Cover Page for Statistical analysis plan

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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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Statistical Analysis Plan

Trial ID: NN1218-4101

Efficacy and Safety of Faster-acting insulin aspart compared to NovoRapid® both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes

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Author:

Name: ▮▮▮▮▮▮▮▮▮▮▮▮▮

Department: ▮▮▮▮▮▮▮▮▮▮▮

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the curve
BG	blood glucose
BMI	body mass index
CGM	continuous glucose monitoring
CI	confidence interval
CTR	clinical trial report
FAS	full analysis set
FPG	fasting plasma glucose
HDL	high density lipoprotein
ICH	international council on harmonisation
IG	interstitial glucose
IMP	investigational medicinal product
ISPAD	International Society for Paediatric and Adolescent Diabetes
LDL	low density lipoprotein
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
PG	plasma glucose
PP	per protocol
PPG	postprandial glucose
SAP	statistical analysis plan
SD	standard deviation
SMPG	self-measured plasma glucose
TEAE	treatment emergent adverse event
WHO	World Health Organization

1   Introduction

1.1   Trial information

This is a 26-week randomised, partly double-blind, multicentre, multinational, active controlled, treat-to-target, three-armed parallel group trial with a 12-week run-in period comparing the effect and safety of meal-time fast-acting insulin aspart[1] vs. meal-time NovoRapid® both in combination with insulin degludec once daily in a basal-bolus regimen in type 1 diabetes mellitus Subjects from 1 year to less than 18 years of age (For Serbia only: 2 years to less than 18 years of age). The trial will also include a 26-week open-label post-meal fast-acting insulin aspart dosing arm in combination with insulin degludec.

For each Subject, the total trial duration is approximately 45 weeks consisting of the following periods (see Figure 1–1):
- Up to 2 weeks for screening
- A 12-week run-in period primarily with the aim of optimising the insulin degludec dose
- A 26-week treatment period
- A 7-day and a 30-day follow-up period

A subgroup of Subjects, age $\geq$ 8 years old at screening (Visit 1), will have blinded continuous glucose monitoring (CGM) and a standardised meal test at two occasions during the trial leading up to Visit 14 and Visit 40. The Subjects will have the blinded CGM for at least 11 days and up to 13 days before randomisation and up to 13 days before the end of the 26-week treatment period. The standardised meal test will be performed at baseline (Visit 14) and at the End of Treatment. The CGM and meal test subgroup and procedures are described in the CGM and meal test protocol Appendix B.

The trial includes a screening visit to assess the Subject's eligibility. At Visit 2, the eligible Subjects will be enrolled in a 12-week run-in period where all Subjects will be switched from their previous insulin treatment to insulin degludec once daily and meal-time NovoRapid®. During the 12-week run-in period the Investigator will focus on optimisation of the basal insulin on a weekly basis to individual fasting plasma glucose (FPG) targets. After the run-in period, Subjects with HbA$_{1c}$ $\leq$ 9.5% (80 mmol/mol) who based on the Investigator's judgement have shown ability and willingness to adhere to the trial protocol will be randomised (1:1:1) to receive meal-time fast-acting insulin aspart, post-meal fast-acting insulin aspart or meal-time NovoRapid®, all in combination with insulin degludec. Here, Meal-time dosing is defined as injecting 0 - 2 minutes before the meal, and Post-meal dosing, is defined as injecting 20 minutes after the start of the meal.

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[1] In the protocol fast-acting insulin aspart was referred to as faster-acting insulin aspart.
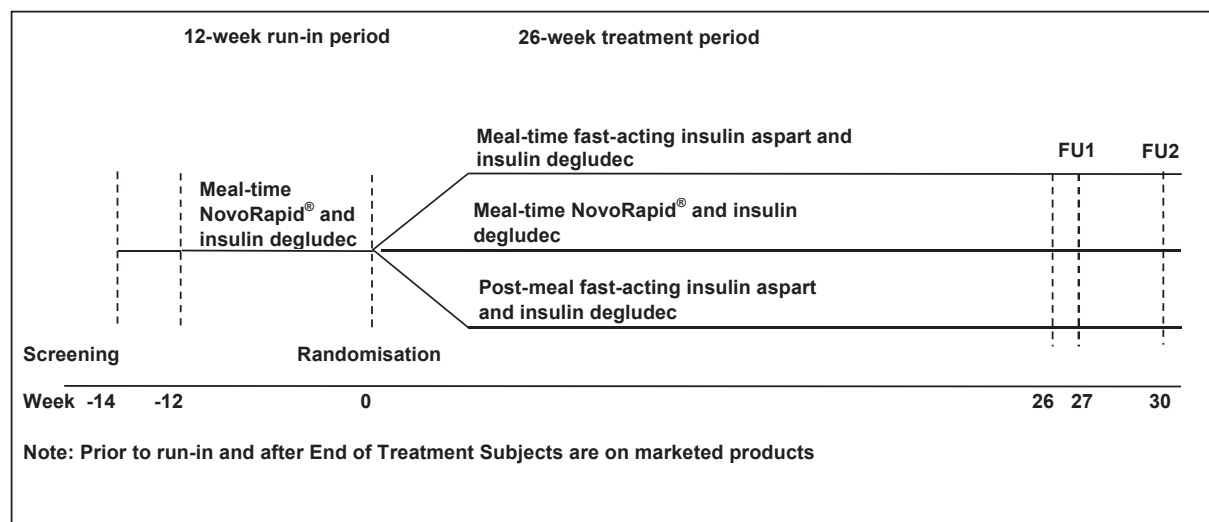
Figure 1–1   Trial design

