - amylase (U/L)
  - lipase (U/L)
- Biomarkers
  - IGF-1 (ng/mL)
  - IGFBP 3 (ng/mL)
- Hormones
  - calcitonin (pmol/L)
  - estradiol (for girls) (pmol/L)
  - testosterone (for boys) (nmol/L)
  - prolactin (mIU/L)
  - TSH/thyrotropin (mIU/L)
  - FSH (mIU/mL)
  - LH (mIU/mL)
  - DHEAS (µmol/L)

The biomarker-, biochemistry and hormone-related safety endpoints will be evaluated using the primary analysis for the secondary estimand based on SAS using the on-treatment observation

period. Endpoints will be analysed separately as described above for continuous efficacy endpoints. Results will be presented at week 26 and 52. Amylase and lipase endpoints will be log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

Anti-semaglutide antibodies endpoints

Anti-semaglutide antibodies endpoints during 57 weeks:

- Anti-semaglutide antibody status.
- Anti-semaglutide antibody titer.
- Anti-semaglutide antibodies with *in vitro* neutralising effect to semaglutide
- Anti-semaglutide antibodies cross reacting with endogenous GLP-1
- Cross reacting antibodies with in vitro neutralising effect to endogenous GLP-1)

The categorical antibodies endpoints will be summarised descriptively as counts and relative frequencies.

Other supportive safety endpoints

The following will be assessed at week 26 and 52:

- Height velocity (cm/year)

Height will be summarised descriptively by treatment arm and visit.

The height velocity will be calculated at week 26 and week 52. The week 26 velocity will be the difference in height at week 26 and baseline, divided by the actual time elapsed in that period. Similarly the height velocity at week 52 will be based on the heights at weeks 26 and 52. As some of the subjects will be at an age where they are no longer growing, the height velocity will be tabulated both for all subjects, and also only for subjects still growing (a height velocity <1.0 cm/year is defined as no longer growing).

Safety assessments

Change from baseline (week 0) to week 26 and to week 52 in:

- Height SDS
- Bone age assessment, X-ray (only at week 52) (years)
- Pubertal assessment (Tanner staging) (stage 1-5 where 5 is full sexual maturity)
- Pulse rate (beats/minute)

Change from pre-dose to post-dose (25 and 40 minutes) at week 12 and week 26 in:

- Lactate (mmol/L)

The safety assessments will be summarised descriptively by treatment arm and visit.

Supportive secondary pharmacokinetic endpoints

PK sampling of semaglutide from eight visits over the treatment period of 52 weeks with three samples performed during the dose escalation period will be included in a population PK analysis (for more details, see section 10.4 in protocol) comparing the following PK properties to historical adult data, at steady state:

- Apparent clearance (CL/F) (L/h)
- Average concentration (C_{avg}) (nmol/L)

SNAC PK samples collected in this trial will be evaluated using relevant summary statistics and compared to historical adult data:

- SNAC plasma concentrations (ng/mL)

4.4 Exploratory Endpoints Analysis

Exploratory efficacy endpoints

Evaluated after intake of first tablet (week 0) and after 26 weeks:

- Swallowability of semaglutide tablet (questionnaire)

This will be evaluated using relevant summary statistics.

Change from baseline (week 0) to week 26 and to week 52 in:

- Glucose metabolism
  - fasting insulin (pmol/L)
  - fasting pro-insulin (pmol/L)
  - pro-insulin to insulin ratio (%)
  - fasting glucagon (pg/mL)
  - fasting C peptide (nmol/L)
  - homeostasis model assessment (HOMA-B and HOMA-IR) (ratio to baseline)
- Fasting lipid profile
  - cholesterol, LDL, VLDL, HDL and triglycerides (mmol/L)

Glucose metabolism will be summarised descriptively by treatment arm and visit. In addition, glucose metabolism will be evaluated by use of basal insulin at randomisation (yes/no). Fasting lipids will be analysed separately using similar model approaches as for the primary endpoint with the associated baseline value as a covariate. Glucose metabolism and fasting lipids will be log-transformed, and for fasting lipids will be done prior to analysis with the associated log-transformed baseline value as a covariate.

Change from baseline (week 0) to week 26 and to week 52:

- Adiponectin
  - total adiponectin (ng/mL)
  - HMW (ng/mL)

Adiponectin related endpoints will be evaluated using both the treatment policy estimand and the hypothetical estimand. The above continuous endpoints will be analysed separately using similar model approaches as for change from baseline to week 26 in HbA_{1c} with the associated baseline

response as a covariate. Furthermore, the endpoints will be explored using descriptive statistics based on FAS, including relevant summary statistics for total adiponectin, HMW adiponectin and HMW adiponectin –to–total adiponectin ratio.

OGTT-derived endpoints

The endpoints are change from baseline (week 0) to week 52 in:

- Incremental C-peptide ($iAUC_{cp,0\text{-}120\ min}$) (nmol/L)
- Incremental insulin ($iAUCins,_{0\text{-}120\ min}$) (pmol/L)
- Incremental glucose ($iAUC_{g,0\text{-}120\ min}$) (mmol/L)
- 2-hour glucose value (mmol/L)
- C-peptide index: Δ C-peptide from 0-30 minutes/Δ glucose from 0-30 minutes [$\Delta C_{30}/\Delta G_{30}$]) (nmol/mmol)
- Insulinogenic index: Δ insulin from 0-30 minutes/Δ glucose from 0-30 minutes [$\Delta I_{30}/\Delta G_{30}$]) (pmol/mmol)
- C-peptide derived oral disposition index (DIo; C-peptide index adjusted for insulin sensitivity [$\Delta C_{30}/\Delta G_{30}$]) x 1/IF) (1/nM)
- Insulin derived oral disposition index (DIo; insulinogenic index adjusted for insulin sensitivity [$\Delta I_{30}/\Delta G_{30}$]) x 1/IF) (1/nM)
- Incremental glucagon relative to glucose ($iAUC_{glucagon,0\text{-}120\ min}$) (pg/mL)
- Early phase glucagon response relative to glucose after oral glucose ingestion (Δ glucagon from 0-30 minutes x Δ glucose from 0-30 minutes [$\Delta Glucagon_{30}$ x ΔG_{30}]) (pg/mL x mmol)

The C-peptide index and the C-peptide derived oral disposition index endpoints will be evaluated using both the treatment policy estimand and the hypothetical estimand. These will be analysed separately using similar model approaches as for change from baseline to week 26 in HbA_{1c} with the associated baseline response as a covariate. All other OGTT related endpoints will be explored using relevant summary statistics

Exploratory endpoints related to the 12-week follow-up period

The following endpoints will be evaluated as change from baseline (week 0) to week 57 and to week 64:

- HbA_{1c} (%-point and mmol/mol)
- FPG (mmol/L)
- Body weight (kg)
- Body weight (relative change, %)
- Waist circumference (cm)
- BMI percentile (age and gender adjusted) (%)
- BMI (kg/m^2)
- BMI (Percent change, %)
- BMI percentage of the 95th percentile (% points)
- Systolic and diastolic blood pressure (mmHg)
- Glucose metabolism
    - fasting insulin (pmol/L)
    - fasting pro-insulin (pmol/L)
    - pro-insulin to insulin ratio (%)

- fasting glucagon (pg/mL)
- fasting C peptide (nmol/L)
- homeostasis model assessment (HOMA-B and HOMA-IR) (ratio to baseline)

The above endpoints will be summarised descriptively by treatment arm and visit based on FAS. In addition, glucose metabolism related endpoints will be evaluated by use of basal insulin at randomisation (yes/no). Glucose metabolism related endpoints will be log-transformed.

Change from baseline (week 0) to week 64:

- Adiponectin
  - total adiponectin (ng/mL)
  - HMW (ng/mL)

Adiponectin related endpoints will be evaluated using similar estimands as for the primary endpoint. The above continuous endpoints will be analysed separately using similar model approaches as for change from baseline to week 26 in HbA_{1c} with the associated baseline response as a covariate. Furthermore, the endpoints will be explored using descriptive statistics based on FAS, including relevant summary statistics for total adiponectin, HMW adiponectin and HMW adiponectin–to–total adiponectin ratio.

OGTT-derived endpoints

The endpoints are change from baseline (week 0) to week 64 in:

- Incremental C-peptide ($iAUC_{cp,0\text{-}120\ min}$) (nmol/L)
- Incremental insulin ($iAUCins,_{0\text{-}120\ min}$) (pmol/L)
- Incremental glucose ($iAUC_{g,0\text{-}120\ min}$) (mmol/L)
- 2-hour glucose value (mmol/L)
- C-peptide index: Δ C-peptide from 0-30 minutes/Δ glucose from 0-30 minutes [$\Delta C_{30}/\Delta G_{30}$]) (nmol/mmol)
- Insulinogenic index: Δ insulin from 0-30 minutes/Δ glucose from 0-30 minutes [$\Delta I_{30}/\Delta G_{30}$]) (pmol/mmol)
- C-peptide derived oral disposition index (DIo; C-peptide index adjusted for insulin sensitivity [$\Delta C_{30}/\Delta G_{30}$]) x 1/IF) (1/nM)
- Insulin derived oral disposition index (DIo; insulinogenic index adjusted for insulin sensitivity [$\Delta I_{30}/\Delta G_{30}$]) x 1/IF) (1/nM)
- Incremental glucagon relative to glucose ($iAUC_{glucagon,0\text{-}120\ min}$) (pg/mL)
- Early phase glucagon response to relative to glucose after oral glucose ingestion (Δ glucagon from 0-30 minutes x Δ glucose from 0-30 minutes [$\Delta Glucagon_{30}$ x ΔG_{30}]) (pg/mL x mmol)

The C-peptide index and the C-peptide derived oral disposition index endpoints will be evaluated using similar estimands as for the primary endpoint. These will be analysed separately using similar model approaches as for change from baseline to week 26 in HbA_{1c} with the associated baseline response as a covariate. All other OGTT-related endpoints will be explored using relevant summary statistics.

4.5 Other Safety Analysis

Not applicable.

4.5.1 Extent of Exposure

Not applicable.

4.5.2 Adverse Events

Not applicable.

4.6 Other Analysis

4.6.1 Other Variables and/or Parameters

Not applicable.

4.6.2 Subgroup Analysis

Subgroup analyses of the primary endpoint will be performed across ethnic groups (Not Hispanic or Latino, Hispanic or Latino), age group (<14 years of age or ≥14 years of age), sex (Male, Female), race (Asian, Black Or African American, Native Hawaiian Or Other Pacific Islander, Other, White) and region (Europe, Asia, North America or Other).

Subgroup analyses of the primary endpoint addressing the primary estimand will be carried out using the same imputation approaches and statistical models as used in the analyses of the primary endpoint. The treatment by subgroup interaction will be added to the ANCOVA model specified in section 4.2.2. For subgroup analyses by sex or age group, stratification group (sex * age group) will be replaced in the model by age group or sex, respectively.

The results of the subgroup analyses will be presented with treatment difference and treatment-by subgroup interaction p-values in table form and forest plots.

If a treatment arm has less than 5 subjects within a subgroup, the subgroup will be merged with another, until the criteria of at least 5 subjects per treatment arm and subgroup is reached. For ordered subgroups (age group), the merging will be done according to the order. For unordered subgroups (e.g. race, region), it will be done by merging the subgroups with the lowest number of subjects.

4.7 Interim Analysis

No interim analyses will be performed.

4.8 Changes to Protocol-planned Analysis

The main analyses were described in the protocol. However, clarifications, more detailed descriptions of endpoints and analyses are provided in the SAP. The changes from the protocol are summarized below:

- Details on the tipping point analysis for secondary estimand had been added in section 4.2.3
- The units of following endpoints in the Protocol and SAP are not available in the data. The TFLs will be based on the units available in the data:

Endpoints	Unit in Protocol/SAP	Unit in data
IGFBP 3	ng/mL	mg/L
FSH	mIU/mL	IU/L

Calcitonin	pmol/L	ng/L
Estradiol	pmol/L	ng/L
IGF-1	ng/mL	ug/L

5 Sample size determination

Please refer to section 10.1 in the protocol.

6 Supporting Documentation

6.1 Appendix 1: Definition and calculation of endpoints, assessments and derivations

Type	Title	Time frame	Unit	Details
Primary endpoint	Change from baseline to week 26 in HbA_{1c}	From baseline to week 26	% and mmol/mol	
Confirmatory secondary endpoint	• Change from baseline (week 0) to week 26 in FPG • Change from baseline (week 0) to week 26 in BMI SDS	From baseline (week 0) to week 26	mg/dL	
Supportive secondary endpoint	• Change from baseline (week 0) to week 52 in: o HbA1c (%-point and mmol/mol) o FPG (mg/dL) o BMI SDS • Change from baseline (week 0) to week 26 and to week 52 in: o Body weight (kg) o Body weight (relative change, %) o Waist circumference (cm) o BMI percentile (age and gender adjusted) (%) o BMI (kg/m^2) o BMI (Percent change, %) o BMI percentage of the 95th percentile (% points) o Systolic and diastolic blood pressure (mmHg) • The binary HbA1c endpoints are: o HbA1c <7.0% (53 mmol/mol) at week 26 (yes/no), ADA target and ISPAD guidelines from 2018 o HbA1c ≤6.5% (48 mmol/mol) at week 26 (yes/no), AACE target o HbA1c <7.0% (53 mmol/mol) at week 52 (yes/no), ADA target and ISPAD guidelines from 2018 o HbA1c ≤6.5% (48 mmol/mol) at week 52 (yes/no), AACE target o HbA1c <7.0% (53 mmol/mol) without severe or BG confirmed symptomatic hypoglycaemia episodes at week 26 (yes/no) o HbA1c <7.0% (53 mmol/mol) without severe or BG confirmed symptomatic hypoglycaemia episodes at week 52 (yes/no) • Time to event: o Time to additional anti-diabetic medication (to support the treatment policy estimand)	• From baseline (week 0) to week 52 • From baseline (week 0) to week 26 and to week 52		

Type	Title	Time frame	Unit	Details
	○ Time to rescue medication (to support the hypothetical estimand) • Safety Endpoints: ○ Adverse events ○ Number of treatment-emergent AEs (TEAEs) during exposure to trial product, assessed up to approximately 57 weeks • Hypoglycaemic episodes: ○ Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes from randomisation to week 26 ○ Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks ○ Treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episode from randomisation to week 26 (yes/no) ○ Treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episode during exposure to trial product, assessed up to approximately 57 weeks (yes/no) Other safety endpoints • Change from baseline (week 0) to week 26 and to week 52 in: ○ Biochemistry ○ amylase (U/L) ○ lipase (U/L) ○ Biomarkers ○ IGF-1 (ng/mL) ○ IGFBP 3 (ng/mL) ○ Hormones ○ calcitonin (pmol/L) ○ estradiol (for girls) (pmol/L) ○ testosterone (for boys) (nmol/L) ○ prolactin (mIU/L) ○ TSH/thyrotropin (mIU/L) ○ FSH (mIU/mL) ○ LH (mIU/mL) ○ DHEAS (µmol/L) • Anti-semaglutide antibodies endpoints during 57 weeks: ○ Anti-semaglutide antibody status. ○ Anti-semaglutide antibody titer.			

Type	Title	Time frame	Unit	Details
	○ Anti-semaglutide antibodies with in vitro neutralising effect to semaglutide ○ Anti-semaglutide antibodies cross reacting with endogenous GLP-1 ○ Cross reacting antibodies with in vitro neutralising effect to endogenous GLP-1) • Supportive safety endpoints ○ Height velocity (cm/year) at week 26 and 52 • Change from baseline (week 0) to week 26 and to week 52 in: ○ Height SDS ○ Bone age assessment, X-ray (only at week 52) (years) ○ Pubertal assessment (Tanner staging) (stage 1-5 where 5 is full sexual maturity) ○ Pulse rate (beats/minute) • Change from pre-dose to post-dose (25 and 40 minutes) at week 12 and week 26 in: ○ Lactate (mmol/L) • Pharmacokinetic endpoints ○ Apparent clearance (CL/F) (L/h) ○ Average concentration (Cavg) (nmol/L) ○ SNAC plasma concentrations (ng/mL)			

Type	Title	Time frame	Unit	Details
Exploratory efficacy endpoints	Evaluated after intake of first tablet (week 0) and after 26 weeks: o Swallowability of semaglutide tablet (questionnaire)			
	Change from baseline (week 0) to week 26 and week 52 in: • fasting lipid profile • cholesterol, low density lipoprotein (LDL), very low density lipoprotein (VLDL), high density lipoprotein (HDL) and triglycerides (mmol/L)	Change from baseline (week 0) to week 26 and week 52		
	Change from baseline (week 0) to week 26, week 52 and week 64 in: • adiponectin • total (ng/mL) • high molecular weight (HMW) (ng/mL)	Change from baseline (week 0) to week 26, week 52 and week 64		
	Change from baseline (week 0) to week 26, week 52, week 57, and week 64 in: • glucose metabolism • fasting insulin (pmol/L) • fasting pro-insulin (pmol/L) • pro-insulin to insulin ratio (%) • fasting glucagon (pg/mL) • fasting C-peptide (nmol/L) • homeostasis model assessment (HOMA-B and HOMA-IR) (ratio to baseline)	Change from baseline (week 0) to week 26, week 52, week 57, and week 64		
	Change from baseline (week 0) to week 57 and to week 64 in: • HbA_{1c} (%-point and mmol/mol) • FPG (mg/dL) • Body weight (kg) • Body weight (relative change, %) • Waist circumference (cm) • BMI SDS • BMI percentile (age and gender adjusted) (%) • BMI (kg/m^2) • BMI (Percent change, %) • BMI percentage of the 95th percentile (% points) • Systolic and diastolic blood pressure (mmHg)	Change from baseline (week 0) to week 57 and to week 64		
	Change from baseline (week 0) to week 52 and to week 64 in: • OGTT-derived endpoints • Incremental C-peptide ($iAUC_{cp,0\text{-}120\ min}$) (nmol/L) • Incremental insulin ($iAUC_{ins,0\text{-}120\ min}$) (pmol/L) • Incremental glucose ($iAUC_{g,0\text{-}120\ min}$) (mmol/L) • 2-hour glucose value (mmol/L)	Change from baseline (week 0) to week 52 and to week 64		

Type	Title	Time frame	Unit	Details
	• C-peptide index: Δ C-peptide from 0-30 minutes/Δ glucose from 0-30 minutes [$\Delta C_{30}/\Delta G_{30}$]) (nmol/mmol) • Insulinogenic index: Δ insulin from 0-30 minutes/Δ glucose from 0-30 minutes [$\Delta I_{30}/\Delta G_{30}$]) (pmol/mmol) • C-peptide derived oral disposition index (DIo; C-peptide index adjusted for insulin sensitivity [$\Delta C_{30}/\Delta G_{30}$]) x $1/I_F$) (1/nM) • Insulin derived oral disposition index (DIo; insulinogenic index adjusted for insulin sensitivity [$\Delta I_{30}/\Delta G_{30}$]) x $1/I_F$) (1/nM) • Incremental glucagon relative to glucose ($iAUC_{glucagon,0\text{-}120\ min}$) (pg/mL) • Early phase glucagon response relative to glucose after oral glucose ingestion (Δ glucagon from 0-30 minutes x Δ glucose from 0-30 minutes [$\Delta Glucagon_{30} \times \Delta G_{30}$]) (pg/mL x mmol)			

7 References

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