Cover Page for Statistical Analysis Plan

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Note: The date in the header of page 2 is the date of the compilation of the documents and not of an update to content.

9.1.9 Documentation of statistical methods

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Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

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Statistical Analysis Plan

Efficacy and safety of oral semaglutide 50 mg once daily in East Asian participants with overweight or obesity (OASIS 2)

Semaglutide

[redacted]

Data Science - Biostatistics and Programming, Global Business Services (GBS)

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Version History

SAP Version	Date	Change	Rationale
1.0	22Sep023	Not Applicable	Original version

List of abbreviations

AD	available but treatment discontinued
AE	adverse event
ANCOVA	analysis of covariance
AT	available on randomised treatment
BMI	body mass index
bpm	beats per minute
CI	confidence interval
cm	centimetre
COA	clinical outcome assessment
CVD	cardiovascular disease
FAS	full analysis set
FPG	fasting plasma glucose
HbA1c	glycated haemoglobin
HDL	high density lipoprotein
J2R-MI	Multiple imputation using jump to reference
ICH	International Council on Harmonization
kg	kilogram
LAO-OT	last available observation during the on-treatment period
LDL	low density lipoprotein
LR	logistic regression
MAR	missing at random
MD	missing and treatment discontinued
MedDRA	medical dictionary for regulatory activities
mg	milligrams

mg/dL	milligrams per decilitre
MI	multiple imputation
mmHg	millimetre of mercury
mmol/mol	millimoles per mol
MMRM	mixed model for repeated measurements
MT	missing on randomised treatment
OR	odds ratio
RD-MI	multiple imputation using retrieved participants
SAP	statistical analysis plan
SAS	safety analysis set
SFA	subcutaneous fat area
T2D	type 2 diabetes
TFL	tables, figures and listings
VLDL	very low density lipoprotein
VFA	visceral fat area

1 Introduction

This SAP is based on protocol version 4.0 dated 28 October 2022. Changes from protocol are provided in section 4.9.

1.1 Objectives, Endpoints, and Estimands

1.1.1 Primary, secondary and exploratory objectives and estimands

The primary and secondary objectives of the study are listed below followed by an introduction of the estimands used to address the efficacy-related objectives. The objectives and endpoints are summarised in Table 1-1.

Table 1-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	Title	Time frame	Unit
• To confirm superior efficacy on body weight reduction of oral semaglutide 50 mg once daily versus placebo as adjuncts to reduced-calorie diet and increased physical activity in participants with overweight or obesity	Co-primary:		
	Relative change in body weight	From baseline (week 0) to end of treatment (week 68)	%-point
	Achievement of body weight reduction ≥ 5% (Yes/No)	At end of treatment (week 68)	Count of participants
Secondary	Title	Time frame	Unit
• To confirm superior efficacy on physical function improvement of oral semaglutide 50 mg once daily versus placebo as adjuncts to reduced-calorie diet and increased physical activity in participants with overweight or obesity	Confirmatory secondary		
	Achievement of body weight reduction ≥ 10% (Yes/No)	At end of treatment (week 68)	Count of participants
	Change in Physical function domain (5-items) score (IWQOL-Lite-CT)	From baseline (week 0) to end of treatment (week 68)	Score points
• To estimate the efficacy on cardio-metabolic parameters of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in participants with overweight or obesity	Supportive secondary:		
	Achievement of body weight reduction ≥ 15% (Yes/No)	At end of treatment (week 68)	Count of participants
	Achievement of body weight reduction ≥ 20% (Yes/No)	At end of treatment (week 68)	Count of participants
	Change in body mass index (BMI)	From baseline (week 0) to end of treatment (week 68)	kg/m^2
	Change in waist circumference measured according to the JASSO guideline[1]	From baseline (week 0) to end of treatment (week 68)	cm
	Change in Visceral Fat Area (VFA) measured by CT scan in a subset of the Japanese study population	From baseline to end of treatment (week 68)	%-point

Objectives	Endpoints		
	Change in Visceral Fat Area (VFA) measured by CT scan in a subset of the Japanese study population	From baseline to end of treatment (week 68)	cm^2
	Change in systolic blood pressure	From baseline (week 0) to end of treatment (week 68)	mmHg
	Change in diastolic blood pressure	From randomisation (week 0) to end of treatment (week 68)	mmHg
	Change in HbA_{1c}	From baseline (week 0) to end of treatment (week 68)	%-point
	Change in lipids: • Total cholesterol • HDL cholesterol • LDL cholesterol • VLDL cholesterol • Triglycerides • Free fatty acids	From baseline (week 0) to end of treatment (week 68)	Ratio to baseline
	Change in high sensitivity C-Reactive Protein	From baseline (week 0) to end of treatment (week 68)	Ratio to baseline
• To compare the safety and tolerability of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in participants with overweight or obesity.	Number of treatment emergent adverse events	From baseline (week 0) to end of study (week 75)	Count of events
	Number of serious adverse events	From baseline (week 0) to end of study (week 75)	Count of events
Exploratory	Title	Time frame	Unit
• To confirm superior efficacy on physical function reduction of oral semaglutide 50 mg once daily versus placebo as adjuncts to reduced-calorie diet and increased physical activity in participants with overweight or obesity	Change in IWQOL-Lite-CT • Physical domain score • Psychosocial domain score • Total score	From baseline (week 0) to end of treatment (week 68)	Score points
	Change in Short Form-36 (SF-36) Acute • Physical functioning score • role-physical score • bodily pain score • general health score • vitality score • social functioning score • role-emotional score • mental health score • physical component summary • mental component summary	From baseline (week 0) to end of treatment (week 68)	Score points

Objectives	Endpoints		
	Change in Impact of Weight on Daily Activities (IWDAQ) total score	From baseline (week 0) to end of treatment (week 68)	Score points
• To estimate the efficacy on cardio-metabolic parameters of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in participants with overweight or obesity	Change in fasting plasma glucose (FPG)	From baseline (week 0) to end of treatment (week 68)	mg/dL
	Change in fasting serum insulin	From baseline (week 0) to end of treatment (week 68)	Ratio to baseline
The following exploratory endpoints are used for participants with T2D at baseline:			
• To estimate the efficacy on cardio-metabolic parameters of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in participants with overweight or obesity	Achievement of $HbA_{1c} < 7.0\%$ (53 mmol/mol) (yes/no)	At end of treatment (week 68)	Count of participants
	Achievement of $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) (yes/no)	At end of treatment (week 68)	Count of participants
• To compare the safety and tolerability of oral semaglutide 50 mg once daily versus placebo as an adjunct to reduced-calorie diet and increased physical activity in participants with overweight or obesity.	Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes	From baseline (week 0) to end of study (week 75)	Count of events

The estimands for the primary objective are introduced below and the attributes of the estimands are summarised in Table 1-2. Additional details are available in Section 4.

The secondary estimands with confirmatory and supportive secondary endpoints are similar to the co-primary estimands except for the endpoint attribute. The secondary estimands with continuous endpoints for secondary objectives are similar to the co-primary estimand for relative weight change, with the exception of endpoints with units of ratio to baseline, for which the population-level summary is the ratio between treatment conditions. The secondary estimands with binary endpoints for secondary objectives are similar to the co-primary estimand for body weight reduction $\geq 5\%$.

Table 1-2 Estimands

Objective	Estimand category	Attributes				
		Treatment condition	**Variables / endpoints**	**Population of interest**	**Intercurrent events and strategy**	**Population-level summary measure**
Primary objective: To confirm superior efficacy on body weight reduction of oral semaglutide 50 mg once daily versus placebo as adjuncts to reduced-calorie diet and increased physical activity in participants with overweight or obesity	Co-primary	The effect of oral semaglutide and regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery) versus the effect of placebo and regardless of initiating other anti-obesity therapies (weight management drugs or bariatric surgery)each as adjunct to reduced-calorie diet and increased physical activity	From baseline to week 68: • relative change in body weight • Achievement of body weight reduction ≥ 5% (yes/no)	Participants with overweight or obesity	**Treatment policy** strategy for: • Premature randomised treatment discontinuation • initiation of other anti-obesity • therapies	• Difference in means in relative weight change • Treatment odds-ratio for proportion of participants achieving body weight reduction ≥ 5%
	Additional *	The effect of oral semaglutide without other anti-obesity therapies versus the effect of placebo without other anti-obesity therapies , each as adjunct to reduce-			**Hypothetical strategy** for: • Premature randomised treatment discontinuation • Initiation of rescue intervention	

Objective	Estimand category	Attributes				
		Treatment condition	**Variables / endpoints**	**Population of interest**	**Intercurrent events and strategy**	**Population-level summary measure**
		calorie diet and increased physical activity				

* Not related to the confirmatory hypotheses

1.2 Study Design

The study design is provided in the protocol section 4.1.

2 Statistical Hypotheses

The superiority tests of oral semaglutide 50 mg once daily vs. placebo will be carried out as follows:

Let $\mu_{semaglutide}$ and $\mu_{placebo}$ denote the true mean of % weight change for oral semaglutide 50 mg once daily and placebo group, respectively. The hypothesis and alternative hypothesis tested are

$$H_0: \mu_{semaglutide} \geq \mu_{placebo} \text{ vs}$$
$$H_A: \mu_{semaglutide} < \mu_{placebo}$$

The null hypothesis will be rejected, and superiority claimed, if the upper limit of the estimated two-sided 95% CI is below 0.

The estimated odds ratios (OR) between oral semaglutide 50 mg once daily and placebo will be reported together with the associated two-sided 95% CIs and corresponding p-values.

Let $OR_{semaglutide/placebo}$ denote the true odds ratio between oral semaglutide 50 mg once daily and placebo. The hypothesis and alternative hypothesis tested are:

$$H: OR_{semaglutide/placebo} \leq 1 \text{ vs}$$
$$H_A: OR_{semaglutide/placebo} > 1.$$

The null hypothesis will be rejected, and superiority claimed, if the lower limit of the estimated two-sided 95% CI is above 1.

2.1 Multiplicity Adjustment

All tests are done on a 5% (two sided) level of significance in a pre-defined fixed-sequence hierarchical order Table 2-1, i.e. all previous hypotheses must be rejected in order to proceed to the next hypothesis test thereby preserving the type I error rate.

Table 2-1 Hierarchical order for hypothesis testing

Test order	Endpoint	Target	Comparator
1	Relative change in body weight	Semaglutide	Placebo
2	Achievement of body weight reduction ≥ 5% (Yes/No)	Semaglutide	Placebo
3	Achievement of body weight reduction ≥ 10% (Yes/No)	Semaglutide	Placebo
4	Change in Physical function domain (5-items) score (IWQoL-Lite for CT)	Semaglutide	Placebo

3 Analysis Sets

The following populations are defined:

Table 3-1 Defined populations

Population	Description
Full analysis set (FAS)	All participants randomised. Participants will be analysed according to the randomised treatment
Safety analysis set (SAS)	All participants randomly assigned to trial treatment and who take at least 1 dose of IMP. Participants are analysed according to the treatment they actually received.

Two observation periods are defined for each participant:

- In-study: The in-study period is defined as the uninterrupted time interval from date of randomisation to date of last contact with study site.
- On-treatment (with IMP): In general, the on-treatment period will be from the date of first IMP administration to date of last IMP administration plus 3 days, except when randomised treatment is temporarily discontinued. If randomised treatment is temporarily discontinued, the on-treatment period ends 3 days after the treatment discontinuation and resumes on the day randomised treatment is resumed. Hence, the on-treatment period can consist of several disjoint periods.

In general, the on-treatment period will therefore be from the date of first IMP administration to date of last IMP administration excluding potential off-treatment time intervals of at least 3 consecutive days.

For the evaluation of adverse events the lag time for each on-treatment time interval is 7 weeks.

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

The estimands using the treatment policy strategy for intercurrent events use all data from the in-trial observation period and estimands using the hypothetical strategy use data from the ontreatment observation period until first treatment discontinuation or initiation of other anti-obesity therapy.

Efficacy endpoints will be analysed using the FAS; safety endpoints will be analysed using the SAS.

4 Statistical Analyses

4.1 General Considerations

Results from statistical analyses will generally be accompanied by two-sided 95% confidence intervals (CIs) and corresponding p-values. Superiority will be claimed if p-values are less than 5% and the estimated treatment contrasts favours oral semaglutide 50 mg once daily.

Taxonomy of week 68 assessments

For each participant, a given week 68 assessment may be available or missing as specified in Table 4-1. The assessment availability is defined by participant and by assessment; thus, for body weight at week 68, a participant may be characterised as 'available on randomised treatment (AT)', whereas for waist circumference, the participant may be characterised as 'missing on randomised treatment (MT)'.

Table 4-1 Taxonomy for participants based on week 68 assessments

Availability	participants on randomised treatment at week 68	Description	Abbreviation
Available	Yes	**Available on randomised treatment**: Participants who complete the study on randomised treatment with an assessment at week 68: Includes those that stop and restart IMP.	AT
	No	**Available but discontinued** Participants who discontinued randomised treatment prematurely but returned to have an assessment at week 68. These are also called retrieved participants	AD
Missing	Yes	**Missing on randomised treatment**: Participants who complete the study on randomised treatment without an assessment at week 68: Includes those that stop and restart IMP.	MT
	No	**Missing and discontinued**: Participants who discontinued randomised treatment prematurely and did not return to have an assessment at week 68. These are also called non-retrieved participants	MD

Handling of missing baseline data

The last available and eligible observation at or before randomisation is used as the baseline value. If no assessments are available, the mean value at randomisation across all participants is used as the baseline value. Missing baseline visceral fat area(VFA), missing baseline subcutaneous fat area(SFA) are individually imputed using population mean and missing baseline VFA/SFA ratio is imputed using the population mean(VFA)/population mean(SFA) ratio.

4.2 Co-primary endpoints analyses

4.2.1 Definition of Endpoint

Relative change from baseline (week 0) to week 68 in body weight (%)

Relative change from baseline (week 0) to week 68 in body weight (%) is defined as:

$$\% \text{ weight change} = \frac{(\text{body weight at week } 68 - \text{body weight at baseline})}{\text{body weight at baseline}} \times 100.$$

Achievement of body weight reduction ≥ 5%

A body weight reduction of at least X% from baseline (week 0) to week 68 is defined as

$$\text{X\% responder} = \begin{cases} 1 \text{ if } \% \text{ weight change} \leq -X\% \\ 0 \text{ if } \% \text{ weight change} > -X\% \end{cases}$$

4.2.2 Main Analytical Approach

Analyses addressing the co-primary estimands

The analysis model for % weight change is a linear regression (ANCOVA) of % weight change with randomised treatment as a factor and baseline body weight (kg) as a covariate. The estimated treatment differences between oral semaglutide 50 mg once daily and placebo will be reported together with the associated two-sided 95% CIs and corresponding p-values.

The analysis model for the 5% responder endpoint is a logistic regression using randomised treatment as a factor and baseline body weight (kg) as covariate. The estimated odds ratios (OR) between oral semaglutide 50 mg once daily and placebo will be reported together with the associated two-sided 95% CIs and corresponding p-values.

Where response rates close to 0% or 100% in any treatment group lead to non-convergence, Firth's maximum-likelihood estimation will be used when performing the logistic regression.

In addition to the estimated OR, the estimated treatment differences (ETDs) will be provided by calculating the responder probabilities and treatment differences between responder probabilities based on the logistic regression model, with confidence intervals for treatment differences obtained using the delta method.

Non-retrieved participants as non-responders:

For the 5% responder analysis an analysis using non-retrieved participants as non-responders in the logistic regressions will be done

Handling of missing week 68 values for the treatment policy strategy

All available data at week 68 (AT and AD) are used and missing values (MT and MD) at week 68 will be imputed and the endpoints will be derived from the imputed values. Several approaches for imputation will be applied. First, a description of the primary imputation approach to address the estimands applying the treatment policy strategy for the co-primary endpoints is given followed by a description of the sensitivity analyses used to assess the robustness of the conclusions. The sensitivity analyses investigate how assumptions on body weight development after discontinuation of randomised trial treatment impact the estimated treatment contrasts between oral semaglutide 50 mg once daily and semaglutide placebo.

Primary imputation approach using the treatment policy strategy

The co-primary estimand addresses the main clinical question of interest: What is the efficacy of oral semaglutide 50 mg on body weight in participants with overweight or obesity regardless of premature randomised treatment discontinuation and initiation of rescue intervention?

For this estimand, the treatment policy strategy is applied for all intercurrent events. Results based on the co-primary estimand are expected to mirror the clinical practice scenario because the estimand considers both the efficacy and tolerability of the randomised treatment.

Multiple imputation approach using retrieved drop-outs (RD-MI): The primary imputation approach for estimands applying the treatment policy strategy is a multiple imputation similar to the one described by McEvoy [2]. Missing body weight measurement at week 68 for non-retrieved participants (MD) are imputed using assessments from retrieved participants (AD) in each randomised treatment arm. This will be done according to the timing of last available observation on treatment (LAO-OT) of body weight. Missing body weight measurements at week 68 for participants on randomised treatment (MT) are imputed by sampling from available measurements at week 68 from participants on randomised treatment (AT) in the relevant randomised treatment arm. The multiple imputation approach is done in three steps:

1. **Imputation:** Defines an imputation model using retrieved participants (AD) from FAS and done within groups defined by randomised treatment. The model will be a linear regression of body weight (kg) at week 68 with gender (male/female), as factors and baseline body weight (kg), timing of LAO-OT and LAO-OT of body weight (kg) as covariates. No interactions will be included. If the imputation model cannot be fit the model will be reduced until the model can be fit. Reduction will be done in a fixed order by first removing gender , If the imputation model with LAO-OT of body weight (kg) cannot be fit, the imputation will be done regardless of the randomised treatment arm. If no LAO-OT exists post-baseline then LAO-OT will be the baseline body weight. If any participants are MT, an imputation model for missing body weight measurements at week 68 for MT participants will also be defined using AT participants in a similar way. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 68 body weight values for each randomised treatment arm. This will be done 1,000 times and results in 1,000 complete data sets.

2. **Analysis**: Analysis of each of the 1,000 complete data sets, using the analysis models (ANCOVA) results in 1,000 estimations.

3. **Pooling:** The results obtained from analysing the datasets will be combined using Rubin's formula [3].

The multiple imputations will be generated using Novo Nordisk study number 99324738 as seed number.

4.2.3 Additional analysis addressing hypothetical strategy

The additional estimand applying the hypothetical strategy for % weight change addresses the efficacy of semaglutide 50 mg once daily and will be assessed using a 'MMRM for efficacy'. Week 68 assessments for retrieved drop-outs (AD) are not used in this analysis. The MMRM for efficacy will use assessments only from participants who are taking the randomised treatment until end- of -treatment or until first discontinuation of randomised treatment. The date of the last dose before first discontinuation of randomised treatment plus 3 days will be used as the latest date for using assessments in this MMRM. The assessment closest in time and before the date of the last dose

before first discontinuation of randomised treatment plus 3 days will be used as last assessment on randomised treatment.

For participants who initiate any other anti-obesity therapies before completion or first discontinuation of randomised treatment, the date of starting weight management drugs or undergoing bariatric surgery will be used as latest date for using assessments in this MMRM. Similarly, the assessment closest in time and before the date of starting weight management drugs or undergoing bariatric surgery will be used as last assessment on randomised treatment.

The MMRM for efficacy will be fitted using % weight change with randomised treatment as a factor and baseline body weight (kg) as a covariate all nested within visit. An unstructured covariance matrix for measurements within the same participant will be employed, assuming that measurements for different participants are independent.

The estimand applying the hypothetical strategy for 5% responders will be assessed using the same MMRM for efficacy. For participants with missing body weight at week 68, individual values for body weight will be predicted from the MMRM and used to classify each subject as 5% responder or not. This classification will then be analysed using a logistic regression model with randomised treatment as a factor and baseline body weight (kg) as covariate.

For change in HbA1c and FPG, whose planned measurement visits differ depending on T2D status at baseline, only the visits where the measurements are planned for all subjects will be included in the MMRM.

4.2.4 Sensitivity Analysis

Jump to reference multiple imputation approach (J2R-MI): Missing values of body weight at week 68 (MT and MD) for all treatment groups are imputed by sampling among all available assessments at week 68 in the placebo group (AT and AD). This approach is based on the assumption that participants instantly after discontinuation lose any effect of randomised treatment beyond what can be expected from placebo treatment as adjunct to reduced-calorie diet and increased physical activity [4]. The multiple imputation approach is done as above with the first imputation step replaced by the following:

1. **Imputation**: Defines an imputation model using semaglutide placebo participants from FAS with a week 68 measurement (AT and AD). The model will be a linear regression of body weight (kg) at week 68 with gender (male/female and baseline body weight (kg) as covariate. No interactions will be included. If the imputation model cannot be fit the model will be reduced by removing gender. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 68 body weight values for each randomised treatment arm. This will be done 1,000 times and results in 1,000 complete data sets.

The jump to reference approach is the basis for the sample size calculations.

Tipping-point multiple imputation analysis (TP-MI): This sensitivity analysis evaluates the robustness of the superiority conclusions to violations of the MAR assumption. First, missing body weight data are imputed according to the primary multiple imputation approach. Then, a penalty is added to the imputed values at week 68. The approach is to explore a range of penalties for both

treatment groups, and the impact these would have on the study conclusions. A 2-dimensional space of penalties will be explored for the two treatment groups.

Mixed model for repeated measurements (MMRM): This MMRM for treatment policy estimand' will use all assessments regardless of adherence to randomised treatment, including assessments at week 68 for retrieved drop-outs (AD). The MMRM for treatment policy estimand will be fitted using the same factor and covariate as for the primary analyses all nested within visit. An unstructured covariance matrix for measurements within the same participant will be employed, assuming that measurements for different participants are independent.

4.2.5 Supplementary analyses

As a supplementary analysis, the primary statistical model for relative weight change will be fitted by adding a treatment times glycaemic baseline status interaction as a factor and baseline body weight (kg) . The imputation model will remain the same as for the primary statistical analysis. Glycaemic status at baseline will be defined as diagnosed with T2D at randomisation (yes/no).

4.3 Confirmatory Secondary Endpoints Analyses

All confirmatory secondary endpoints are tested for superiority of oral semaglutide 50 mg versus semaglutide placebo. Confirmatory secondary endpoints are listed in Section 1.1

Analyses addressing the confirmatory secondary endpoints

The continuous confirmatory secondary endpoint will be analysed using the same analysis and imputation models as used to address the co-primary estimand for the primary continuous endpoint.

The binary confirmatory secondary endpoint will be analysed using the same analysis and imputation models as used to address the co-primary estimand for the primary binary endpoint.

Sensitivity analyses for confirmatory secondary endpoints

The tipping-point sensitivity analysis will not be performed for confirmatory secondary endpoints.

An overview of all analysis and imputation methods to address the secondary estimands for the confirmatory secondary endpoints is given in Table 4-2.

Table 4-2 Analysis and imputation methods to address the primary and secondary estimands for the primary and confirmatory secondary endpoints in the statistical testing hierarchy

Objective	Endpoint	Test order	Endpoint type	Strategy	Analysis set	Statistical model	Imputation approach	Sensitivity analyses	Other
Co-primary endpoints									
Primary	% weight change	1	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	J2R-MI TP-MI MMRM	Supplemantary analysis
				Hypothetical	FAS	MMRM	-	-	Supplemantary analysis
Primary	<=-5% responders	2	Binary	Treatment policy	FAS	LR	RD-MI	J2R-MI TP-MI MMRM Non-responder	
				Hypothetical	FAS	LR	MMRM	-	
Confirmatory secondary endpoints									
Secondary	<=-10% responders	3	Binary	Treatment policy	FAS	LR	RD-MI	J2R-MI MMRM Non-responder	
				Hypothetical	FAS	LR	MMRM	-	
Secondary	IWQoL-Lite PFD score change	4	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	J2R-MI MMRM	
				Hypothetical	FAS	MMRM	-	-	

FAS = full analysis set; ANCOVA = analysis of covariance; RD-MI = multiple imputation using retrieved participants; J2R-MI = jump to reference multiple imputation; TP-MI = tipping point multiple imputation; MMRM = mixed model for repeated measurements; LR = logistic regression; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite for Clinical Trials; PFD = physical function domain;

4.4 Supportive Secondary Endpoints Analyses

All supportive secondary endpoints are tested for superiority of oral semaglutide 50 mg versus semaglutide placebo. Supportive secondary endpoints are listed in Section 1.1.

Analyses addressing the treatment policy strategy

The effect-related supportive secondary endpoints will be analysed using the same imputation approach as used for the co-primary endpoints using a treatment policy. The imputation model is the same as for the co-primary endpoints with body weight replaced by assessments of the endpoint to be analysed. The statistical model for continuous endpoints will be ANCOVA with factor and covariate as for the co-primary endpoint % weight change with baseline body weight replaced by the baseline assessment of the endpoint to be analysed.

For endpoints where the endpoint is 'ratio to baseline', e.g. lipids, the ratio between post randomisation measurements and baseline will be calculated instead of differences, and both the dependent variable and covariate will be log-transformed.

The statistical model for responder endpoints relating to COAs will be logistic regression with randomised treatment as a factor and the baseline assessment of the endpoint to be analysed as covariate.

Analyses addressing the hypothetical strategy

The supportive secondary endpoints will be analysed using a hypothetical strategy with the same MMRM for efficacy described for the co-primary endpoints.

Sensitivity analyses for supportive secondary endpoints

For supportive secondary endpoints no sensitivity analysis will be carried out

Supplementary analyses of supportive secondary endpoints

As a supplementary analysis, the statistical model for change in HbA_{1c} and fasting glucose will be fitted - with - treatment times baseline glycaemic status interaction as a factor and baseline . The imputation model will remain the same as for the supportive secondary statistical analysis. Glycaemic status at baseline will be defined as diagnosed with T2D at randomisation (yes/no).

Additional considerations for statistical analyses

The supportive secondary endpoint change from baseline to week 68 in VFA (cm2 and %) as measured by CT scan will be defined as absolute change from baseline (cm2) and %change from baseline (%).

4.5 Safety Endpoints Analyses

Adverse events will be defined as “treatment-emergent” (TEAE) if the onset of the event occurs in the on-treatment period (see definition in Section 3 of protocol). TEAEs and SAEs will be summarised by descriptive statistics, such as frequencies and rates. No formal statistical inference will be carried out based on the number of TEAEs and SAEs. All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA 26.1).

An overview of all analysis and imputation methods to address supportive secondary endpoints is given in Table 4-3.

Table 4-3 Analysis and imputation for supportive secondary endpoints

Objective	Endpoint	Endpoint type	Strategy	Analysis set	Statistical model	Imputation approach	Sensitivity analyses	Other
Supportive secondary endpoints (effect related)								
Secondary	Achievement of body weight reduction <=-15% (Yes/No)	Binary	Treatment policy	FAS	LR	RD-MI	-	
			Hypothetical	FAS	LR	MMRM	-	
Secondary	Achievement of body weight reduction <=- 20% (Yes/No)	Binary	Treatment policy	FAS	LR	RD-MI	-	
			Hypothetical	FAS	LR	MMRM	-	
Secondary	BMI change (kg/m^2)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Secondary	Waist circumference according to the JASSO guideline(cm)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Secondary	Change in Visceral Fat Area (VFA) measured by CT scan in a subset of the Japanese study population (%, ,cm^2)	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI	-	
			Hypothetical	FAS	MMRM	-	-	

Objective	Endpoint	Endpoint type	Strategy	Analysis set	Statistical model	Imputation approach	Sensitivity analyses	Other
Secondary	sBP change (mmHg)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Secondary	dBP change (mmHg)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Secondary	Change in HbA1c(%, mmol/mol)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	Supplemantary analysis
			Hypothetical	FAS	MMRM	-	-	Supplemantary analysis
Secondary	Total cholesterol change (mg/dL, mmol/L)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Secondary	HDL change (mg/dL, mmol/L)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Secondary	LDL change (mg/dL, mmol/L)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Secondary	VLDL change (mg/dL, mmol/L)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Secondary	FFA change (mg/dL, mmol/L)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Secondary	Triglycerides change (mg/dL, mmol/L)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Secondary	hsCRP change (mg/L)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Secondary	Weight change (kg)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Secondary	Waist circumference according to the WHO guideline(cm)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Secondary	Glycaemic status ####	categorical		FAS			-	Descriptuve statistics
Supportive secondary endpoints (safety related)								
Secondary	Number of TEAEs	Continuous	-	SAS	-	-	-	
Secondary	Number of SAEs	Continuous	-	SAS	-	-	-	
Secondary	Pulse change (bpm)	Continuous	Hypothetical	SAS	MMRM	-	-	

FAS = full analysis set; ANCOVA = analysis of covariance; RD-MI = multiple imputation using retrieved participants; MMRM = mixed model for repeated measurements; BMI = body mass index; HbA1c = Haemoglobin A1c; FPG = fasting plasma glucose; dBP = diastolic blood pressure; sBP = systolic blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; VLDL = very low density lipoprotein; FFA = free fatty acids; LR = logistic regression; SF-36 = Short Form 36 v2.0 acute; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite for Clinical Trials; PFD = physical function domain; TEAEs = treatment emergent adverse events; SAEs = serious adverse events; # responder value = 14.6; ## responder value = 3.7; ### Analysis performed in participants with BMI≥30 at baseline and response defined as BMI<30 at week 68 (yes/no); #### Glycaemic status defined as: HbA1c < 5.7%: Normo-glycemia, 5.7% ≤ HbA1c < 6.5%: Pre-diabetes, HbA1c ≥ 6.5%: Diabetes

4.6 Exploratory Endpoint Analyses

The exploratory endpoints listed in section 1.1 will be analysed using the same analysis and imputation models as used to address the co-primary estimand for the primary continuous endpoint.