In order to ensure a comparable number of Subjects of similar age in each treatment group the randomisation is stratified by age at randomisation according to the following categorisation: $1 \leq$ age < 3 years, $3 \leq$ age < 6 years, $6 \leq$ age < 12 years and $12 \leq$ age < 18 years. This categorisation of age will henceforth be referred to as strata.

Subjects prematurely discontinued from trial product should continue with the per protocol planned visits after 12 weeks (Visit 26) and 26 weeks (Visit 40) from randomisation depending on when the Subject discontinues trial product.

For further details on handling of Subjects that prematurely discontinue from trial product and the trial in general, please see the trial protocol.

1.2   Scope of the statistical analysis plan

This statistical analysis plan (SAP) is based on the protocol *Efficacy and Safety of Faster-acting insulin aspart compared to NovoRapid® both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes*, version 5.0 (dated 16 January 2017). The statistical analyses and derivations of endpoints presented in this SAP are almost identical to those described in the protocol. It contains minor clarifications for derivations, calculation of endpoints and analyses as well as a few additions.

The changes to the statistical considerations proposed in this SAP and the reasons for the changes are described in section 3 and will be reported in the clinical trial report (CTR).

2 Statistical considerations

General considerations

In general, for endpoints evaluated as a change from baseline and/or where a baseline adjustment is made, baseline is defined as information collected at the randomisation visit (Visit 14). In case a measurement is not available at the randomisation visit, the most recent measurement prior to the randomisation visit will be used as baseline.

Two observation periods are defined, "in trial" and "on treatment", and it will be specified which period each analysis will use.

- In trial: the observation period from date of randomisation and until last trial-related Subject-site contact. The in trial observation period includes data collected after treatment discontinuation.

- On treatment: the observation period from date of first dose of randomised NovoRapid®/fast-acting insulin aspart and no later than 7 days after the day of last dose of NovoRapid®/fast-acting insulin aspart. The on treatment observation period includes data collected up to and including 7 days after treatment discontinuation.

All primary and secondary efficacy endpoints will be summarised and analysed using the full analysis set (FAS), unless otherwise stated. Safety endpoints will be summarised using the safety analysis set (SAS) and analysed using the FAS, unless otherwise stated.

Presentation of results from a statistical analysis will include the estimated mean treatment effects (LSMeans) for change from baseline, if applicable. Estimated mean treatment differences (or ratios) will be presented together with two-sided 95% confidence intervals for all endpoints analysed statistically.

For endpoints measured over time mean values will be plotted to explore the trajectory over time. For survival endpoints, e.g. drop-out pattern, Kaplan-Meier plots are presented for each treatment.

Data collected before randomisation (Visit 14) will only be summarised descriptively.

Selected tables and figures will also be presented by age group, where age group refers to the following categorisation of age: $1 \leq$ age < 6 years, $6 \leq$ age < 12 years and $12 \leq$ age < 18 years.

Testing strategy and estimands

The primary objective, confirming the effect of treatment with meal-time fast-acting insulin aspart in children and adolescents with type 1 diabetes will be assessed using a non-inferiority approach comparing the change from baseline HbA_{1c} to meal-time NovoRapid®, where both treatments are

combined with insulin degludec . More specifically the upper limit of the 95% confidence interval should be compared to a non-inferiority margin of 0.4. If it is below or equal to 0.4 non-inferiority will be considered established and the effect demonstrated.

The trial also aims to confirm the effect of treatment with post-meal fast-acting insulin aspart and to confirm superiority of meal-time fast-acting insulin aspart both in combination with insulin degludec in children and adolescents with type 1 diabetes. In order to control the family-wise type I error rate in the strong sense, a hierarchical (fixed sequence) testing procedure will be deployed. This is based on a priority ordering of the null-hypotheses, and testing them in this order using the two-sided 95% confidence interval approach until an insignificant result appears. The effect is that rejection of the null hypothesis will only be confirmed for analyses where all previous null-hypotheses have been rejected in favour of fast-acting insulin aspart. This is done using a hierarchical testing procedure with three steps:

Step 1: HbA_{1c} non-inferiority of meal-time fast-acting insulin aspart versus meal-time NovoRapid[®] both in combination with insulin degludec

Step 2: HbA_{1c} non-inferiority of post-meal fast-acting insulin aspart versus meal-time NovoRapid[®] both in combination with insulin degludec

Step 3: HbA_{1c} superiority of meal-time fast-acting insulin aspart versus meal-time NovoRapid[®] both in combination with insulin degludec

Primary estimand

The primary estimand is defined as the treatment difference between Subjects randomised to fast-acting insulin aspart and NovoRapid[®] both in combination with insulin degludec, in children and adolescents with type 1 diabetes assessed by change from baseline HbA_{1c} 26 weeks after randomisation for all randomised Subjects regardless of treatment discontinuation or use of ancillary therapies.

The primary estimand assesses the expected difference in glycaemic benefit for a subject if prescribed to fast-acting insulin aspart as compared to NovoRapid[®] both in combination with insulin degludec in children and adolescents with type 1 diabetes. By not putting any restrictions on the treatment adherence, this estimand aims at a difference as close as possible to the one that can be expected in real-world clinical practice. Thereby the primary estimand provides a clinically relevant treatment difference for clinicians concerning the glycaemic effect of fast-acting insulin aspart compared to NovoRapid[®] in the day to day life in individual children and adolescents with type 1 diabetes, where both treatments are combined with insulin degludec.

The confirmatory analyses are made under the framework of the primary estimand.

Secondary estimand

As an alternative to the primary estimand, a secondary estimand is defined as the treatment difference in change from baseline HbA_{1c} 26 weeks after randomisation between fast-acting insulin aspart and NovoRapid® both in combination with insulin degludec in children and adolescents with type 1 diabetes aged 1 to less than 18 years if Subjects continue on treatment until 26 weeks.

The secondary estimand assesses the expected difference in glycaemic benefit for a Subject if prescribed to fast-acting insulin aspart as compared to NovoRapid® both in combination with insulin degludec in children and adolescents with type 1 diabetes if all Subjects adhered. This estimand provides a more hypothetical treatment difference, but may also be more sensitive for a non-inferiority comparison, since the marketed product that Subjects discontinuing from randomised treatment are switched to may equalize the treatment effect.

Visit reallocation

Subjects that prematurely discontinue from treatment or withdraw from trial will attend end of treatment visit called Visit 40A. Data collected at this visit will be reallocated to the next scheduled visit where the given assessment is planned. As a general rule, all observed values from randomised Subjects will be used in all statistical analyses, but in case two different values are associated to the same visit in time, the use of a given value will depend on the estimand of interest. For the primary estimand the reallocated on treatment value will not be used and for the secondary estimand the reallocated on treatment value will be used.

2.1 Sample size calculation

The primary objective of the trial is to confirm the effect of treatment with meal-time fast-acting insulin aspart in terms of glycaemic control measured by change from baseline in HbA_{1c} 26 weeks after randomisation by comparing it to treatment with meal-time NovoRapid®, both in combination with insulin degludec, using a non-inferiority approach in children and adolescents with type 1 diabetes. The sample size is determined using a non-inferiority limit of 0.4%.

The trial also aims to confirm the effect of treatment with post-meal fast-acting insulin aspart and to confirm superiority of meal-time fast-acting insulin aspart, both in combination with insulin degludec in children and adolescents with type 1 diabetes. This is done using a hierarchical testing procedure with three steps:

Step 1: HbA_{1c} non-inferiority of meal-time fast-acting insulin aspart versus meal-time NovoRapid® both in combination with insulin degludec

Step 2: HbA_{1c} non-inferiority of post-meal fast-acting insulin aspart versus meal-time NovoRapid® both in combination with insulin degludec

Step 3: HbA_{1c} superiority of meal-time fast-acting insulin aspart versus meal-time NovoRapid®, both in combination with insulin degludec

The sample size is determined to ensure sufficient power for the first step and the second step in the hierarchical testing procedure.

Power for the non-inferiority steps are based on a t-statistic under the assumption of a one-sided test of size 2.5%. A zero mean treatment difference for the comparison between meal-time fast-acting insulin aspart and meal-time NovoRapid® is expected, and for the comparison of post-meal fast-acting insulin aspart and meal-time NovoRapid® a mean difference of 0.05% in favour of meal-time NovoRapid® is expected.

Based on experience from previous trials, and taking into account that the in trial observation period includes data collected after treatment discontinuation, the standard deviation for change in HbA_{1c} is assumed to be 1.3%. With this standard deviation, a sample size of 250 Subjects per group (750 in total) will ensure more than 93% power to show non-inferiority, given that the actual treatment difference is 0%. This sample size will ensure a power of 85% to show non-inferiority of post-meal fast-acting insulin aspart compared to meal-time NovoRapid®.

The number of Subjects to prematurely discontinue trial product is expected to be less than 10% based on previous trials. The number of Subject to withdraw from trial is expected to be less than 5%.

2.1.1 Sample size calculation for the CGM and meal test subgroup

The CGM and meal test subgroup is included in the trial in order to compare additional assessments for evaluation of postprandial and overall glucose regulation between the treatment arms. As this additional assessment is exploratory in nature, this subgroup is not strictly powered to demonstrate a statistical significant difference between treatment arms in any particular endpoint. Fifty (50) Subjects per treatment arm have been chosen as this number is considered enough to provide sufficient information for evaluation in this exploratory analysis, and as this is a similar number to what have been included in previous trials using CGM subgroups.

2.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance[1]:

- FAS includes all randomised Subjects. In exceptional cases randomised Subjects may be excluded from the FAS. In such cases the reason for exclusion will be justified and documented. Subjects in the FAS will contribute to the evaluation "as randomised"

- Per Protocol (PP) Analysis Set includes all Subjects in the full analysis set that comply with inclusion and exclusion criteria. Subjects in the PP set will contribute to the evaluation "as treated"

- SAS includes all Subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set will contribute to the evaluation "as treated"

Randomised Subjects who are lost to follow up, and where no exposure information of the investigational product or its comparator is available after randomisation, will be handled as unexposed.

Before data are released for statistical review after 26 weeks, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. Furthermore, extreme values and outliers will be identified by the statistician during programming and data review, according to ICH-E9[1].

If any Subjects or observations are excluded, 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.

2.3   Primary endpoint

The primary endpoint to address all three confirmatory objectives is:

Change from baseline in HbA_{1c} 26 weeks after randomisation

Primary analysis

1) The primary estimand will be addressed by the below primary analysis on all Subjects included in FAS and using the in trial observation period. Note that if Subjects withdraw consent to contribute additional information or are completely lost to follow-up, actual missing data will occur. The primary analysis will be implemented as a statistical model using multiple imputation where the Subjects without any available HbA_{1c} measurements at scheduled visits will have their change from baseline HbA_{1c} value(s) imputed from the available information from the treatment the Subject has been randomised to. Note that this resembles in essence a mixed model of repeated measurements analysis. Subjects without post-randomisation measurements contribute to the analysis, as the missing values will be imputed. The analysis will be implemented as follows:

- In the first step, intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each group separately and 100 copies of the dataset will be generated.

- In the second step, for each of the 100 copies of the dataset, an analysis of variance model with region and strata as factors and baseline HbA_{1c} as covariate is fitted to the change in HbA_{1c} from baseline to week 12 for each treatment group separately. The estimated parameters, and their variances, from these models are used to impute missing values at week 12 for Subjects in each treatment group, based on region, strata, and baseline HbA_{1c}.

- In the third step, for each of the 100 copies of the dataset, missing values at week 26 are imputed in the same way as for week 12. The imputations are based on an analysis of variance model with region and strata as factors and baseline HbA_{1c} and HbA_{1c} at week 12 as covariates.

- For each of the complete data sets, the change from baseline to week 26 is analysed using an analysis of variance model with treatment, region and strata as factors, and baseline HbA_{1c} as a covariate.

- The estimates and standard deviations for the 100 data sets are pooled to one estimate and associated standard deviation using Rubin's formula:

$$m_{MI} = \frac{1}{100}\sum_{i=1}^{100} m_i, \quad SD_{MI} = \sqrt{\frac{1}{100}\sum_{i=1}^{100} SD_i{}^2 + \left(1 + \frac{1}{100}\right)\left(\frac{1}{100-1}\right)\sum_{i=1}^{100}(m_i - m_{MI})^2},$$

- where m_i and SD_i are the estimated means and standard deviations for the 100 copies of the dataset, and m_{MI} and SD_{MI} are the pooled estimates.

- From m_{MI} and SD_{MI}, the 95% confidence interval for the treatment differences is calculated.

All three objectives will be addressed by treatment differences and associated 95% confidence interval obtained from the same primary statistical model described above.

Non-inferiority of meal-time fast-acting insulin aspart will be considered confirmed if the upper boundary of the two-sided 95% confidence interval is below or equal to 0.4% or equivalent if the p-value for the one-sided test of

H_0: D > 0.4%   against H_A: D ≤ 0.4%,

is less than or equal to 2.5%, where D is the mean treatment difference (meal-time fast-acting insulin aspart minus meal-time NovoRapid®).

If the primary objective is confirmed, the effect of treatment with post-meal fast-acting insulin aspart in terms of glycaemic control is to be investigated by showing that post-meal fast-acting insulin aspart is non-inferior to NovoRapid® both in combination with insulin degludec in terms of glucose lowering effect, as assessed by change from baseline in HbA_{1c} 26 weeks after randomisation. This will be determined in the same way as above where treatment difference is set to (post-meal fast-acting insulin aspart minus meal-time NovoRapid®).

Finally, if both the primary and the first secondary confirmatory hypotheses are fulfilled, the superiority of the meal-time fast-acting insulin aspart as compared to meal-time NovoRapid® will be tested in terms of glycaemic control. This will be assessed by comparing the upper limit of the 95% CI from the primary analysis to 0. If the upper 95% CI is below 0 then superiority will be confirmed.

Sensitivity analyses for the primary analysis addressing the primary estimand

2) First, the primary analysis in 1) will be repeated, but excluding all factors except treatment from the multiple imputation and analysis of variance models while still including baseline HbA_{1c} as a covariate. This analysis will explore the influence of the different factors. The analysis will use the in-trial observation period.

3) The primary analysis approach chosen for this trial relies on the assumption that missing data is missing at random (MAR). This assumption implies that the HbA_{1c} for Subjects leaving the trial, after their withdrawal, develops in a similar way as the HbA_{1c} for similar Subjects that remain in the trial (not necessarily on treatment) and had similar development of HbA_{1c} before withdrawal. The MAR assumption may be questionable for Subjects withdrawing at own will or at the discretion of the Investigator. Therefore the statistical model using multiple imputation will be repeated with the following alterations:

   a. Imputation will be done from the treatment arm that the Subject was randomised to and a value of 0.4% (the non-inferiority margin) is added to the change in HbA_{1c} at 26 weeks for Subjects, on either of the fast-acting insulin aspart arms, with an imputed value at week 26[2]. This will serve as a sensitivity analyses for the non-inferiority analyses. The analysis will use the in trial observation period.

   b. Imputation will be done from the comparator arm (NovoRapid®). This will serve as a sensitivity analysis for the superiority analysis. The imputation will be done conditional on observed information for Subjects on fast-acting insulin aspart without a measurement at week 26 such that the treatment effect diminishes gradually (copy reference/conditional imputation). It does not rely on the MAR assumption, but assumes that Subjects on fast-acting insulin aspart without a measurement at week 26 switch to NovoRapid®. The analysis will use the in trial observation period.

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c. Imputation will be done from the comparator arm (NovoRapid®). This will serve as a supplementary sensitivity analysis for the superiority analysis. The imputation will be done with no regard to observed information for Subjects on fast-acting insulin aspart without a measurement at week 26 such that the treatment effect diminishes immediately (jump to reference/unconditional imputation). It does not rely on the MAR assumption, but assumes that Subjects on fast-acting insulin aspart without a measurement at week 26 switch to NovoRapid®. The analysis will use the in trial observation period.

d. A tipping point analysis based on a statistical model using multiple imputations similar to 1), using the in trial observation period, will be made. In this analysis, observations for Subjects without a measurement are imputed based on the treatment arm they were randomised to and Subjects without a measurement in the fast-acting insulin aspart group under investigation are given a penalty. Specifically, for treatment differences involving the meal-time fast-acting insulin aspart group, only Subjects in this group are given a penalty, and vice versa for treatment differences involving the postmeal fast-acting insulin aspart group. This is done to investigate the robustness of the conclusion in the primary analysis with respect to the MAR assumption and mimics a scenario where the HbA_{1c} of the Subjects without a measurement in the fast-acting insulin aspart group under investigation evolve less favourably than predicted. As a first step imputations will be done without penalty assuming MAR in the treatment group. Second, a penalty will be added to the imputed values for week 26 in the fast-acting insulin aspart group under investigation. This is done repeatedly, gradually increasing the penalty until the conclusions of the primary analysis no longer hold. The specific value of the penalty that changes the conclusion will be used to evaluate the robustness of the conclusion of the primary analysis.

Analyses addressing the secondary estimand

4) The secondary estimand will be analysed using the same statistical model using multiple imputation as the primary analysis in 1) except using the on treatment observation period. The analysis will use the FAS.

5) A tipping point analysis based on a statistical model using multiple imputation, similar to sensitivity analysis 3)-d except using the on treatment observation period.

6) A tipping point analysis based on a statistical model using multiple imputation, similar to 5) but with the modification that Subjects without a measurement that discontinued treatment due to non-eligibility (Subjects discontinuing fast-acting insulin aspart/NovoRapid® prematurely due to criteria 1, 2, 3, and 4 of Section 6.6 in the trial protocol) in the fast-acting insulin aspart

group under investigation will not have a penalty added to the imputed values. These analyses are motivated by the fact that data from Subjects prematurely discontinuing fast-acting insulin aspart/NovoRapid® due to non-eligibility can reasonably be assumed to be missing completely at random. The analysis will use the on treatment observation period.

7) The same statistical model using multiple imputation as the primary analysis in 4), but using the PP analysis set and analysed using the on treatment observation period. This analysis will investigate the situation that Subjects deviate from the ideal treatment during the on treatment observation period and will serve as a sensitivity analysis for the non-inferiority analysis.

2.4   Secondary endpoints

2.4.1   Supportive secondary endpoints

For all supportive secondary endpoints, meal-time fast-acting insulin aspart will be compared to meal-time NovoRapid®, and post-meal fast-acting insulin aspart will be compared to meal-time NovoRapid®. Change from baseline refers to the change from randomisation to 26 weeks after randomisation.

2.4.1.1   Efficacy endpoints

All endpoints except insulin dose in this section will be assessed using the FAS and the in trial observation period and repeated using the on treatment observation period. Insulin dose will only be presented using the on treatment observation period.

The following endpoints will be assessed 26 weeks after randomisation:

Change from baseline in 8-point profiles.

PPG increments based on the 8-point profiles will be derived separately for plasma glucose (PG) measurements made 1 hour after the meal. In the following section this distinction will be considered implicit and without further explanation. PPG will be recorded by the Subject as part of two 8-point profiles prior to the visits. PPG increment for each meal (breakfast, lunch, main evening meal) will be derived from the 8-point profile as the difference between PPG values and the PG value before meal in each separate profile. The mean of the derived increments will then be calculated separately for each meal. Mean PPG increment over all meals will be derived as the mean of all corresponding mean meal increments.

- Change from baseline in mean PPG and PPG increment over all three meals

Mean PPG and PPG increment will be analysed separately using a model similar to 1), except with the corresponding baseline value as covariate.

- Change from baseline in individual meal (breakfast, lunch and main evening meal) PPG and PPG increment from 8-point profile

PPG and PPG increment endpoints for the individual meals (breakfast, lunch, main evening meal) will be analysed separately using a model similar to 1) except with the corresponding baseline value as covariate.

- Change from baseline in mean of the 8-point profile

The mean of the 8-point profile is defined as the area under the profile divided by the measurement time, and is calculated using the trapezoidal method. Mean of the 8-point profile will be analysed using a model similar to 1) except with the corresponding baseline value as covariate.

- Fluctuation in 8-point profile

The fluctuation in the 8-point profile is defined as

$$\frac{1}{T}\int_0^T \left| PG(t) - \overline{PG} \right| dt \,,$$

where T, $PG(t)$ and $\overline{PG}$ denotes the length of the profile, the PG value at time t and the mean of the profile, respectively. Fluctuation in the 8-point profile will be logarithmically transformed and analysed in the same way as mean of the profile is analysed except with the corresponding log-transformed baseline values as covariate. Estimated treatment means and the estimated treatment difference with corresponding 95% CI will be back-transformed to the original scale, resulting in estimated geometric means, a treatment ratio and a 95% CI for the treatment ratio.

- Change from baseline in FPG

  Change from baseline in FPG will be analysed using a model similar to 1) except with baseline FPG as covariate.

- Change from baseline in 1,5-anhydroglucitol

  Change from baseline in 1,5-anhydroglucitol will be using a model similar to 1) except with baseline 1,5-anhydroglucitol as covariate.

- Percentage of Subjects reaching HbA_{1c} target (HbA_{1c} <7.5%) according to ISPAD guidelines[3]

  This dichotomous (responder/non-responder) endpoint will be defined based on whether a Subject has met the ISPAD HbA_{1c} target (HbA_{1c} < 7.5%) 26 weeks after randomisation. This responder endpoint will be analysed based on a logistic regression model using treatment, region and strata as factors, and baseline HbA_{1c} as covariate. In the in trial

observation period analysis, Subjects withdrawn from trial are included as non-responders. In the on treatment observation period analysis, both Subjects who prematurely discontinue fast-acting insulin aspart/NovoRapid[®] or withdraw from trial are included as non-responders. Subjects without HbA_{1c} at week 26 will be treated as non-responders for both the in trial and on treatment observation period analyses.

- Percentage of Subjects reaching HbA_{1c} target (HbA_{1c} <7.5%) according to ISPAD guidelines, without severe hypoglycaemia[3].
  This dichotomous (responder/non-responder) endpoint will be defined based on whether a Subject has met the ISPAD HbA_{1c} target (HbA_{1c} < 7.5%) 26 weeks after randomisation without treatment emergent severe hypoglycaemic episodes[3].
  This responder endpoint will be analysed based on a logistic regression model using treatment, region and strata as factors, and baseline HbA_{1c} as covariate. In the in trial observation period analysis, Subjects withdrawn from trial are included as non-responders. In the on treatment observation period analysis, both Subjects who prematurely discontinue fast-acting insulin aspart/NovoRapid[®] or withdraw from trial are included as non-responders. Subjects without HbA_{1c} at week 26, will be treated as non-responders for both the in trial and on treatment observation period analyses.

- Insulin dose (total basal, total bolus and individual meals insulin dose).
  Bolus insulin doses will be recorded together with time of administration. The insulin doses will be summarised descriptively by treatment week according to regimen, both by meal type and as total daily dose in units and units/kg (total daily and separately for each meal-time dose). Insulin doses will be summarised using the on treatment observation period and using the SAS.

Supportive secondary CGM related efficacy endpoints

The following endpoints will be assessed 26 weeks after randomisation:

- Change from baseline of time spent in low interstitial glucose (IG) (IG ≤ 3.9 mmol/L [70 mg/dL])

The time spent in low IG is defined for each Subject at each CGM period as the accumulated time in hours spent below or equal to 3.9 mmol/L from the first valid sensor value divided by the actual duration of the entire profile. To report the endpoint in minutes per 24 hours the ratio is multiplied by 1440. The endpoint will be analysed using an analysis of variance model including treatment, region and strata as factors and the baseline value of time in low IG as covariate.

- Incidence of episodes and percentage of time spent with IG ≤2.5, 3.0, 3.9 mmol/l [45, 54, 70 mg/dL]) and IG >10.0, 12.0, 13.9 mmol/l [180, 216, 250 mg/dL])

- Percentage of time spent within IG target range 4.0-10.0 mmol/L (71-180 mg/dL)

- Change from baseline in mean of the IG profile

  The mean of the IG profile will be defined as:

  $$\overline{IG} = \frac{1}{T}\int_0^T IG(t)dt,$$

  where T is the time length of the profile and $IG(t)$ is the IG value at time t. (Here $t=0$ represents the time point for the start of the profile.) This mean will be calculated by means of the linear trapezoidal technique.

- Variation in the IG profile

  The variation in the IG profile will be presented by the fluctuation, which is defined as:

  $$\frac{1}{T}\int_0^T |IG(t) - \overline{IG}|dt,$$

  where T is the time length of the profile, $IG(t)$ is the IG value at time t, and $\overline{IG}$ is the mean of the IG profile as defined above. (Again, here $t=0$ represents the time point for the start of the profile.) The integral will be calculated by the linear trapezoidal technique. The coefficient of variation (CV%) will also be calculated to describe the IG variation.

IG measurements during meal test will be excluded.

All CGM endpoints will be summarised descriptively by treatment.

Supportive secondary CGM and meal-characteristics efficacy endpoints

The following endpoints will be assessed 26 weeks after randomisation:

Change from baseline in meal characteristics of IG profile (4 hours after start of each meal), measured as:

- Change from baseline in mean IG increment (0-1 hours and 0-2 hours after start of the meal)

The mean IG (meal) increment will be defined as the mean across main meals of the prandial increments, i.e. the difference between IG 1 hours (or 2 hours, respectively) after the meal and IG before the meal

- Change from baseline in mean IG peak after start of meal

The mean IG peak after start of meal will be derived as mean across main meals of the IG maximum values within 4 hours after start of the meal.

- Change from baseline in mean time to the IG peak after meal

The mean time to the IG peak after meal is derived as the mean time to the IG peak across main meals.

These endpoints will also be derived for each main meal separately (breakfast, lunch and main evening meal). IG measurements during meal test will be excluded. The endpoints will be analysed separately, using an analysis of variance model including treatment, region and strata as factors and the corresponding baseline value as covariate.

All CGM endpoints will be summarised descriptively by treatment.

Supportive secondary meal test related efficacy endpoints

The following endpoints will be assessed 26 weeks after randomisation:

- Change from baseline in 30-min PPG and PPG increment
- Change from baseline in 1-hour PPG and PPG increment
- Change from baseline in 2-hour PPG and PPG increment

Laboratory measured plasma glucose from the meal test will be analysed for 30-min, 1-hour and 2-hour PPG separately. The corresponding PPG increments will be derived separately using each PPG measurement minus the pre-prandial PG.

Change from baseline 26 weeks after randomisation in PPG and PPG increment endpoints will be analysed separately using an analysis of variance model including treatment, region and strata as factors and the corresponding baseline value as covariate.

All PPG endpoints will be summarised descriptively by treatment.

Supportive secondary CGM and meal test related efficacy endpoints

Endpoints listed below will be assessed during meal test and based on CGM measurements.

The following endpoints will be assessed 26 weeks after randomisation:

- Change from baseline in $AUC_{IG,0-15min}$
- Change from baseline in $AUC_{IG,0-30min}$
- Change from baseline in $AUC_{IG,0-1h}$
- Change from baseline in $AUC_{IG,0-2h}$

- Change from baseline in $AUC_{IG,0-4h}$
- Change from baseline in time to the IG peak after start of meal
- Change from baseline in IG peak after start of meal

$AUC_{IG,0-15 \, min}$, $AUC_{IG,0-30 \, min}$, $AUC_{IG,0-1h}$, $AUC_{IG,0-2h}$, and $AUC_{IG,0-4h}$ will be calculated as the area under the IG curve using the trapezoidal method and weighted by duration. The endpoint will also be calculated as increment where an average of the IG concentrations immediately before the meal is subtracted from the weighted AUC. Each endpoint will be analysed using an analysis of variance model including treatment, region and strata as factors and the corresponding baseline value as covariate.

IG peak and time to IG peak 26 weeks after randomisation will be compared separately between treatments using an analysis of variance model including treatment, region and strata as factors and with the corresponding baseline value as covariate.

All CGM endpoints will be summarised descriptively by treatment.

2.4.1.2 Safety endpoints

All safety endpoints will be compared using the on treatment observation period. In terms of adverse events, as a minimum, serious adverse events will be tabulated separately also using the in trial observation period.

All events in the in trial observation period will be listed with information about whether it appeared in the on treatment observation period or not.

Classification of Hypoglycaemia:

<u>Treatment emergent:</u> hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of treatment with investigational medicinal product (IMP) after randomisation, and no later than 1 day after the last day on IMP.

<u>Nocturnal hypoglycaemic episodes:</u> are episodes occurring between 23:00 and 07.00 both inclusive.

Hypoglycaemic episodes are classified according to ISPAD's definition of severe hypoglycaemia[4], as well as Novo Nordisk classification of hypoglycaemia (see Figure 2–1) and the ADA classification of hypoglycaemia[5] (see Figure 2–2).

Novo Nordisk classification of hypoglycaemia in paediatrics

In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L (56 mg/dL)[6]. Therefore, Novo Nordisk has included hypoglycaemia with PG levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see Figure 2–1) in addition to the ADA classification:

- Severe hypoglycaemia according to the ISPAD classification[4]: Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value < 3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by PG value < 3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ISPAD classification[4] or BG confirmed by a PG value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- BG confirmed hypoglycaemia: An episode that is BG confirmed by a PG value < 3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ISPAD classification[4] or BG confirmed by a PG value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.
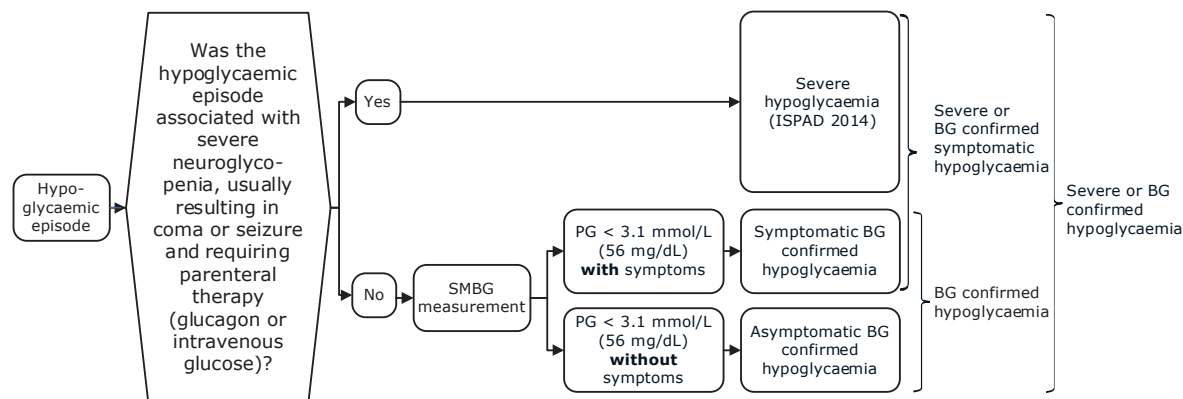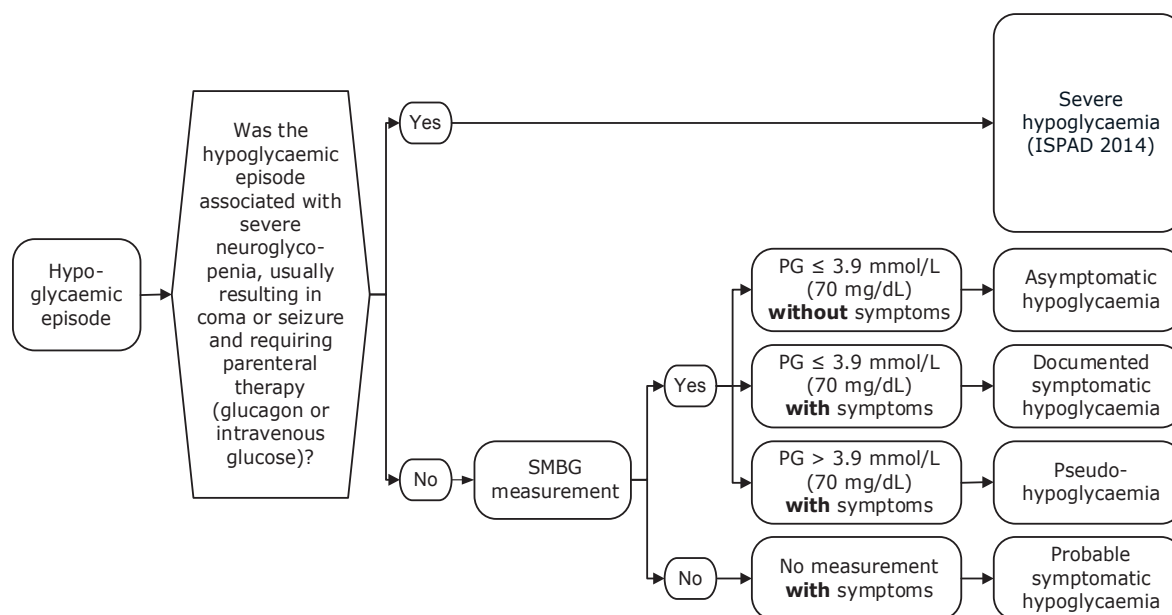

Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 2–1 Novo Nordisk classification of hypoglycaemia in paediatrics

ADA[5]/ISPAD classification of hypoglycaemia in paediatrics

- Severe hypoglycaemia according to the ISPAD classification[4]: Was the hypoglycaemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)?
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured PG concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a PG determination but that was presumably caused by a PG concentration ≤ 3.9 mmol/L (70 mg/dL).

Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 2–2   ADA/ISPAD classification of hypoglycaemia in paediatrics

The following safety endpoints will be assessed:
- