Cover Page for Statistical Analysis Plan

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Statistical Analysis Plan

Effect and safety of liraglutide 3.0 mg on weight management in children with obesity aged 6 to <12 years: 56-week, double-blind, randomised, placebo-controlled trial

Substance: liraglutide

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

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Version History

This Statistical Analysis Plan (SAP) for study NN8022-4392 is based on the protocol version 4.0 dated 19MAY2022.

SAP Version	Date	Change	Rationale
1.0		Not Applicable	Original version

List of abbreviations

AD	available but discontinued
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AT	available on randomised treatment
BMI	body mass index
BMI SDS	body mass index standard deviation score
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CRF	case report form
C-SSRS	columbia suicidality severity rating scale
CSR	clinical study report
CV	coefficient of variance
FAS	full analysis set
FPG	fasting plasma glucose
FDA	US Food and Drug Administration
HbA_{1c}	glycosylated haemoglobin
HDL	high density lipoprotein
HOMA-B	homeostasis model assessment of beta-cell function
HOMA-IR	homeostasis model assessment of insulin resistance
ICH	International Council on Harmonization
LDL	low density lipoprotein
MD	missing drop-out
MedDRA	Medical Dictionary for Regulatory Activities
MHP	mental health professional
MI	multiple imputation
MMRM	mixed model for repeated measurements
MT	missing on treatment
OR	odds ratio
PD	pharmacodynamics
PK	pharmacokinetics
PYE	patient years of exposure
RD-MI	multiple imputation using retrieved subjects
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous
SD	standard deviation
T2D	type 2 diabetes
TEAE	treatment-emergent adverse event
LAR	legally acceptable representative

SMQs	standardized MedDRA queries
TFL	tables, figures and listings
VLDL	very low-density lipoprotein
WHO	World Health Organisation

1 Introduction

1.1 Objectives, Endpoints, and Estimands

1.1.1 Objectives

Main Phase

Primary objective

To compare the effect of liraglutide 3.0 s.c. once daily versus liraglutide placebo on weight management in children aged 6 to <12 years with obesity.

"Liraglutide placebo" will hereafter be referred to as "placebo".

Secondary objectives

To compare the effect of liraglutide 3.0 mg s.c. once daily versus placebo in children aged 6 to <12 years with obesity on:

- Cardiovascular risk factors
- Glucose metabolism

To evaluate the safety and tolerability of liraglutide 3.0 mg s.c. once daily versus placebo in children aged 6 to <12 years with obesity.

Extension Phase

To investigate the effect and safety of liraglutide 3.0 mg and lifestyle intervention in:

- Subjects randomised to liraglutide treatment in the main phase who continue liraglutide treatment in the open-label extension, compared to
- Subjects randomised to placebo treatment in the main phase who initiate liraglutide treatment in the open-label extension.

To evaluate the long-term (2-years after open label treatment) effect and safety of liraglutide 3.0 mg in:

- Subjects randomised to liraglutide treatment in the main phase who continue liraglutide treatment in the open-label extension, compared to
- Subjects randomised to placebo treatment in the main phase who initiate liraglutide treatment in the open-label extension

1.1.2 Endpoints

1.1.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Relative change in BMI	From baseline (week 0) to week 56	Percent

1.1.2.2 Confirmatory secondary endpoints

Endpoint title	Time frame	Unit
Effect endpoints		
Relative change in body weight	From baseline (week 0) to week 56	Percent
Subjects achieving ≥5% reduction of BMI	From baseline (week 0) to week 56	Count of subjects

1.1.2.3 Supportive secondary endpoints

Endpoint title	Time frame	Unit
Effect endpoints		
Change in body weight	From baseline (week 0) to week 56	kg
Change in BMI standard deviation score (WHO.int)[3]	From baseline (week 0) to week 56	Score points
Subjects achieving ≥10% reduction of BMI	From baseline (week 0) to week 56	Count of subjects
Change in BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov)[2]	From baseline (week 0) to week 56	Percent point
Change in waist circumference	From baseline (week 0) to week 56	cm
Change in systolic blood pressure	From baseline (week 0) to week 56	mmHg
Change in diastolic blood pressure	From baseline (week 0) to week 56	mmHg
Change in HbA1c[a]	From baseline (week 0) to week 56	Percent point
Safety endpoints		
Treatment emergent adverse events (TEAEs)	From baseline (week 0) to week 82	Number
Treatment emergent serious adverse events (SAEs)	From baseline (week 0) to week 82	Number

[a] Only for subjects without type 2 diabetes at screening.

1.1.2.4 Exploratory endpoints

Endpoint title	Time frame	Unit
Effect endpoints		
Change in homeostasis model assessment (HOMA-B)	From baseline (week 0) to week 56	Percent point
Change in HOMA-IR	From baseline (week 0) to week 56	Score
Body weight reduction ≥5% from baseline	From baseline (week 0) to week 56	Yes/no
Low density lipoprotein (LDL) cholesterol	From baseline (week 0) to week 56	mmol/L
High density lipoprotein (HDL) cholesterol	From baseline (week 0) to week 56	mmol/L
Triglycerides	From baseline (week 0) to week 56	mmol/L
Relative change in BMI	From baseline (week 0) to week 140 From baseline (week 0) to week 244	Percent
Relative change in body weight	From baseline (week 0) to week 140 From baseline (week 0) to week 244	Percent
Change in waist circumference	From baseline (week 0) to week 140 From baseline (week 0) to week 244	cm

Change in BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov)	From baseline (week 0) to week 140 From baseline (week 0) to week 244	Percent point
Safety endpoints		
Treatment emergent adverse events (TEAEs)	From baseline (week 0) to week 142 From baseline (week 0) to week 244	Numbers
Treatment emergent serious adverse events (SAEs)	From baseline (week 0) to week 142 From baseline (week 0) to week 244	Numbers
Safety endpoints (for children with T2D only)		
Number of treatment emergent hypoglycaemic episodes	From baseline (week 0) to week 142 From baseline (week 0) to week 244	Numbers

1.1.3 Estimands

1.1.3.1 Primary estimand

The primary estimand will quantify the average treatment difference of liraglutide 3.0 mg relative to placebo after 56 weeks, in all randomised subjects regardless of adherence to treatment or initiation of rescue interventions (such as weight management drugs or bariatric surgery) ("effectiveness"/ "treatment policy" estimand). The estimand will cover all effect-related objectives.

The primary estimand is described by the following attributes:

- **Population:** Children with obesity aged 6 to <12 years
- **Endpoint:** relative change from baseline to week 56 in body mass index (BMI).
- **Treatment condition:** the randomised treatment regardless of adherence to treatment or initiation of rescue interventions (as defined above).
- **Remaining intercurrent events:** none, all intercurrent events are captured by the treatment condition attribute and handled by the treatment policy strategy.
- **Population-level summary:** difference in mean changes

Rationale for estimand: The primary estimand take into account both safety and efficacy and reflect clinical practice to the extent possible in a clinical study. The primary estimand are thus relevant to support regulatory decision making.

1.1.3.2 Secondary estimand

The secondary estimands for the secondary and exploratory endpoints are similar to the primary estimands except for the endpoint attribute. For continuous endpoints, the secondary estimands for primary and secondary objectives are similar to the primary estimand for % BMI change. For binary endpoints, the secondary estimands for primary and secondary objectives differ only by endpoint and population level summary. For confirmatory secondary endpoint ≥ 5% BMI reduction, odds ratio between treatment condition will be reported.

1.1.3.3 Additional estimand

The estimand will quantify the average treatment difference of liraglutide 3.0 mg relative to placebo after 56 weeks, in all randomised subjects had they remained on their randomised treatment for the entire planned duration of the trial and not started any rescue intervention (such as weight management drugs or bariatric surgery) ("efficacy"/ "hypothetical" estimand).

The additional estimands differ only by endpoint and population level summary. The additional estimands are described by the following attributes:

- **Population:** Children with obesity aged 6 to <12 years
- **Endpoint:** relative change from baseline to week 56 in body mass index (BMI)

- **Treatment condition:** the randomised treatment if participants remained on their randomised trial product for the entire planned duration of the trial and not started any rescue intervention (as defined above).

- **Remaining intercurrent events:** none, all intercurrent events (discontinuation or initiation of rescue intervention) are captured by the treatment condition attribute. Discontinuation or rescue intervention are handled by the hypothetical strategy.

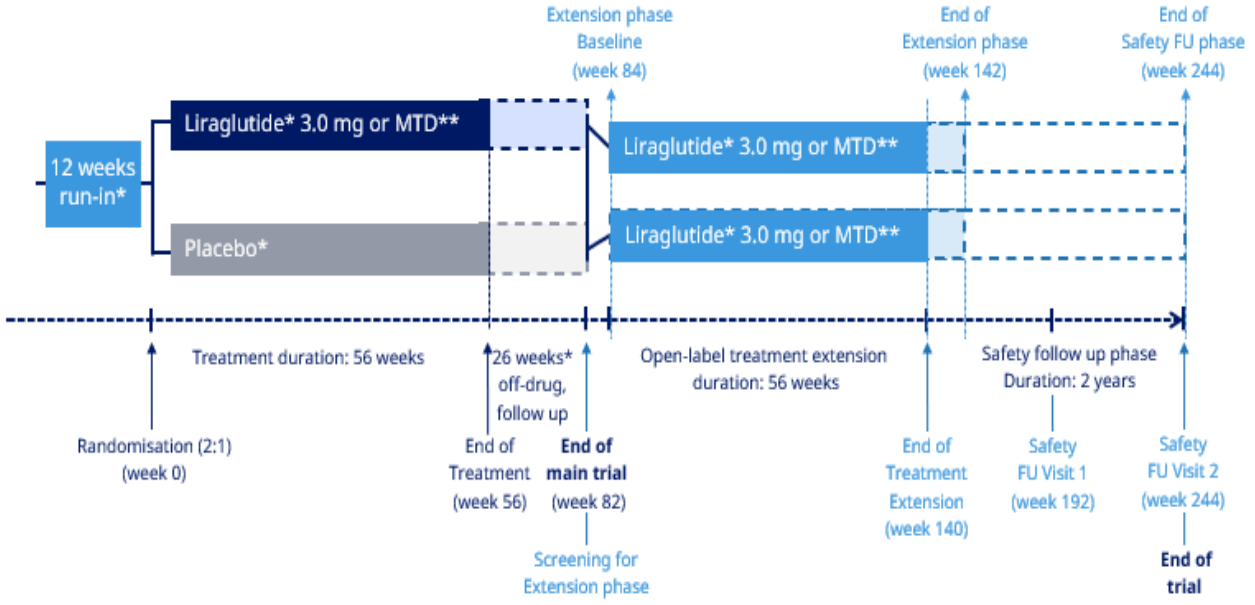
- **Population-level summary:** difference in mean changes

Rationale for estimand: The additional estimand aims at reflecting the treatment effect without the confounding effects of rescue intervention or trial product discontinuation.

A similar additional estimand also applies to all primary and secondary objectives in the population.

1.2 Study Design

Figure 1.1 Study design with the different phases



*As an adjunct to a reduced-calorie diet and increased physical activity in children with obesity; Dose initiation from 0.3 mg for children with body weight <45 kg and from 0.6 mg for children with ≥45 kg and will be escalated further.

**MTD, Maximum Tolerated Dose

This is a double-blind, randomised, parallel group, placebo-controlled, multi-national clinical trial comparing liraglutide 3.0 mg s.c. once daily with placebo in children, aged 6 to <12 years, with obesity with or without comorbidities.

Main Phase

The Main phase of the trial includes a 2-week screening, 12-week run-in and a 56-week treatment period with an off-drug follow-up period of 26-weeks (Figure 1-1).

In the Main phase, subjects who have fulfilled the randomisation criteria will be randomised 2:1 to receive liraglutide 3.0 mg s.c. or placebo s.c. once daily. Randomisation will be stratified by gender and Tanner stage (Tanner 1 [premature adrenarche included] vs 2-3 vs 4-5).

Extension Phase

The Extension phase consists of an open-label treatment period with a 2-week screening, a 56-week treatment period, and a 2-week off-drug follow-up period, followed by a safety, follow-up phase with yearly visits for 2 years.

During the safety, follow-up phase subjects will not receive study intervention (i.e. neither intervention with healthy nutrition and physical activity counselling nor active treatment) and will thus be considered off-treatment. After end of the open-label treatment period (week 142), subjects can be treated at the discretion of the investigator (including anti-obesity medication), and participation in other clinical studies is also allowed.

All subjects (and parent(s)/LAR) will receive counselling in healthy nutrition and physical activity from run-in (week 12) until end of the 2-week off-drug, follow-up period (week 142), for a total of 154 weeks.

Further details are described in the protocol section 6.

2 Statistical Hypotheses

The primary endpoint is relative change in BMI from baseline (week 0) to week 56

The superiority tests of liraglutide 3.0 mg vs. placebo will be carried out as follows.

Let μliraglutide and μplacebo denote the true mean of relative change in BMI for s.c. liraglutide 3.0 mg once-daily and placebo group, respectively. The null and alternative hypotheses tested are

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

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

2.1 Multiplicity Adjustment

The primary endpoint followed by the two confirmatory secondary endpoints will be evaluated using a hierarchical testing procedure starting with the treatment difference between the relative change in BMI. In the case of a significant treatment difference in the relative change in BMI, the test procedure proceeds to test the treatment difference between the relative change in body weight followed by the treatment difference between the subjects achieving ≥5% reduction of BMI. This test procedure will protect the family-wise type 1 error in the strong sense on a 5% level of significance.

3 Analysis Sets

Main Phase

Two analysis sets are defined in accordance with the ICH E9.

Table 1 Analysis sets

Participant Analysis Set	Description
Full analysis set (FAS)	• All randomised participants. Participants will be included in the analyses according to the planned treatment
Safety analysis set	• All participants who are exposed to at least one dose of the randomised treatment. Participants will be included in the analyses according to the treatment they actually received.

Any observation excluded from the analysis database will be documented before database lock with the reason for exclusion provided.

Two observation periods are defined for each subject:

- In-trial: The in-trial period is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site.

- On treatment: defined as events with onset date on or after the first day of trial product administration and no later than whatever comes first: a) 14 days after the last day on trial product, b) FU visit (subjects with trial product discontinued), or c) last study visit (early withdrawn subjects without FU visit).

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 following data points sets are defined:

Table 2 Defined data point sets

Data Points Sets	Description
DPS1	• For participants who discontinue treatment and/or receive rescue therapy, all post-discontinuation or post-rescue observations will be included in the analysis set.
DPS2	• For participants who discontinue treatment and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included in the analysis set.

FAS and DPS1 are used to estimate the primary estimand for primary and secondary objectives.

FAS and DPS2 are used to estimate the additional estimand for the primary and the secondary objectives.

Extension Phase

Analysis set for Extension phase is defined as follows.

Full analysis set: All subjects exposed to at least 1 dose of trial product.

Two observation periods are defined for each subject:

- Extension in-trial: The extension in-trial period is defined as the uninterrupted time interval from date of the start of the Extension phase to date of last contact with trial site.

- Extension on-treatment (with trial product): A time-point is considered as 'on-treatment' for the Extension phase if defined as events with onset date between the first day of trial product administration in the Extension phase and whatever comes first: a) 14 days after the last day on trial product, b) first follow-up visit (V42 for subjects with trial product discontinued), or c) last study visit (subjects withdrawn without follow-up visit).

The Extension phase 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.

4 Statistical Analyses

4.1 General Considerations

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

Results from statistical analyses will generally be accompanied by two-sided 95% confidence intervals and corresponding p-values. Superiority of confirmatory endpoints will be claimed if p-values are less than 5% and the estimated treatment contrasts favour liraglutide 3.0 mg.

Handling of missing values at baseline

If an assessment has been made both at screening and randomisation, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment was made at screening, the screening value will be used as the baseline value.

The definition of the analysis sets is given in Section 3

4.2 Primary Estimands Analyses

4.2.1 Definition of Endpoint

Primary endpoint: Relative change in BMI

Relative change from baseline (week 0) to week 56 in BMI is defined as

$$\text{Relative change in BMI} = \frac{(\text{BMI at week 56} - \text{BMI at baseline})}{\text{BMI at baseline}} \times 100.$$

4.2.2 Main Analytical Approach

The analysis model for relative change in BMI (%) is a linear regression (ANCOVA) assuming unequal variances between the treatment arms on randomised treatment and stratification group (gender and Tanner stage group and their interaction) as factors, and baseline BMI (kg/m^2) as covariate.

The estimated treatment difference between liraglutide 3.0 mg and placebo will be reported together with the associated two-sided 95% CI and corresponding p-value.

Table 3 Taxonomy for subjects based on week 56 assessments being available or missing

Assessment at week 56	**Subjects on randomised treatment at week 56**	**Type description**	**Type Abbreviation**
Available	Yes	**Available on randomised treatment**:	AT

		Subjects who complete the trial on randomised treatment with an assessment at week 56: Includes those that stop and restart trial product.	
	No	**Available but discontinued:** Subjects who discontinued randomised treatment prematurely but returned to have an assessment at week 56. These are also called retrieved subjects	AD
Missing	Yes	**Missing on randomised treatment**: Subjects who complete the trial on randomised treatment without an assessment at week 56: Includes those that stop and restart trial product.	MT
	No	**Missing and discontinued**: Subjects who discontinued randomised treatment prematurely and did not return to have an assessment at week 56. These are also called non-retrieved subjects	MD

Primary imputation approach for handling missing values addressing the primary estimand

Multiple imputation approach using retrieved subjects (RD-MI): The primary imputation approach for the primary estimand is a multiple imputation similar to the one described by McEvoy[1]

In this method missing BMI measurement at week 56 for non-retrieved dropouts (MD) are imputed by sampling from values obtained from retrieved dropouts (AD) in each randomised treatment arm. This will be done according to the timing (monthly) of last available observation (of BMI measurement) on randomised treatment (LAO-OT). Missing BMI measurements at week 56 for subjects on drug treatment (MT) are imputed by sampling from subjects 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 subjects (AD) from FAS and done within groups defined by randomized treatment. The model will be a linear regression of BMI (kg/m^2) at week 56 on stratification group (gender and Tanner stage group and their interaction) as factors and baseline BMI (kg/m^2), timing of LAO-OT of BMI (kg/m^2) and LAO-OT of BMI (kg/m^2) as covariates. If the imputation model cannot be fit, then the model will be reduced until the model can be fit. Reduction will be done in a fixed order by first removing Tanner stage, then removing gender and finally removing baseline BMI. If the model still 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 BMI. An imputation model for missing BMI measurements at week 56 for MT subjects will also be defined using AT subjects 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 56 BMI values for each randomised treatment arm. This will be done 1000 times and result in 1000 complete data sets.

2. **Analysis**: Analysis of each of the 1000 complete data sets, using the analysis model (ANCOVA), resulting in 1000 estimations.

3. **Pooling**: Pool the 1000 estimation results into a final result using Rubin's formula.

The multiple imputations will be generated using Novo Nordisk trial number 80224392 as seed number.

4.2.3 Sensitivity Analysis

To investigate the sensitivity of the results of the main analysis of the primary endpoint with regards to the handling of missing data, the following sensitivity analyses will be performed:

Jump to reference multiple imputation approach (J2R-MI): The approach for multiple imputations of missing values of BMI (kg/m^2) at week 56 (type MT+MD for both the liraglutide 3.0 mg and placebo group is by sampling all available assessments at respective landmark visits in the placebo group (type AT+AD). This approach is also known as jump to reference and makes the assumptions that subjects 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. The multiple imputation approach is done as above with the first step replaced by:

1. **Imputation**: Defines an imputation model using placebo subjects from FAS with a week 56 measurement (AT and AD). The model will be a linear regression of BMI (kg/m^2) at week 56 on stratification group (gender and Tanner stage group and their interaction) as a factors and baseline BMI (kg/m^2) as covariate. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 56 BMI values for each randomised treatment arms. This will be done 1000 times and result in 1000 complete data sets.

Wash-out multiple imputation approach (WO-MI): In this method missing BMI measurement at week 56 will be imputed using same framework (Imputation, Analysis, Pooling) as described above in primary imputation method with the first step replaced by:

1. **Imputation**: Defines an imputation step procedure utilizing different imputation models depending on randomised treatment group and end of treatment status (on-drug/off-drug) as described in the following steps:

    i. For on-drug subjects in the liraglutide 3.0 mg arm, missing BMI (kg/m^2) at week 56 are imputed based on observed data from the on-drug subjects in the liraglutide 3.0 mg arm and according to the RD-MI procedure described above. This will result in 1,000 complete data sets for on-drug subjects in the liraglutide 3.0 mg arm.

ii. For the subjects in placebo arm, missing BMI (kg/m^2) at week 56 are imputed based on all observed data at all time points in the placebo arm, and using an MMRM model with stratification group (gender and Tanner stage group and their interaction) as a factor and baseline BMI (kg/m2) as covariate – all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent. Each missing value of BMI (kg/m^2) at week 56 is imputed 1,000 times by random sampling from normal distribution with the MMRM-predicted value at week 56 as mean and variance as a sum of prediction variance and residual variance.

iii. For off-drug subjects in the liraglutide 3.0 mg arm, missing BMI (kg/m^2) at week 56 are imputed from the placebo arm 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 as defined above. An imputation model will be fitted to each of 1,000 complete data sets resulting from MMRM imputation for the placebo arm in the previous step. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation model from each of 1,000 fits is then used to impute missing week 56 BMI (kg/m^2), ultimately resulting in 1,000 complete data sets for off-drug subjects in liraglutide 3.0 mg arm.

iv. Data sets obtained in steps i-iii are combined resulting in 1,000 complete data sets for all randomised participants.

ANCOVA for equal variance: An alternative analysis model similar to the primary analysis model (ANCOVA), following the primary imputation approach (RD-MI), but assuming equal variances instead of unequal variances. The analysis model will be fitted with stratification group (gender and Tanner stage group and their interaction) as a factors and baseline BMI (kg/m2) as covariate. The estimated treatment difference between liraglutide 3.0 mg and placebo will be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

The multiple imputations will be generated using Novo Nordisk trial number 80224392 as seed number.

4.2.4 Supplementary Analysis

The additional estimand for % BMI change addresses the efficacy of liraglutide 3.0 mg and will be assessed using a MMRM for efficacy. The MMRM for efficacy will use post baseline assessments only from subjects who are taking the randomised treatment until planned end of treatment or until first discontinuation of randomised treatment. Week 56 assessments for retrieved dropouts (AD) will not be used in this analysis. For subjects who initiate other anti-obesity therapies (i.e., weight management drugs or bariatric surgery) 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 % BMI change and the same factors and covariate as for the primary analysis all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

Table 4 Analysis and imputation methods to address the primary and additional estimands for primary endpoints

Endpoint	Endpoint type	Analysis Set	Estimand	Statistical model	Imputation model	Sensitivity Analysis
Change in BMI (%) from week 0 to week 56	Continuous	FAS	Treatment policy	ANCOVA	RD-MI	J2R-MI, WO-MI, ANCOVA (Assuming equal variance)
			Hypothetical	MMRM	-	-

4.3 Secondary Estimands Analysis

4.3.1 Confirmatory Secondary Estimands

Confirmatory secondary estimands are defined in Section 1.1.2.2

4.3.1.1 Definition of Endpoints

The confirmatory secondary endpoints are:

- Relative change in body weight from baseline (week 0) to end of treatment (week 56)
- ≥5% BMI reduction (yes/no) from baseline (week 0) to end of treatment (week 56)

4.3.1.2 Main Analytical Approach

The effect-related confirmatory secondary endpoints will be analysed using the same imputation approach as used for the primary endpoint to address the primary estimand. The imputation model is the same as for the primary endpoint with BMI replaced by the endpoint to be analysed.

The statistical model for continuous endpoints will be analysed using ANCOVA assuming unequal variances with factors and covariate used as for the primary endpoint % change in BMI with baseline BMI assessment replaced by the baseline body weight.

The statistical model for the responder endpoints relating to BMI will be analysed using logistic regression. The response will be a binary outcome (yes/no) indicating for each subject whether the respective minimum reduction in BMI has been achieved. The model will include treatment, stratification factor for gender and Tanner stage and their interaction as factors, and baseline BMI as covariates. The treatment differences will be presented as odds ratios together with the associated 95% CIs.

If there are no responders for ≥5% BMI reduction at week 56 for one treatment group, the logistic regression will not fit. Thus, Firth's approximation will be implemented in order to provide valid inference in this situation.

4.3.1.3 Sensitivity Analysis

For the change in body weight, sensitivity analysis same as primary endpoint will be carried out. For binary confirmatory secondary endpoint, a sensitivity analysis using non-retrieved participants as non-responders will be carried out.

4.3.1.4 Supplementary Analysis

The confirmatory secondary endpoints will be analysed using the same analysis model as used to address the additional estimand for the primary endpoints.

The analysis model for change in body weight will be a mixed model for repeated measurements (MMRM). The MMRM will be fitted using same factors and covariates used for the primary endpoint with baseline BMI assessment replaced by baseline body weight assessment all nested within visit. An unstructured covariance matrix for measurements within the same participants will be employed, assuming that measurements for different participants are independent.

The analysis model for the responder endpoints will be a logistic regression where any missing values at week 56 will be predicted from the MMRM. The predicted values will be used to classify each participant as a responder or not. This classification will then be analysed using a logistic regression model with randomised treatment as a factor and baseline BMI as covariate.

Table 5 Analyses and imputation methods to address the secondary estimands for the confirmatory secondary endpoints

Endpoint	Endpoint type	Analysis Set	Estimand	Statistical model	Imputation model	Sensitivity Analysis
Change in body weight (%) from week 0 to week 56	Continuous	FAS	Treatment policy	ANCOVA	RD-MI	J2R-MI, WO-MI, ANCOVA assuming equal variances
			Hypothetical	MMRM	-	-
≥5% BMI reduction from week 0 to week 56	Binary	FAS	Treatment policy	LR	RD-MI	Non-responder
			Hypothetical	LR	MMRM	-

4.3.2 Supportive Secondary Endpoints Analysis

Analyses addressing the supportive secondary estimand

The effect-related supportive secondary endpoints will be analysed using the same imputation approach as used for the primary endpoint to address the primary estimand. The imputation model is the same as for the primary endpoint with BMI replaced by the endpoint to be analysed.

The statistical model for continuous endpoints will be analysed using ANCOVA assuming unequal variances with factors and covariate used as for the primary endpoint % change in BMI with baseline BMI assessment replaced by the baseline assessment of the endpoint.

The statistical model for the responder endpoints relating to BMI will be analysed using logistic regression. The response will be a binary outcome (yes/no) indicating for each subject whether the respective minimum reduction in BMI has been achieved. The model will include treatment, stratification factor for gender and Tanner stage as factors and baseline value of the endpoint as

covariate. The treatment differences will be presented as odds ratios together with the associated 95% CIs.

In case of no responder for ≥10% BMI reduction at week 56 for one treatment group, the logistic regression will not fit. Thus, Firth's approximation will be implemented in order to provide valid inference in this situation.

Analyses addressing the additional estimand

The supportive secondary endpoints will be analysed using the same approach as used for the primary endpoints to address the additional estimand.

Table 6 Analyses and imputation methods to address the secondary and additional estimands for supportive secondary endpoints

Endpoint	Unit	Endpoint type	Strategy	Analysis set	Statistical model	Imputation approach
Change in body weight from week 0 to week 56	kg	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in BMI standard deviation score from week 0 to week 56	Unitless	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
≥10% BMI reduction from week 0 to week 56	Count of participant	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM
Change in BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov) from week 0 to week 56	Percent point	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in waist circumference from week 0 to week 56	cm	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in systolic blood pressure from week 0 to week 56	mmHg	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in diastolic blood pressure from week 0 to week 56	mmHg	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in HbA_{1c} from week 0 to week 56[a]	%-point mmol/mol	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	

[a] Only for subjects without type 2 diabetes at screening

Analyses addressing the primary, secondary and additional estimands for responder endpoints

For all analyses of responder endpoints including both primary and secondary responder endpoints (≥5%, ≥10% BMI reduction from week 0 to week 56), in addition to the estimated odds ratio, 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.

Analyses corrected to address the situation if there is no responder for ≥5%, ≥10% BMI reduction from week 0 to week 56 in one treatment group

If there is no responder for ≥5%, ≥10% BMI reduction at week 56 for one treatment group, the logistic regression will not fit. Thus, the Firth's logistic regress will be applied in order to make the model successfully run.

4.4 Exploratory Endpoints Analyses

Exploratory endpoints are listed in Section 1.1.2.4 and will be analysed as follows.

Main Phase

- **Analyses addressing the secondary estimand**

The effect-related exploratory endpoints will be analysed using the same imputation approach as used for the primary. The imputation model is the same as for the primary endpoint with BMI replaced by assessments of the endpoint to be analysed. The statistical model for continuous endpoints will be ANCOVA assuming unequal variance with factor and covariate as for the primary endpoint % change in BMI with baseline BMI replaced by the baseline assessment of the endpoint to be analysed.

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

For LDL cholesterol, Triglycerides, HOMA-B and HOMA-IR, a multiplicative model will be used, i.e. 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 calculation of the HOMA endpoints will be done as follows:

Beta-cell function (%) = 20·fasting insulin[mU/L]/ (FPG [mmol/L]-3.5)
Insulin resistance (%) = fasting insulin [mU/L] ·FPG [mmol/L]/ 22.5

Analyses addressing the additional estimand

The exploratory endpoints measured at week 56 will also be analysed to address the additional estimand using the same MMRM for efficacy described for the primary endpoint.

An overview of all analysis and imputation methods to address the effectiveness and efficacy estimands for effect-related exploratory endpoints is given in Table 7.

Extension Phase

- **Analysis addressing the exploratory endpoints in extension phase**

Exploratory endpoints for the extension phase listed in Section 1.1.2.4 and will be analysed as follows.

The exploratory endpoints and assessments at scheduled timepoints will be summarised descriptively by treatment group based on the FAS, using the extension on-treatment observation period, and the extension in-trial observation period. Descriptive statistics (mean, standard deviation (SD), median, and range for continuous variables and proportion for categorical variables) will be used.

Table 7 Statistical analysis to address the exploratory endpoints

Exploratory Effect Endpoint						
Main phase						
Endpoint	**Unit**	**Endpoint type**	**Strategy**	**Analysis set**	**Statistical model**	**Imputation approach**
Change in HOMA-B from week 0 to week 56	%-point	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in HOMA-IR from week 0 to week 56	Score	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Body weight reduction >=5% from week 0 to week 56	Count of participant	Binary	Treatment policy	FAS	LR	RD-MI
			Hypothetical	FAS	LR	MMRM
Change in low density lipoprotein (LDL) cholesterol from week 0 to week 56	mg/dL mmol/L	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in high density lipoprotein (HDL) cholesterol from week 0 to week 56	mg/dL mmol/L	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in triglycerides from week 0 to week 56	mg/dL mmol/L	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in very low density lipoprotein (VLDL) cholesterol from week 0 to week 56	mg/dL mmol/L	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Change in total cholesterol from week 0 to week 56	mg/dL mmol/L	Continuous	Treatment policy	FAS	ANCOVA	RD-MI
			Hypothetical	FAS	MMRM	
Extension phase (only descriptive statistics)						
Endpoint	Unit	Endpoint type	Strategy	Analysis set	Statistical model	Imputation approach

Exploratory Effect Endpoint						
Relative change in BMI from week 0 to week 140 & week 244	Percent	Continuous	NA	FAS	-	-
Change in body weight from week 0 to week 140 & week 244	Percent	Continuous	NA	FAS	-	-
Change in Waist circumference from week 0 to week 140 & week 244	cm	Continuous	NA	FAS	-	-
Change in BMI percentage of the 95th percentile on gender and age-specific growth charts (CDC.gov) from week 0 to week 140 & week 244	Percent point	Continuous	NA	FAS	-	-

Analysis of safety endpoints

Main phase
AEs will be defined as “treatment-emergent” (TEAE), if the onset of the event occurs in the on-treatment period. TEAEs and SAEs will be summarised by descriptive statistics, such as frequencies and percentages. No formal statistical inference will be carried out based on the number of TEAEs and SAEs.

Observed data for exploratory safety endpoints and other safety assessments will be summarised by descriptive statistics.

Hypoglycaemic episodes (for T2D subjects only) will be summarised by descriptive statistics, such as frequencies and rates. No formal statistical inference will be carried out based on the number of hypoglycaemic episodes.

Extension phase
AEs will be defined as “treatment-emergent” (TEAE) if the onset of the event occurs in the on-treatment period. TEAEs and SAEs will be summarised descriptively by treatment group, based on FAS using the extension on-treatment observation period and the extension in-trial observation period. Descriptive statistics such as frequencies and percentages will be used. No formal statistical inference will be carried out based on the number of TEAEs and SAEs.

Hypoglycaemic episodes (for T2D subjects only) will be summarised for the open label treatment period just as for the Main phase.

4.5 Other Safety Analysis

Anti-liraglutide antibodies, bone age, carcinoembryonic antigen (CEA), hormone levels, bone metabolism markers, pubertal status, and height standard deviation score (SDS) will be assessed in both the main phase and the extension phase.

The AEs will be coded using the most recent version of the MedDRA. They will be presented in terms of the number and percentage of subjects with at least one event, the number of events and the event rate per 1000 years.

4.6 Other Analyses

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

Anti-liraglutide antibodies

Anti-liraglutide antibodies will be summarised in terms of the number and percentage of subjects per visit that are antibody-positive, antibody-negative, cross-reacting, and in vitro neutralising, respectively.

In addition, a comparison of the change in body weight between antibody-positive and antibody-negative subjects will be performed using descriptive statistics. Listings with the individual antibody results will also contain information about the body weight measurements. The impact of anti-liraglutide antibodies on safety will be similarly assessed by descriptive comparisons between antibody-positive and antibody-negative subjects.

4.6.1 Subgroup Analysis

Descriptive statistics will be provided for the primary and confirmatory secondary endpoints for the subgroups defined in Table 8. Wherever possible, subgroup analysis will be performed, and results will be presented as summaries or plots.

The result of the subgroup analysis will be reported outside CSR in submission package as part of clinical summaries.

Table 8 Definition of subgroups

Subgroup	Levels
Age	6 - =<9 years; 10 - =<12 years
Sex	Female; Male
Ethnicity	Hispanic or Latino; Not Hispanic or Latino
Race	White; Non-white
Tanner stage	1; 2-3; 4-5
BMI CDC	<120% of the 95th percentile; ≥120% – <140% of the 95th percentile; >140% of the 95th percentile
Region	USA; Non-USA

4.7 Pharmacokinetic and/or pharmacodynamic modelling

The Pharmacokinetic and pharmacodynamic analysis will be done as mentioned in the protocol section 11.4.

Exposure-response analysis

Data from this trial may be included in exploratory analyses of PK and exposure-response relationships, which may also include data from other trials.

4.8 Interim Analysis

No interim analysis planned for this trial.

4.9 Changes to Protocol-planned Analysis

- The Firth's logistic regression has been specified for the situation of no responder for ⩾5%, ⩾ 10%, ⩾ BMI reduction and ⩾5% body weight reduction in one treatment group.
- It is clarified that, in addition to OR, ETD will be reported for logistic regression analyses.
- It is clarified that, for confirmatory secondary endpoint a sensitivity analysis considering non-retrieved subjects as non-responders will be carried out.
- Model reduction steps have been pre-specified for situation when model cannot fit.

5 Sample size determination

See protocol section 11.1.

6 Supporting Documentation

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

- **BMI percentage of the 95th percentile (CDC.gov)**

The growth charts from the CDC consist of a series of percentile curves that illustrate the distribution of selected body measurements in children from Unites States.

The BMI-for-age reference data applies to children and adolescents (2-20 years).

In practice when using the growth reference data, then the age in months is used to look up the 95th percentile. E.g. if a subject is 180.2 months when being measured, then the 95th percentile to be used is obtained from the 180.5 month reference, since this reference covers the interval from 180 to 180.99 months. According to CDC[2] the percentiles at a finer age can be obtained using linear interpolation.

Hence, in order to calculate an exact percentage above the 95th percentile for a given age in months, linear interpolation of the 95th percentile is applied between the lower 95th percentile in months and the upper 95th percentile in months.

- **BMI Standard deviation score (BMI SDS) and Height Standard deviation score (Height SDS)**

BMI SDS and height SDS will be calculated using growth reference data on BMI and height from WHO[3]

The following procedure is recommended to calculate a SDS score (sometimes referred to as z-score) for an individual child with measurement y at age t:

1: Calculate

$$Z_{ind} = \frac{[y/M(t)]^{L(t)} - 1}{S(t)\,L(t)}$$

2: Compute the final z-score (Z^{*}_{ind}) of the child for the indicator as:

$$z^{*}_{ind} = \begin{cases} z_{ind} & if \quad |z_{ind}| \le 3 \\ 3 + \left(\dfrac{y - SD3pos}{SD23pos} \right) & if \quad z_{ind} > 3 \\ -3 + \left(\dfrac{y - SD3neg}{SD23neg} \right) & if \quad z_{ind} < -3 \end{cases}$$

Where:

- L(t), M(t) and S(t): Box-cox power, median and CV respectively
- y: Individual BMI or height value
- SD3pos: is the cut-off 3 SD calculated at t (age) by LMS method:

$$SD3pos=M(t)[1+L(t)*S(t)*(3)]^{1/L(t)}$$

- SD3neg: is the cut-off -3 SD calculated at t by the LMS method:

$$SD3neg=M(t)[1+L(t)*S(t)*(-3)]^{1/L(t)}$$

- SD23pos: is the difference between the cut-offs 3 SD and 2 SD calculated at t by LMS method:

$$SD23pos=M(t)[1+L(t)*S(t)*(3)]^{1/L(t)} - M(t)[1+L(t)*S(t)*(2)]^{1/L(t)}$$

- SD23neg: is the difference between the cut-offs -2 SD and -3 SD calculated at t by LMS method:

$$SD23neg = M(t)[1+L(t)*S(t)*(-2)]^{1/L(t)} - M(t)[1+L(t)*S(t)*(-3)]^{1/L(t)}$$

To illustrate the procedure, an example with BMI-for-age for boys is provided below and displayed in Figure 1.

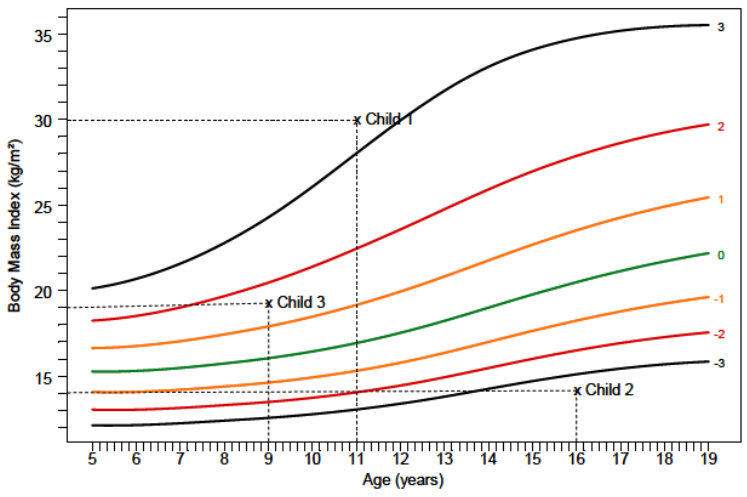


Figure 1 Examples of children/adolescents ranked according to the 2007 WHO BMI-for-age reference.

Child 1: 11-year-old boy with BMI=30

L=1.7862 M=16.9392 S=0.11070

$$Z=\frac{[30.0/16.9392]^{((-1.7862))}(-1)}{0.11070*(-1.7862)} = 3.24 > 3$$

$SD3=16.9392*[1+(-1.7862)\ *0.11070*(3)]^{1/\ (-1.7862)} = 28.03$

$SD2=16.9392*[1+(-1.7862)\ *0.11071*(2)]^{1/\ (-1.7862)} = 22.45$

$SD23 = 28.03 – 22.45 = 5.58$

$Z^{*}_{ind}= 3+(30 - 28.03/5.58) = 3.35$ (BMI SDS)

Similar calculation will be done for height SDS.

- **C-SSRS parental card**

The C-SSRS parental card version is a short questionnaire assessing both suicidal behaviour and suicidal ideation. The questionnaire can be used at the investigator's discretion as an interview tool. The questionnaire will be available in a linguistically validated translated version. When answering the questions on the C-SSRS parental card version after screening (V1), the subject and the subject's parent(s)/LAR should be instructed to answer the questions having the period since the last clinic visit in mind. If the child answers 'yes' to any question on the questionnaire the child must be evaluated as soon as possible by a MHP. No formal statistical inference will be carried out for C-SSRS parental card data.

- **New classification of hypoglycaemia**

Refer Appendix 9 in protocol

7 References

1. McEvoy BW. Missing data in clinical trials for weight management. J Biopharm Stat. 2016;26(1):30-6.
2. Centers for Disease Control and Prevention. Stature-for-age charts, 2 to 20 years, LMS parameters and selected smoothed stature percentiles in centimeters, by sex and age [Internet] 2018 [Cited August 2018].
3. World Health Organization. World Health Organization: Growth reference 5-19 years. Accessed at: http://www.who.int/growthref/who2007_bmi_for_age/en/ [updated 2 March 2018; cited 2018 2 March].