Cover Page for Statistical Analysis Plan

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

16.1.9 Documentation of statistical methods

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

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Trial ID: NN8022-4179

Statistical Analysis Plan

Effect of liraglutide for weight management in paediatric subjects with Prader-Willi Syndrome

A randomised, placebo controlled, parallel group, multi-centre, multi-national trial with a 16-week double-blind period and 36-week open-label period

Trial Phase: 3a

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Version history

This Statistical Analysis Plan (SAP) for trial NN8022-4179 is based on the final protocol version 5.0 16July2020.

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Original version

1 Introduction

1.1 Objectives and endpoints

1.1.1 Objectives

Primary objective

To compare the efficacy of liraglutide versus placebo on weight loss in paediatric subjects with obesity and PWS at 16 weeks and versus no treatment at 52 weeks.

Secondary objectives

- To compare the efficacy of liraglutide versus placebo on glycaemic control in children and adolescents with obesity and PWS at 16 weeks and versus no treatment at 52 weeks.
- To estimate the liraglutide steady state exposure in children and adolescents with obesity and PWS after 16 weeks of treatment.
- To compare the safety of liraglutide versus placebo in children and adolescents with obesity and PWS at 16 weeks and versus no treatment at 52 weeks.

1.1.2 Endpoints

1.1.2.1 Primary endpoints

There are two co-primary endpoints:

- Change in body mass index (BMI) standard deviation score (SDS) from baseline to 16 weeks
- Change in body mass index (BMI) standard deviation score (SDS) from baseline to 52 weeks

1.1.2.2 Secondary endpoints

1.1.2.2.1 Key supportive secondary efficacy endpoints

- Percent of subjects achieving ≥ 5% reduction in baseline BMI at weeks 16 and 52
- Percent of subjects achieving ≥ 10% reduction in baseline BMI at weeks 16 and 52

Change from baseline to 16 and 52 weeks in:

- BMI
- Body weight (kilogram (kg), pounds (lb) and percent (%))
- Hyperphagia score:
  - total score and
  - hyperphagic behaviour, drive and severity score
- Systolic and diastolic blood pressure
- Glucose metabolism: glycosylated haemoglobin (HbA_{1c}), fasting plasma glucose (FPG)

Further details are described in the protocol section 4.2.

Specifications of tables, figures and listings (TFL) and other specifications not included in this SAP will be described in the statistical programming specification (SPS).

1.2 Trial design

This is a multi-centre, multi-national randomised, parallel group, placebo-controlled trial with a 16-week double-blind period and a 36-week open-label period. This trial consists of a part A and a part B. Part A of the trial is conducted in adolescents (≥ 12 and < 18 years, Tanner stage 2−5) with obesity and PWS. Part B of the trial is conducted in children (≥ 6 and < 12 years, Tanner stage below 2 (defined as Tanner stage 1 with or without premature adrenarche)) with obesity and PWS. Entry into part A and part B of the trial will be sequential. The randomisation will be stratified according to pubertal status (part A) and by presence/absence of dysglycaemia (Parts A and B). After all subjects in part A have completed the 16-week double-blind period, an independent external Data Monitoring Committee (DMC) will review the PK data and safety data from part A. The DMC will recommend to the Novo Nordisk safety committee whether children in part B should be randomised and exposed to liraglutide/liraglutide placebo. In addition, the tolerability/safety and PK data from trial NN8022-4181 in children with obesity 7-11 years (both inclusive) will be reviewed to allow adjustments in part B.

The maximum duration of treatment of a single subject, from first trial product administration to last trial product administration will be 52 weeks, and the maximum dose will be 3.0 mg/day in part A and for children in part B with a body weight ≥ 45 kg. For children in part B with a body weight of < 45 kg the maximum dose will be 2.4 mg/day.

At least 30% of subjects will be from areas with lifestyle and nutrition comparable to that in the European Union (EU).

Further details are described in the protocol section 5.

2 Statistical hypotheses

The two co-primary endpoints are:

- Change from baseline in BMI SDS after 16 weeks of treatment
- Change from baseline in BMI SDS after 52 weeks of treatment

The hypotheses of equality between liraglutide and placebo for each of the two endpoints are tested in a hierarchical manner in the order in which the endpoints are presented. The implication is that liraglutide will only be considered statistically significantly better than placebo at 52 weeks if it is considered statistically significantly better with respect to the first primary endpoint.

The primary analysis will include subjects from all strata, i.e. both from part A and part B (provided that the external DMC recommends that part B will be conducted).

BMI SDS will be summarised using descriptive statistics according to the stratification factor for Tanner stage and stratification factor for glycaemic category. In case there are a very low number of subjects within one glycaemic category, the description may be done according to stratification factor for Tanner stage alone.

The analysis of each of the co-primary endpoints will use the same approach and is described below.

The objective is to show that liraglutide is superior to placebo in obtaining weight loss.

Let $\mu_{liraglutide}$ and $\mu_{placebo}$ denote mean change in BMI SDS for liraglutide and placebo respectively. The null-hypothesis and the alternative hypothesis are:

H_0: $\mu_{liraglutide} = \mu_{placebo}$ against the alternative H_A: $\mu_{liraglutide} \neq \mu_{placebo}$

The null-hypothesis will be rejected on a 5% level if the two-sided 95% confidence interval of the treatment difference $\mu_{liraglutide} - \mu_{placebo}$ excludes 0. If the upper limit is below 0 superiority of liraglutide against placebo can be concluded.

3 Sample size determination

Refer protocol section 17.1.

4 Analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guideline.

Table 4-1 Overview of subject analysis set

Subject Analysis Set	Description
Full Analysis Set	All randomised subjects who have received at least one dose of trial product and have any post-randomisation data. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation "as randomised".
Safety Analysis Set	All subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation "as treated".

Data from nominal visits (V10x and V19x) will be used prior to imputation of remaining missing data unless otherwise stated.

Before data are locked for statistical analysis, a blind review of all data will take place. Any decision to exclude a subject or single observation from the statistical analysis is the joint responsibility of the trial statistician, the ITM and the medical specialist. Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

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

Table 4-2 Overview of defined analysis set

Defined Analysis Data Sets	Description
In-trial	The time period where the subject is supposed to be in the trial. The in-trial period begins at date of first dose of trial product and ends at the date of: • The last direct subject-site contact, which is planned to take place at a follow-up visit • Withdrawal date for subjects who withdraw informed consent • The last subject-investigator/site contact as defined by investigator for subjects who are lost to follow up • Date of death for subjects who die before any of the above

On-treatment	The time period where subjects are treated with trial product. The on-treatment period begins on the date of first dose of trial product and at the earliest date of: • The follow-up visits (subjects with trial product discontinued) • Last day on trial product + 14 days • Last study visit (early withdrawn subjects without FU visit). On-treatment period is defined for Liraglutide 3.0 mg as week 0-52 and for Placebo week 0-16.
Double blinded	The double blind period is from first dose of trial product to week 16 (0-16). For the events occurring in double blinded period (AE and Hypoglycaemic episode) • For liraglutide double blinded period will be from (week 0) to (week 16) • For placebo double blinded period will be from (week 0) to (week 16 + 14 days)
Open label	The open label period is of duration 36 weeks that is from end of week 16 to week 52. For the events occurring in open label period (AE and Hypoglycaemic episode) • For Liraglutide open label period will be from (end of week 16) to (52 weeks + 14 days) • For placebo open label period will be from (end of week 16 +14 days) to (week 52)

5 Statistical analyses

5.1 General considerations

Results from the statistical analysis will generally be presented by two-sided confidence intervals (CIs) with a confidence level of 95%. Superiority will be claimed if the two-sided p-value is less than 5% and the treatment estimate favours liraglutide. If the upper limit is below 0, superiority of liraglutide against placebo can be concluded.

The full analysis set (FAS) will be used in the analysis of the efficacy endpoints. For the safety endpoints, the safety analysis set (SAS) will be used. The definition of the analysis sets is given in Section 4.
The baseline value will be defined as the last measured and available value from V3 (randomisation) and V2 (screening). Laboratory and PK values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

All analysis will be performed for part A , part B and all subject (which includes both part A and B).

5.2 Subject disposition

Refer mock TFLs.

5.3 Primary endpoints analysis

5.3.1 Primary endpoints

The two co-primary endpoints are:

- Change from baseline in BMI SDS after 16 weeks of treatment
- Change from baseline in BMI SDS after 52 weeks of treatment

The hypothesis mentioned in section 2 will be tested using an analysis of covariance (ANCOVA) model using including the factors, covariates and interaction term listed in below table.

Table 5-1 Factors and covariates for the analysis of the primary endpoints

Factors and covariates at baseline	Type	Categories
Randomised treatment	Factors	Liraglutide 3.0 mg, Placebo
Sex	Factors	Female, Male
Region	Factors	Asia, Europe, North America, Oceania
Glycaemic category	Factors	Yes, No*
Tanner stage, Glycaemic category	Interaction factor	Not applicable
Tanner stage	Factors	Part A: stage 2 and 3 together, Stage 4 and 5 together Part B: stage 1 with or without premature adrenarche
BMI SDS	Covariate	Not applicable
Age	Covariate	Not applicable

*Yes: dysglycaemic, No: non-dysglycaemic.

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.

Missing data will in the main analysis be handled by the following multiple imputation (MI) method. A pattern mixture model approach is applied where withdrawn subjects with missing values are assumed to respond as if treated with placebo for the entire trial. Multiple copies (N = 1000) of the full dataset will be generated by imputing missing values based on estimated parameters for the placebo group. These missing data will be handled as mentioned in protocol section 17.3.

Table 5-2 Taxonomy for subjects based on of week 16 and 52 assessments being available or missing

Assessment at week 16 and 52	On randomised treatment at week 16 and 52	Type description	Type abbreviation
Available	Yes	Available on randomised treatment: Subjects who did not discontinue randomised treatment prematurely with an assessment at week 16 and 52.	AT
	No	Available drop-outs: Subjects who discontinued randomised treatment prematurely but returned to have an assessment at week 16 and 52; also called retrieved drop-outs.	AD
Missing	Yes	Missing on randomised treatment: Subjects who did not discontinue randomised treatment prematurely without an assessment at week 16 and 52.	MT
	No	Missing drop-outs: Subjects who discontinued randomised treatment prematurely and did not return to have an assessment at week 16 and 52; also called non-retrieved drop-outs.	MD

5.3.2 Main analytical approach

5.3.2.1 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 is missing at the randomisation visit and an assessment was available at screening, then the screening value will be used as the baseline value.

5.3.2.2 Handling of missing values at weeks 16 and 52

Missing values at weeks 16 and 52 will be imputed and the relevant endpoints will be analysed from the imputed values. Several approaches for imputation of missing values at weeks 16 and 52 will be applied. First, a description of the primary imputation approach used to address the effectiveness for the primary endpoint is given. This is followed by a description of several sensitivity analyses.

Primary approach for handling missing values

The primary approach for multiple imputations of missing values of BMI SDS at week 16 and 52 (type MT+MD Table 5-2) 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 diet and exercise[3]. The multiple imputation approach is done in four steps.

Imputation: Step 1: 1000 copies of the dataset will be generated.
Analysis: Step 2: Impute the missing value from placebo completers by fitting enriched regression model. Model will be fitted with the factors, covariates and interaction term in the same order as mentioned in Table 5-3. The estimated parameters and their variances from this model were used to impute missing values at 16 weeks (or 52 weeks) for subjects in both treatment arms, based on their factor levels and the values of the covariates.

Analysis: Step 3: For each of the 1000 complete datasets, the change from baseline in BMI SDS at 16 weeks (or 52 weeks) will be analysed using the main ANCOVA model with factors and covariates and interaction term as mentioned in Table 5-1.

Pooling: Step 4: Pool the 1000 estimation results into final result using Rubin's formula.

If N = 1000 copies are insufficient to obtain stable results, a higher number will be used.

The imputation model in step 2 uses placebo subjects from FAS with non-missing BMI SDS at baseline and 16 weeks (or 52 weeks). The imputation model is a linear regression of BMI SDS at 16 weeks (or 52 weeks) on the factors and covariates listed in Table 5-3 (except randomised treatment arm) with interaction term included in the model. The order of the factors and covariates has been retained as mentioned in Table 5-3 while fitting imputation model. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation model is then used to impute missing 16 weeks (or 52 weeks) BMI SDS values for both randomised treatment arms.

Table 5-3 Factors and Covariate for imputation model

Factors and covariates at baseline	Type	Categories	Order
Sex	Factors	Female, Male	1
Region	Factors	Asia, Europe, North America, Oceania	2
Tanner stage	Factors	Part A: Stage 2 and 3 together, Stage 4 and 5 together Part B: Stage 1 with or without premature adrenarche	3
Glycaemic category	Factors	Yes, No	4
Glycaemic category, Tanner stage	Interaction factor	Not applicable	5
BMI SDS	Covariate	Not applicable	6

The multiple imputations will be generated using Novo Nordisk trial number 80224179 as seed number.
If the imputation ANCOVA model cannot be estimated due to too few placebo subjects with available data, explanatory variables will be removed in the following order until the model is estimable: region, sex, baseline BMI SDS, Tanner stage, baseline glycaemic category and interaction between baseline glycaemic category and stratification factor for Tanner stage.

Table 5-4 Statistical analysis to address primary objectives

SI No.	Endpoints	Landmark visits	Endpoint type	Imputation approach and Statistical model	Analysis set	Sensitivity analyses
Primary Endpoint						
1	Change from baseline in BMI SDS	Week 16, Week 52	Continuous	J2R-MI ANCOVA	FAS	• ANCOVA (LOCF) • ANCOVA (BOCF) • ANCOVA (no imputation, with 16-week (or 52 weeks) completers) • MMRM

Due to the outbreak of the coronavirus (COVID-19), the primary endpoint assessments (body weight and height) for very few subjects could not be performed on-site at the end of the double-blind period of the trial – Visit 10 (Week 16) or at the end of the open-label period of the trial – Visit 19 (Week 52). It was recommended to have the body weight and height measured at the subject's family doctor, if possible, and alternatively to perform home weight and height measurements based on instructions provided. These measurements as well as measurements for subjects who were unable to perform or have body weight and height measured due to COVID-19 will not be part of the primary analysis but will be included in sub analysis. This is applicable only for part B as only subjects from part B were enrolled in the trial during the pandemic.

5.3.3 Sensitivity analysis

To investigate the sensitivity of the results of the main analysis of the primary endpoint about the handling of missing data, the following sensitivity analyses will be performed.

An ANCOVA will be performed with imputation of missing values according to the last observation carried forward (LOCF) method. The model will include factors, covariates and interaction term as listed in Table 5-1. The response variable will be the last available measurement of BMI SDS obtained within the 16-week double-blind period of the trial. Data from nominal visits (V10x and V19x) will not be used for this analysis.

- The same type of ANCOVA as above will be performed but using an imputation of missing values according to the baseline observation carried forward (BOCF) method. Missing measurements of BMI SDS at 16 weeks will with this method be imputed by the corresponding baseline values. Data from nominal visits (V10x and V19x) will not be used for this analysis.
- The same type of ANCOVA as above will be performed without imputation by only including subjects who completed the 16-week double-blind period. Data from nominal visits (V10x and V19x) will not be used for this analysis.
- A mixed model for repeated measurements (MMRM) will be applied where all post baseline BMI SDS measurements obtained at planned visits during the 16-week double-blind period will enter as the dependent variables, and the factors, covariates and interaction term as listed in Table 5-1 will be included in the model. . All these factors and covariates will be nested under visit, which is technically the same as introducing the corresponding interaction terms in the model. An unstructured covariance matrix for the BMI SDS measurements within subject will be employed. Data from nominal visits (V10x and V19x) will not be used for this analysis.

The sensitivity analyses will be repeated for the week 52 co-primary endpoint.

The ANCOVA model with LOCF assumes that post treatment discontinuation, the body weight is on average stable in both treatment arms. If the assumption holds, the treatment effect (effectiveness estimand) in each arm and the treatment difference can be estimated from this analysis unbiased. If the withdrawal and the development in both arms are similar, the treatment difference can be estimated from this analysis unbiased. If the development in body weight after treatment discontinuation differs between active and placebo, this analysis might provide an optimistic or over-conservative estimate, depending on the actual circumstances. The analysis is included to be able to compare the results with legacy obesity programs, where this analysis was the main analysis of the primary endpoints.

The ANCOVA model with BOCF assumes that post treatment withdrawn subjects with missing values returns to a body weight in the proximity of their baseline body weight regardless of the timing of withdrawal. This analysis is expected to provide a conservative estimate (effectiveness estimand) of the treatment effect (in each arm). The impact of this assumption on the treatment difference depends on withdrawal pattern over time and development of body weight post withdrawal and reason for withdrawal. The analysis is typically expected to provide a conservative estimate of the treatment difference (effectiveness estimand).

The ANCOVA analysis in completers is expected to give more positive results than the primary analysis. However, this analysis has its own clinical interpretation and will serve as a benchmark and provide an estimate of the efficacy estimand in the population that tolerate the trial product and endure the diet and exercise counselling program.

The MMRM model assumes that withdrawn subjects, had they completed the trial, would not have behaved differently than completing subjects from the same treatment arm with the same baseline characteristics and change in body weight at time of withdrawal. This analysis estimates the treatment difference had all subjects stayed on the randomised treatment (efficacy estimand).

5.4 Secondary endpoints analysis

All the secondary supportive efficacy endpoints listed below will be analysed as per protocol section 17.4.

5.4.1 Supportive secondary endpoints

5.4.1.1 Efficacy endpoints

BMI

The changes in BMI from baseline at 16 and 52 weeks will be analysed separately with the same type of ANCOVA with MI as used for the main analysis of the primary endpoint, but with the baseline BMI as covariate instead of the baseline BMI SDS.

In addition, the following categorical endpoints related to BMI will be evaluated:

- Percentage of subjects achieving ≥ 5% reduction in baseline BMI at 16 weeks
- Percentage of subjects achieving ≥ 5% reduction in baseline BMI at 52 weeks
- Percentage of subjects achieving ≥ 10% reduction in baseline BMI at 16 weeks
- Percentage of subjects achieving ≥ 10% reduction in baseline BMI at 52 weeks

These endpoints will be analysed separately using a logistic regression model. 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, baseline glycaemic category, stratification factor for Tanner stage and baseline BMI and baseline age as covariates. The treatment differences will be presented as odds ratios together with the associated 95% CIs.

For the analysis of the categorical endpoints, missing BMI values will be imputed using the 1000 complete datasets from the MI performed for the corresponding analysis on the continuous change in BMI. The logistic regression will be performed on each of these datasets. Rubin's formula will then be applied on the 1000 estimates of the log odds ratio and the associated SDs to produce a pooled estimate and SD. These pooled values will lastly be used to calculate the 95% CI for the odds ratio.

During the blinded review of data it has been observed that there were only few subjects achieving ≥ 10% reduction in baseline BMI at week 16 or at week 52.

- Part A: No subject at week 16 and 2 subjects at week 52 experienced a ≥ 10% reduction in baseline BMI .

- Part B: 2 subjects at week 16 and 3 subjects at week 52 experienced a ≥ 10% reduction in baseline BMI .

Because of these findings the statistical analysis (J2R-MI Logistic Regression) will not be performed for this endpoint and will only be summarised descriptively.

BMI SDS: No increase

The percentage of subjects with no increase in BMI SDS at 16 and 52 weeks will be analysed using the same statistical method as the one used for the categorical endpoints related to BMI, but with the baseline BMI SDS as covariate instead of the baseline BMI.

Hyperphagia questionnaire outcome

The questionnaire on hyperphagia will be evaluated similarly to the primary endpoint. That is, the change in hyperphagia score (hyperphagia total score and hyperphagic behaviour, drive and severity score respectively), from baseline at 16 and 52 weeks will be analysed separately using the same type of ANCOVA with MI as used for the main analysis of the primary endpoint, but with the corresponding baseline hyperphagia score instead of the baseline BMI SDS as covariate.

Glycaemic category

The change in glycaemic category (normoglycaemia, pre-diabetes, T2DM) from baseline at 16 and 52 weeks will be summarised using descriptive statistics.

Furthermore, two separate analyses will be performed on the binary variable normoglycaemia (yes/no) at 16 and 52 weeks, using a logistic regression model with the factors treatment, baseline glycaemic category, stratification factor for Tanner stage and baseline age as covariate. Missing data will be handled by a MI method like the one used for the main analysis of the primary endpoint but adapted to the logistic regression model. The treatment differences will be presented as odds ratios together with the associated 95% CIs.

Other efficacy endpoints

The following other efficacy variables will be evaluated:

- Body weight
- Waist circumference
- Waist to hip circumference ratio
- CV biomarker (hsCRP)
- Fasting lipids (TC, LDL-cholesterol, HDL-cholesterol, non-HDL cholesterol, VLDL cholesterol, TG and FFA)
- Systolic and diastolic blood pressure
- Quantitative glucose metabolism parameters (HbA_{1c}, FPG, fasting insulin, C-peptide, HOMA-B and HOMA-IR)

The changes in these variables from baseline at 16 and 52 weeks will be analysed using the same type of ANCOVA with MI as used for the main analysis of the primary endpoint, but with the baseline value of the corresponding variable instead of the baseline BMI SDS as covariate. Each endpoint will be analysed separately. For hsCRP, fasting lipids, fasting insulin, C-peptide, HOMA B and HOMA IR, the response and baseline values will be log transformed prior to the analysis.

Categorical responses will be a binary outcome indicating for each subject whether the respective endpoint is achieved. Missing data will be handled by a MI method similar to the one used for the main analysis of the primary endpoint, but adapted to the logistic regression model. The treatment differences will be presented as odds ratios together with the associated 95% CIs.

For missing glycaemic category, the imputation will be done for missing FPG and HbA1c assessments using the imputation model mentioned in Table 5-5.

In addition to all the supportive secondary efficacy analysis following added endpoints will be analysed similarly as per primary endpoint statistical model mentioned in protocol section 17.3.

- Change from baseline at 16 and 52 weeks:
  - BMI SDS (%)
  - BMI (%)

Table 5-5 Statistical analysis to address the secondary objectives

SI No.	Endpoints	Landmark visits	Endpoint type	Imputation approach and Statistical model	Analysis set	Sensitivity analyses
Secondary Endpoint						
1	Change from baseline in BMI SDS (%)	Week 16, Week 52	Continuous	J2R-MI ANCOVA	FAS	NA
2	Change from baseline in BMI (Kg/m^2)	Week 16, Week 52	Continuous	J2R-MI ANCOVA	FAS	NA
3	Change from baseline in BMI (%)	Week 16, Week 52	Continuous	J2R-MI ANCOVA	FAS	NA
4	Percentage of Subjects achieving >=5% reduction in baseline BMI	Week 16, Week 52	Categorical	J2R-MI Logistic Regression	FAS	NA
5	Percentage of subjects with no increase in BMI SDS	Week 16, Week 52	Categorical	J2R-MI Logistic Regression	FAS	NA

SI No.	Endpoints	Landmark visits	Endpoint type	Imputation approach and Statistical model	Analysis set	Sensitivity analyses
6	Change from baseline in hyperphagia score (hyperphagia total score, hyperphagic behaviour, drive and severity score)	Week 16, Week 52	Continuous	J2R-MI ANCOVA	FAS	NA
7	Change from baseline in Glycaemic category	Week 16, Week 52	Categorical	J2R-MI Logistic Regression	FAS	NA
8	Change from baseline in Body weight (kg, lb and %)	Week 16, Week 52	Continuous	J2R-MI ANCOVA	FAS	NA
9	Change from baseline in Waist circumference (cm)	Week 16, Week 52	Continuous	J2R-MI ANCOVA	FAS	NA
10	Change from baseline in Waist-to-hip circumference ratio (ratio)	Week 16, Week 52	Continuous	J2R-MI ANCOVA	FAS	NA
11	Change from baseline in Cardiovascular biomarker (hsCRP) (mg/L)	Week 16, Week 52	Continuous	J2R-MI ANCOVA (with log transformed response and baseline values)	FAS	NA
12	Change from baseline in TC (mmol/L)	Week 16, Week 52	Continuous	J2R-MI ANCOVA (with log transformed response and baseline values)	FAS	NA

SI No.	Endpoints	Landmark visits	Endpoint type	Imputation approach and Statistical model	Analysis set	Sensitivity analyses
13	Change from baseline in LDL-cholesterol (mmol/L)	Week 16, Week 52	Continuous	J2R-MI ANCOVA (with log transformed response and baseline values)	FAS	NA
14	Change from baseline in HDL-cholesterol (mmol/L)	Week 16, Week 52	Continuous	J2R-MI ANCOVA (with log transformed response and baseline values)	FAS	NA
15	Change from baseline in non-HDL cholesterol (mmol/L)	Week 16, Week 52	Continuous	J2R-MI ANCOVA (with log transformed response and baseline values)	FAS	NA
16	Change from baseline in VLDL (mmol/L)	Week 16, Week 52	Continuous	J2R-MI ANCOVA (with log transformed response and baseline values)	FAS	NA
17	Change from baseline in TG (mmol/L)	Week 16, Week 52	Continuous	J2R-MI ANCOVA (with log transformed response and baseline values)	FAS	NA
18	Change from baseline in FFA (mmol/L)	Week 16, Week 52	Continuous	J2R-MI ANCOVA (with log transformed response and baseline values)	FAS	NA
19	Change from baseline in Systolic Blood Pressure (mmHg)	Week 16, Week 52	Continuous	J2R-MI ANCOVA	FAS	NA
20	Change from baseline in Diastolic Blood Pressure (mmHg)	Week 16, Week 52	Continuous	J2R-MI ANCOVA	FAS	NA
21	Change from baseline in HbA_{1c} (%)	Week 16, Week 52	Continuous	J2R-MI ANCOVA	FAS	NA

SI No.	Endpoints	Landmark visits	Endpoint type	Imputation approach and Statistical model	Analysis set	Sensitivity analyses
22	Change from baseline in FPG (mmol/L)	Week 16, Week 52	Continuous	J2R-MI ANCOVA	FAS	NA
23	Change from baseline in fasting insulin (pmol/L)	Week 16, Week 52	Continuous	J2R-MI ANCOVA (with log transformed response and baseline values)	FAS	NA
24	Change from baseline in C-peptide (nmol/L)	Week 16, Week 52	Continuous	J2R-MI ANCOVA (with log transformed response and baseline values)	FAS	NA
25	Change from baseline in HOMA-B	Week 16, Week 52	Continuous	J2R-MI ANCOVA (with log transformed response and baseline values)	FAS	NA
26	Change from baseline in HOMA-IR	Week 16, Week 52	Continuous	J2R-MI ANCOVA (with log transformed response and baseline values)	FAS	NA
27	Change from baseline in Pulse (beats/min)	Week 16, Week 52	Continuous	J2R-MI ANCOVA	SAS	NA
28	Relative change from baseline in Amylase	Week 16, Week 52	Continuous	MMRM (with log transformed response and baseline values)	SAS	NA
29	Relative change from baseline in Lipase	Week 16, Week 52	Continuous	MMRM (with log transformed response and baseline values)	SAS	NA

5.4.1.2 Supportive secondary PK endpoint

Model-derived area under the curve (AUC) over the dosing interval in steady state.

5.4.1.3 Supportive secondary safety endpoints

Adverse events

AEs will be summarised by System organ class (SOC) and Preferred term (PT) level for the safety analysis set separately for two periods:

- In trial: defined as events with onset date on or after the first day of trial product administration and no later than the last study visit.
- 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).
- A treatment emergent adverse event (TEAE) is defined as an event that occurs in the 'on treatment' period.

In addition, the TEAEs will be summarised for the double blinded (0-16 week) and open label (end of week 16 to week 52.

The AEs will be coded using the most recent version of the Medical Dictionary for regulatory Activities (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. AEs in the screening period will be presented in listings.

Hypoglycaemic episodes

The hypoglycaemic episodes will be summarised descriptively by severity and treatment in terms of the number and percentage of subjects with at least one event and the total number of events. In the same way as for AEs, there will be separate summaries for the "in trial" and "on treatment" periods. Hypoglycaemic episodes in the screening period will be presented in listings.

Hypoglycaemic episodes will also be summarised based on newer classification recommended by International Hypoglycaemia Study Group (IHSG) 2017[12], ADA 2018[13] and ISPAD 2018[14] for clinically significant hypoglycaemia (PG confirmed <3.0 mmol/L) (see Appendix 3 for the new classification)

The hypoglycaemic episodes will be summarised for the double blinded period (0-16 week) and open label period (end of week 16 to week 52).

Anti-liraglutide antibodies

Anti-liraglutide antibodies will be summarised in terms of the number and percentage of subjects at each visit that are antibody-positive and antibody-negative. Similarly, subjects with cross-reactivity against endogenous GLP-1 and in vitro neutralising effect will be summarised.

In addition, a comparison of the change in HbA_{1c} and body weight between antibody-positive and antibody-negative subjects will be performed using descriptive statistics and graphs. Listings with the individual antibody results will also contain information about the HbA_{1c} levels and 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.

ECG

Summary statistics and the frequencies of shifts in ECG status from baseline at 16 and 52 weeks will be tabulated for each treatment group.

Pulse

Summary statistics and the frequencies of shifts from baseline to 16 and 52 weeks will be tabulated for each treatment group. In addition, statistical analyses similar to those made for blood pressure will be performed considering safety analysis set.

Laboratory parameters

Summary statistics will be tabulated for each laboratory parameter. The distributions will also be presented graphically using box plots by treatment and week.

For each laboratory parameter, the values will be compared to the relevant reference range. The results will be presented as follows:

- Shifts from baseline at 16 and 52 weeks will be tabulated. The shift tables will include the number of subjects below, within and above the reference range at each visit
- The proportion of subjects with laboratory values outside the reference range will be tabulated per visit and treatment group
- Individual values outside the reference range (abnormal values) will be listed by treatment and subject

For amylase and lipase the relative change (100*value/baseline) will be analysed with an MMRM model as described under sensitivity analysis in section 5.3.3. The response and baseline values will be log transformed prior to the analysis. Safety analysis set will be considered. All lab parameters will be reported in standard units. However for the parameters like Total Cholesterol, LDL, HDL, Triglycerides, Total bilirubin, Creatinine, calcium, HbA1C, Fasting plasma glucose conventional units will also be provided along with standard units in the descriptive statistics output.

Box plots will be provided for lab parameters like Calcitonin, Lipase, Amylase, ALT, AST and Prolactin

Pubertal status

Tanner stage at screening as well as changes in Tanner stage at 16 and 52 weeks will be summarised using descriptive statistics.

Physical examination

Physical examination at screening and changes in physical examination will be summarised.

Mental health questionnaires

Results from the mental health questionnaires PHQ-9 and C-SSRS from part A will be summarised using descriptive statistics and the frequencies of shifts from baseline to 16 and 52 weeks will be tabulated for each treatment group.

In addition to all the supportive secondary safety endpoints, following endpoints is added.

- Height) velocity in cm/year (if subject is still growing)

Height velocity

Height velocity is the change in height per year and is measured in cm/year.
The height velocity is calculated as the difference between current height and baseline divided by time duration in days between those measurement time points and multiplied by 365 days.

5.5 Exploratory endpoints analysis

Not applicable

5.6 Other safety analyses

Not applicable

5.7 Other analyses

Not applicable

5.8 Interim analyses

No interim analysis is planned for the efficacy data in this trial. PK data from part A will be included in a population PK analysis also including historical data for other populations to aid dose selection for part B. Modelling results and safety data will be reviewed by the DMC before subjects in Part B will be enrolled in the trial. Before the randomisation code break for part A, modelling results will only be communicated to DMC and to individuals involved in dose selection for part B.

5.8.1 Data monitoring committee

Refer section 12.7.2 from Protocol.

6 Supporting documentation

6.1 Appendix 1 List of abbreviations

AE	*adverse event*
ALT	*alanine aminotransferase*
AD	*available drop-out*
ANCOVA	*analysis of covariance*
AST	*aspartate aminotransferase*
AUC	*area under the curve*
AT	*available on treatment*
BMI	*body mass index*
BMI SDS	*body mass index standard deviation score*
BOCF	*baseline observation carried forward*
CI	*confidence interval*
CRF	*case report form*
C-SSRS	*columbia suicidality severity rating scale*
CV	*coefficient of variance*
FAS	*full analysis set*
DMC	*data monitoring committee*
HbA_{1c}	*glycosylated haemoglobin*
hCG	*human chorionic gonadotrophin*
HDL	*high density lipoprotein*
hsCRP	*high sensitivity C reactive protein*
LDL	*low density lipoprotein*
LOCF	*last observation carried forward*
MD	*missing drop-out*
MedDRA	*Medical Dictionary for Regulatory Activities*
MI	*multiple imputation*
MMRM	*mixed model for repeated measurements*
MT	*missing on treatment*
PD	*pharmacodynamics*
PHQ-9	*patient health questionnaire 9*
PK	*pharmacokinetics*
SAE	*serious adverse event*
SAP	*statistical analysis plan*
SAS	*safety analysis set*
LAR	*legally acceptable representative*

6.2 Appendix 2: Changes to protocol-planned analyses

In this SAP the following changes is been made to the statistical consideration in the protocol are as elaborated below for:

6.2.1 Primary endpoints

- Due to the COVID-19 pandemic, the primary endpoint assessments (body weight and height) for very few subjects in part B could not be performed at the end of the double-blind period of the trial – Visit 10 (Week 16) or at the end of the open-label period of the trial – Visit 19 (Week 52). These measurements (missing or performed at home) will not be part of the primary analysis. An additional analysis will be performed by including the subjects impacted by COVID-19 at week16 and 52 for the change from baseline in BMI SDS.
- For the sensitivity analysis using LOCF method the protocol mentions that data from nominal visits (V10x and V19x) will not be used .Similarly for sensitivity analysis using BOCF, MMRM and week 16/52 completer analysis, data from nominal visits (10x and 19x) will be excluded.

6.2.2 Supportive secondary efficacy endpoints

- Additional analysis for changes from baseline at 16 and 52 weeks
  - BMI SDS (%)
  - BMI (%)

It will be analysed with the same type of ANCOVA with MI as used for the main analysis of the primary endpoint, with the corresponding baseline covariate.

- During the blinded review of data it has been observed that there were only few subjects achieving ≥ 10% reduction in baseline BMI at week 16 or at week 52 (as mentioned in section 5.4.1). Therefore the statistical analysis (J2R-MI Logistic Regression) will not be performed for this endpoint and will be summarised descriptively.
- For the analysis of categorical endpoints , the protocol mentions to include treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, and baseline BMI/BMI SDS (wherever applicable) and baseline age as covariates. During the blinded review of data for the categorical endpoints it has been observed that due to the small number of subjects in the trial the model cannot be estimated. To avoid the risk of over fitting and to make the model estimable the following explanatory variables will be removed from the analysis model.: sex, region ,interaction between baseline glycaemic category and stratification factor for Tanner stage.
- During the blinded review of data it has been observed that no subject reported an amylase measurement above 3UNR and only one subject reported a lipase measurement above 3UNR. Due to the few number of subjects having a measurement above 3UNR,for these parameters at any time during treatment, the statistical analysis (Logistic Regression) will not be performed.

6.2.3 Supportive secondary safety endpoints

- Additional safety endpoints, is been added as below.
  - Height velocity in cm/year (if subject is still growing)
- The testosterone analysis (change from baseline values at week 16 and 52) for part B could not be performed as originally planned due to an unforeseen change in the assay used by the central laboratory to measure testosterone during the trial. On 05 Dec 2018, Q2 laboratories moved from the Siemens ADVIA Centaur Testosterone "TSTO" assay to the new "TSTII" assay. The upgraded assay adheres more closely to the LC-MS reference values. This change in methodology prevented a direct comparison of values measured at different time points during the trial. As a result, the changes from baseline for individual subjects at week 16 and 52 are not provided for part B. Testosterone analysis for part A will be performed as mentioned in protocol. A listing of various hormones (LH, FSH and testosterone) analysed at different timepoints during the trial will be provided with reference ranges. Summary statistics for the testosterone analysis using the two different assays will be provided.
- Safety analysis set will be used to analyse change from baseline pulse values at week 16 and 52. Also to analyse MMRM model for relative change from baseline for amylase and lipase values at week 16 and 52.
- C-SSRS will only be summarised using summary statistics (frequency count, percentage) for baseline, week 16 and week 52 and the shift from baseline to 16 and 52 week will not be produced.

6.3 Appendix 3: Definition and calculation of endpoints, assessments and derivations

6.3.1 Endpoint derivations and assessments

6.3.1.1 BMI Standard deviation score (BMI SDS) and Height Standard deviation score (Height SDS)

BMI SDS and height SDS score will be calculated using external reference data on BMI and height from WHO[4]

The following procedure is recommended to calculate a 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:

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

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 6-1.

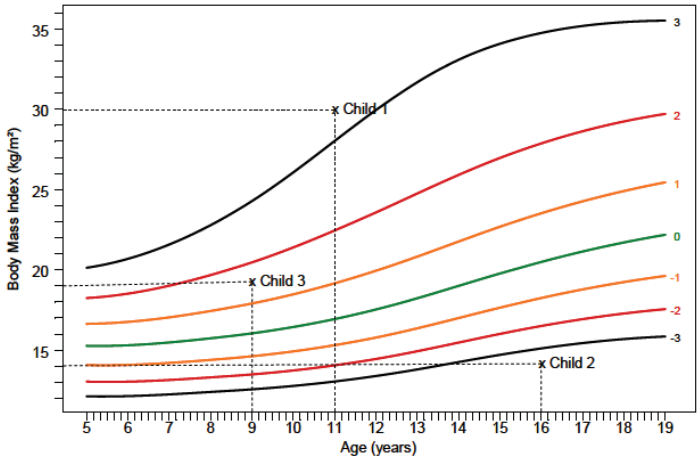

Figure 6-1 Examples of children/adolescents ranked according to the 2007 WHO BMI-for-age reference.

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.

6.3.1.2 C-SSRS questionnaire

The Columbia-Suicide Severity Rating Scale questionnaire is used for part A to assess the subject's mental state. It contains two sets of questions; one meant for the screening/randomisation visit (C-SSRS-01; baseline) and the other for the rest of the visits (C-SSRS-02; since last visit). At screening/randomisation, the questionnaire is part of the exclusion criteria (suicidal behavior, previous suicide attempts). During the trial, the questionnaire is used to evaluate the subject's mental status between visits. The first part of the questionnaire is to build up around 'yes/no' questions, which depending on the answers trigger other parts of the questionnaire

6.3.1.3 PHQ-9 questionnaire

The Patient Health Questionnaire 9 is used for part A to assess the mental health of the subject. PHQ-9 is done throughout the trial period. It contains 9 questions which are answered with a categorical rating (not at all, several days, more than half the days, nearly every day) translated directly into a number (0-3). The numbers are summed at the bottom of the questionnaire by the investigator. Similar to C-SSRS-01, this questionnaire is used at screening/randomisation as part of the exclusion criteria, i.e., if the total score is ≥15 then the subject should be excluded from the trial.

6.3.1.4 Hyperphagia questionnaire

Hyperphagia, a characteristic of patients with PWS, will be assessed using the hyperphagia questionnaire. It contains 13 questions. Out of 13 questions 11 questions are categorised into 3 domains (behaviour, drive and severity) scores. 2 questions will be considered as additional questions. The Total score is the sum of all the 3 domain scores.

12 questions out of 13 are answered with a categorical rating, translated directly into a number (1-5). There is one question, "how old was your child when they first showed an increased interest in food?" which will be answered in to number directly.

6.3.1.5 New classification of hypoglycaemia

Treatment emergent hypoglycaemic episodes will also be summarised by International Hypoglycaemia Study Group (IHSG) 2017[12], ADA 2018[13] and ISPAD 2018[14] for clinically significant hypoglycaemia (PG confirmed <3.0 mmol/L) (see Table 6-1 for the new classification).

Table 6-1 New classification of hypoglycaemia

Level	Glycaemic criteria	Description
Hypoglycaemia alert value (level 1)	< 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (level 2)	< 3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (level 3)	No specific glucose threshold	Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery
Unclassifiable	Unclassifiable	Episodes which could not be classified according to the above new classifications

Notes: The above terms 'hypoglycaemia alert value' for level 1 and 'clinically significant hypoglycaemia' for level 2 were adapted by Novo Nordisk from IHSG 2017, ADA 2018, ISPAD 2018 recommendations for hypoglycaemia. 'Severe hypoglycaemia' (level 3) term was as defined by ADA 2013 and ISPAD 2018.

6.3.2 Analysis Rules

6.3.2.1 Visit Windowing

Primary and secondary endpoints analysis is performed at Visit 10 (week 16) and Visit 19 (week 52).
For subjects who prematurely discontinues trial product or subject and/or the subject's LAR(s) withdraw consent, the investigator must aim to undertake procedures similar to those for the end of treatment (V19) as soon as possible and the follow up visit (V20) two weeks later.

The subjects were asked to attend additional visits depending on when the trial product discontinuation takes place during the trial:

- If trial product is discontinued between V3 and V9, the subject should attend V10x (16 weeks after V3) and V19x (52 weeks (± 5 days) after V3).
- If trial product is discontinued between V11 and V19, the subject should attend V19x (52 weeks (± 5 days) after V3).

The end of double-blind treatment (V10) and end of treatment (V19) collected for prematurely discontinued subject and withdrawn subjects did not exactly taken place in respective endpoint

weeks (i.e., at week 16 and week 52). Hence these records will be reallocated to the respective weeks based on analysis day on when the assessments are done by visit windowing concept.

6.3.2.2 Visits windows

Generally, visit-windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study.

In 4179 the visit windowing will be done only for V10 and V19 visits for prematurely discontinued/withdrawn subjects.

The visit windows are shown in Table 6-2.

In this table, the days are counted since the date of randomization for both safety and efficacy assessments. These visit windows apply to measurements taken at every visit. For assessments collected less often different visit windows will be applied as detailed below.

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. For example, if the Week 4 visit of a subject is delayed and occurs on Day 46 instead of on Day 29, it will be re-aligned to visit window Week 8. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

In general, if two consecutive visits Vt and Vs are x days apart, the upper limit of the visit window for Vt will be Vt+x/2 and the lower limit for the visit Vs will be Vs-x/2 (if x is even, the lower limit for Vs will be Vs-x/2+1, and the upper limit for Vt will be Vt+x/2). The algorithm needs to ensure that visit windows are not overlapping and that there are no gaps, such that each assessment can be uniquely allocated to one visit window, e.g., if Week 8 visit is scheduled for day 57, Week 12 is scheduled at Day 85 and Week 16 is scheduled at Day 113, then the visit window for week 12 extends from Day 79 to Day 106.

Note: The lower limit of first visit will be assigned with -999 which accommodate all assessments occurred before the scheduled day.

The upper limit of last visit will be assigned with 999 which accommodate all assessments occurred after the scheduled day.

Table 6-2 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Visit 1 (screening)	week -2	-15	Day -15 to -8
Visit 2 (screening)	week -1	-8	Day -7 to -3
Visit 3 (week 0)	Randomisation	1	Day -2 to 4

Analysis Visit	Week	Scheduled Day	Visit Window
Visit 4 (week 1)	week 1	8	Day 5 to 11
Visit 5 (week 2)	week 2	15	Day 12 to 18
Visit 6 (week 3)	week 3	22	Day 19 to 25
Visit 7 (week 4)	week 4	29	Day 26 to 50
Visit 8 (week 8)	week 8	57	Day 51 to 78
Visit 9 (week 12)	week 12	85	Day 79 to 106
Visit 10 (week 16)	week 16	113	Day 107 to 134
Visit 10x (week 16 follow-up)	week 16	113	Day 107 to 134
Visit 11 (week 20)	week 20	141	Day 135 to 162
Visit 12 (week 24)	week 24	169	Day 163 to 190
Visit 13 (week 28)	week 28	197	Day 191 to 218
Visit 14 (week 32)	week 32	225	Day 219 to 246
Visit 15 (week 36)	week 36	253	Day 247 to 274
Visit 16 (week 40)	week 40	281	Day 275 to 302
Visit 17 (week 44)	week 44	309	Day 303 to 330
Visit 18 (week 48)	week 48	337	Day 331 to 358
Visit 19 (week 52)	week 52	365	Day 359 to 371
Visit 19x (week 52 follow-up)	week 52	365	Day 359 to 371
Visit 20 (week 54)	week 54	379	Day 372 to 999

6.3.2.3 For parameters which are not collected at every visit (e.g. HEIGHT):

Visit windows defined in Table 6-2 will be combined. For example Table 6-3 show visit windows for HEIGHT.

Table 6-3 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Visit 2 (screening)	week -1	-8	Day -7 to -3
Visit 3 (week 0)	Randomisation	1	Day -2 to 106
Visit 10 (week 16)	week 16	113	Day 107 to 190
Visit 10x (week 16 follow-up)	week 16	113	Day 107 to 190
Visit 13 (week 28)	week 28	197	Day 191 to 274
Visit 16 (week 40)	week 40	281	Day 275 to 358
Visit 19 (week 52)	week 52	365	Day 359 to 371
Visit 19x (week 52 follow-up)	week 52	365	Day 359 to 371

6.3.2.4 For parameters which are collected at 'x' visits:

For premature discontinued subjects a parameter such as 'BODY WEIGHT', 'HEIGHT' is collected at additional visits like 10x and 19x, hence if the visit reallocation for these parameters and related parameters such as 'BMI', 'BMI SDS' are reallocated to x visit instead of normal visit (i.e., visits 10 and 19). Other parameters are reallocated to normal visits.
Note: Withdrawal subjects are reallocated to normal visits.

6.3.3 Analysis eligible records:

If the records are reallocated to the visit which is already collected, then the collected visit record is used for analysis instead of record which is reallocated to that visit.
if the subjects have records for both normal visit (Visit 10 (week 16) and x visit Visit 10x (week 16) then the records which are reallocated are not eligible for analysis.

7 References

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