The binary exploratory endpoints will be analysed using the same analysis and imputation models as used to address the co-primary estimand for the primary binary endpoint.

The exploratory endpoint change from baseline to week 68 in SFA (cm2 and %) as measured by CT scan will be defined as absolute change from baseline (cm2) and %change from baseline (%). Waist circumference change (%) from baseline to week 68 will be defined as %change from baseline (%) .

An overview of all analysis and imputation methods to address exploratory endpoints is given in Table 4-4.

Table 4-4 Analysis and imputation for exploratory endpoints

Objective	Endpoint	Endpoint type	Strategy	Analysis set	Statistical model	Imputation approach	Sensitivity analyses	Other
Exploratory endpoints (effect related)								
Exploratory	IWQOL-Lite-CT PD score change	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	IWQOL-Lite-CT PSD score change	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	IWQOL-Lite-CT total score change	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	IWDAQ total score change	Continuous	-	FAS	-	-	-	Descriptive statistics
Exploratory	SF-36 Physical functioning score	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	SF-36 RP score change	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	SF-36 BP score change	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	SF-36 GH score change	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	SF-36 VT score change	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	SF-36 SF score change	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	SF-36 RE score change	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	SF-36 MH score change	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	SF-36 PCS score change	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	SF-36 MCS score change	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	Change in fasting plasma glucose (FPG),(mg/dL, mmol/L)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	Supplemantary analysis
			Hypothetical	FAS	MMRM	-	-	Supplemantary analysis
Exploratory	Change in fasting serum Insulin(mIU/L, pmol/L)	Continuous	Treatment policy	FAS	ANCOVA	RD-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	Achievement of HbA1c < 7.0% (53 mmol/mol) (yes/no)	Binary	Treatment policy	FAS	LR	J2R-MI	-	
			Hypothetical	FAS	LR	MMRM	-	
Exploratory	Achievement of HbA1c ≤ 6.5% (48 mmol/mol) (yes/no)	Binary	Treatment policy	FAS	LR	J2R-MI	-	
			Hypothetical	FAS	LR	MMRM	-	
Exploratory	Number of treatment emergent severe or blood glucose confirmed symptomatic	-	-	SAS	-	-	-	Descriptive
			-	-	-	-	-	

Objective	Endpoint	Endpoint type	Strategy	Analysis set	Statistical model	Imputation approach	Sensitivity analyses	Other
	hypoglycaemic episodes							
Exploratory	IWQOL-Lite-CT PFD score responder #	Binary	Treatment policy	FAS	LR	RD-MI	-	
			Hypothetical	FAS	LR	MMRM	-	
Exploratory	SF-36 PF score responder ##	Binary	Treatment policy	FAS	LR	J2R-MI	-	
			Hypothetical	FAS	LR	MMRM	-	
Exploratory	SFA change (cm2, %)	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI	-	
			Hypothetical	FAS	MMRM	-	-	
Exploratory	VFA/SFA ratio change	Continuous	Treatment policy	FAS	ANCOVA	J2R-MI	-	
			Hypothetical	FAS	MMRM	-	-	

FAS = full analysis set; ANCOVA = analysis of covariance; RD-MI = multiple imputation using retrieved participants; MMRM = mixed model for repeated measurements; BMI = body mass index; HbA1c = Haemoglobin A1c; FPG = fasting plasma glucose; dBP = diastolic blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; VLDL = very low density lipoprotein; FFA = free fatty acids; LR = logistic regression; IWQoL-Lite = Impact of Weight on Quality of Life-Lite for Clinical Trials; PD = physical domain; PSD =psychosocial domain; IWDAQ = Impact of Weight on Daily Activities Questionnaire; SF-36 = Short Form 36 v2.0 acute; RP = Role-physical; BP = Bodily pain; GH = General health; VT = Vitality; SF = Social functioning; RE = Role emotional; MH = Mental health; PCS = Physical component summary; MCS = Mental component summary, # responder value = 14.6; ## responder value = 3.7

The IWDAQ is a measure under development and validation. OASIS 2 data will be used for psychometric evaluation of the IWDAQ including development of a scoring algorithm. Calculation of the IWDAQ total score is based on a preliminary scoring of the measure. The IWDAQ total score will only be presented as descriptive statistics.

In addition, the following analysis will be performed

- Correlation of VFA (cm2) at baseline and waist circumference (cm) at baseline across treatment arms
- Correlation between VFA change (%) at week 68 and SFA change (%) at week 68 across treatment arms
- Correlation between SFA change (%) at week 68 and body weight change (%) at week 68 across treatment arms
- Correlation between SFA change (%) at week 68 and waist circumference change (%) at week 68 across treatment arms
- Correlation between VFA change (%) at week 68 and body weight change (%) at week 68 across treatment arms
- Correlation between VFA change (%) at week 68 and waist circumference change (%) at week 68 across treatment arms.

The coefficient of correlation (R) will be provided.

Descriptive statistics will be reported for

- Proportion (%) of participants with VFA/SFA =< 0.4 and > 0.4 at baseline and week 68
- Proportion of participants with VFA < and >= 100cm2 at baseline and week 68

4.7 Other Safety Analyses

Observed data for safety assessments will be summarised by descriptive statistics.

4.8 Other Analyses

All collected data that were not defined as endpoints will be summarised by descriptive statistics.

4.9 Changes to Protocol-planned Analyses

- Updated estimand description including:
    - Updated naming of primary estimand for co-primary endpoints to co-primary estimands.
    - Updated naming of primary estimand for confirmatory and supportive secondary endpoints to secondary estimands.
- For the analysis of binary endpoints the following has been clarified: Where response rates close to 0% or 100% in any treatment group lead to non-convergence, Firth's maximum-likelihood estimation will be used when performing the logistic regression.
- In addition to the estimated OR, the estimated treatment differences (ETDs) will be provided by calculating the responder probabilities and treatment differences between responder probabilities based on the logistic regression model, with confidence intervals for treatment differences obtained using the delta method.
- It has been clarified how the imputation model in the primary imputation approach for the treatment policy strategy will be reduced if the model cannot fit. It has also been clarified how the J2R-MI is reduced if the imputation model cannot fit.
- It has been clarified that the J2R-MI sensitivity will be aligned with the RD-MI and not include BMI group as a factor in the imputation model.
- It has been clarified how the 5% responder analysis will be assessed using the MMRM for efficacy.

The following supportive secondary endpoints have been included in Table 4-3

- Change in body weight from baseline (week 0) to end-of-treatment (week 68), kg
- Achievement of ≥14.6-point increase (yes/no) in IWQOL-Lite-CT Physical Function score at end-of-treatment (week 68), count of participants
- Achievement of ≥3.7-point increase (yes/no) in SF-36v2 Physical Functioning score at end of treatment (week 68), count of participants
- Change in glycaemic status from baseline (week 0) to end-of-treatment (week 68)
- Change in pulse from baseline (week 0) to end-of-treatment (week 68), bpm

- It has been clarified that the tipping-point sensitivity analysis will only be performed for the co-primary endpoints.
- For the analyses of VFA, SFA, VFA to SFA ratio, HbA1c<=6.5%, HbA1c<7% and SF-36 related endpoints addressing a treatment policy strategy, the imputation model has been updated from RD-MI to J2R-MI. This is due to lack of convergence of RD-MI even after removal of treatment group from the model.

- The exploratory endpoint "pain/discomfort domain score" was replaced by "physical domain score" in agreement with the final version of the 20 item version of IWQOL-Lite-CT

- Changed the on-treatment period description from "the date of first trial product administration to date of last trial product administration excluding potential off-treatment time intervals of at least 3 consecutive days" to "the date of first trial product administration to date of last trial product administration excluding potential off-treatment time intervals of more than 3 consecutive days"

- It has been clarified that for change in HbA1c and FPG, whose planned measurement visits differ depending on T2D status at baseline, only the visits where the measurements are planned for all subjects will be included in the MMRM

- In supplementary analysis, the primary statistical model for relative weight change will be fitted by adding a treatment times glycaemic baseline status interaction as a factor and baseline body weight (kg)

- The following exploratory endpoints have been added

    - SFA change (cm2, %)

    - Change in VFA/SFA ratio from baseline (week 0) to end-of-treatment (week 68)

    - Proportion (%) of subjects with VFA/SFA =< 0.4 and > 0.4 at baseline and week 68

    - Proportion of subjects with VFA < and >= 100cm2 at baseline and week 68

    - Correlation between VFA change (%) and SFA change (%)

    - Correlation between SFA change (%) and body weight change (%)

    - Correlation between SFA change (%) and waist circumference change (%)

    - Correlation between VFA change (%) and body weight change (%)

    - Correlation between VFA change (%) and waist circumference change (%)

    - Waist circumference according to the WHO guideline (cm)

5 Sample size determination

See protocol section 9.5.

6 References

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2. McEvoy BW. Missing data in clinical trials for weight management. J Biopharm Stat. 2016;26(1):30-6.
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4. Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat. 2013;23(6):1352-71.

Clinical Study Report

Study ID: NN9932-4738 (OASIS 2)

MedDRA searches for safety focus areas

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List of abbreviations and definitions of terms

AE	adverse event
HLT	high level term
MedDRA	Medical Dictionary for Regulatory Activities
NEC	not elsewhere classified
NNMQ	Novo Nordisk MedDRA query
PT	preferred term
SMQ	standardised MedDRA query
SOC	system organ class

1 MedDRA searches for safety focus areas in project

The MedDRA search strings in this document (ordered alphabetically) were used for the NN9932-4738 (OASIS 2) clinical study report. The MedDRA version used was 26.0.

2 Abuse and misuse

Custom query (NNMQ Abuse and Misuse)

- SMQ Drug abuse and dependence (SMQ code 20000101) -*only narrow scope terms included*
- Intentional product misuses (HLT code 10079157)
- Single PTs: Poisoning deliberate, Intentional dose omission, Performance enhancing product use, Completed suicide, Intentional self-injury, Suicide attempt, Assisted suicide, Suspected suicide attempt, Suspected suicide.

3 Acute renal failure

SMQ Acute renal failure (SMQ code 20000003) – *only narrow scope terms*

4 Acute pancreatitis

Custom query (NNMQ Pancreatitis) – *only PTs which are narrow scope terms according to the SMQ and all PTs captured by HLT and not included in the SMQ*

- Acute pancreatitis (SMQ code 20000022)
- Acute and chronic pancreatitis (HLT code 10033646) (including primary and secondary terms)

5 Altered skin sensation

Custom query – *picked PTs related to a clinical picture of altered skin sensation*

- Single PTs: Dysaesthesia, Hyperaesthesia, Paraesthesia, Pain of skin, Skin burning sensation, Neuralgia, Burning sensation, Sensitive skin, Skin discomfort and Skin sensitisation

6 Cardiovascular disorders

Custom query (NNMQ Cardiovascular disorders) - *broad and narrow terms from the following SMQs*

- Central nervous system vascular disorders (SMQ code 20000060)

- Vasculitis (SMQ code 20000174)
- Ischaemic heart disease (SMQ code 20000043)
- Cardiac arrhythmias (SMQ code 20000049)
- Cardiac failure (SMQ code 20000004)
- Cardiomyopathy (SMQ code 20000150)
- Embolic and thrombotic events (SMQ code 20000081)
- Shock (SMQ code 20000066)
- Torsade de pointes/QT prolongation (SMQ code 20000001)

7 COVID-19

SMQ COVID-19 (SMQ code 20000237) – *only narrow scope terms*

8 Gallbladder-related disorders

Custom query (NNMQ Gallbladder-related disorders) – *only narrow scope terms of the SMQs*

- Functional, inflammatory and gallstone related biliary disorders (SMQ code 20000119)
- Infectious biliary disorders (SMQ code 20000120)

9 Gastrointestinal disorders

Custom query (NNMQ Gastrointestinal disorders SOC)

- SOC Gastrointestinal disorders (SOC code 10017947), *primary terms only*

10 Hepatic disorders

SMQ Drug related hepatic disorders - comprehensive search (SMQ code 20000006) – *broad scope search*

11 Hypoglycaemia

SMQ Hypoglycaemia (SMQ code 20000233) – *only narrow scope terms*

12 Immunogenicity related adverse events

Custom Query (NNMQ Allergic reactions) – *only narrow scope terms from the following SMQs*

- Anaphylactic reaction (SMQ code 20000021)
- Angioedema (SMQ code 20000024)
- Severe cutaneous adverse reactions (SMQ code 20000020)
- Anaphylactic/anaphylactoid shock conditions (SMQ code 20000071)
- Hypersensitivity (SMQ code 20000214)

13 Malignant tumours

SMQ Malignant tumours (SMQ code 20000194)

14 Medication errors

SMQ Medication errors (SMQ code 20000224) – *broad scope search*

15 Neoplasms (benign and malignant)

Custom query (NNMQ Neoplasms) – *broad scope search*

- Biliary neoplasms (SMQ code 20000121)
- Breast neoplasms, malignant and unspecified (SMQ code 20000149)
- Liver neoplasms, benign (incl cysts and polyps) (SMQ code 20000012)
- Liver neoplasms, malignant and unspecified (SMQ code 20000011)
- Malignancies (SMQ code 20000090)
- Malignant lymphomas (SMQ code 20000215)
- Oropharyngeal neoplasms (SMQ code 20000110)
- Ovarian neoplasms, malignant and unspecified (SMQ code 20000151)
- Premalignant disorders (SMQ code 20000085)
- Prostate neoplasms, malignant and unspecified (SMQ code 20000152)
- Skin neoplasms, malignant and unspecified (SMQ code 20000173)
- Uterine and fallopian tube neoplasms, malignant and unspecified (SMQ code 20000153)
- Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC code 10029104) – *primary and secondary terms*

Narrow terms scope: All PTs which are 'Narrow' according to the SMQs and all PTs captured by the SOC, which are not already included in the SMQs.

Broad terms scope: All PTs which are 'Broad' according to the SMQs

16 Overdose

Custom query (NNMQ Overdose)

- HLT Overdoses NEC (HLT code 10076292)
- Single PTs: Accidental overdose, Completed suicide, Suicide attempt, Suspected suicide attempt, Suspected suicide

17 Pancreatic neoplasms (malignant)

Custom query (NNMQ Pancreatic cancer)

- All PTs within the HLT Pancreatic neoplasms (HLT code 10033632) which are ALSO within the SMQ Malignant tumours (SMQ code 20000194)

18 Psychiatric disorders

Custom query (*used to capture events within psychiatric disorders broadly*):

- SOC Psychiatric disorders, primary terms only (SOC code 10037175)

19 Rare events

Custom query (NNMQ Rare events) (*presentation excluding events that are included in other safety focus areas*))

- SMQ Agranulocytosis (SMQ code 20000023) - *narrow scope terms only*
- SMQ Guillain-Barre syndrome (SMQ code 20000131) – *narrow scope terms only*
- SMQ Haematopoietic cytopenias affecting more than one type of blood cell (SMQ code 20000028) - *broad and narrow scope terms*
- SMQ Haematopoietic leukopenia (SMQ code 20000030) – *broad and scope terms*
- SMQ Haematopoietic thrombocytopenia (SMQ code 20000031) – *narrow scope terms only*
- SMQ Interstitial lung disease (SMQ code 20000042) *narrow scope terms only*
- SMQ Neuroleptic malignant syndrome (SMQ code 20000044) - *narrow scope terms only*
- SMQ Noninfectious myocarditis/pericarditis (SMQ code 20000239) – *narrow scope terms only*

- SMQ Pseudomembranous colitis (SMQ code 20000080) – *narrow scope terms only*
- SMQ Retroperitoneal fibrosis (SMQ code 20000065) – *narrowscope terms only*
- SOC Congenital, familial and genetic disorders (SOC code 10010331) - *all terms are primary PTs*
- Angioedemas (HLT code 10002425) - *primary and secondary routed PTs*
- Glomerulonephritis and nephrotic syndrome (HLT code 10018365) - *primary and secondary routed PTs*
- Nephritis NEC (HLT code 10029137) - *primary and secondary routed PTs*
- Single PTs: Disseminated intravascular coagulation (PT code 10013442), Hepatic lymphocytic infiltration (PT code 10079686), Multiple organ dysfunction syndrome (PT code 10077361)

20 Retinal disorders

Custom query (NNMQ Retinal disorders and visual impairment):

- SMQ Retinal disorders (SMQ code 20000158) - *narrow terms only*
- HLT Visual impairment and blindness (excl colour blindness) (HLT code 10080708) - *primary routed PTs only*

21 Suspected transmission of an infectious agent via trial product

Custom query (NNMQ Transmission)

- HLT Infectious disorders carrier (HLT code 10021910)
- HLT Infectious transmissions (HLT code 10027684)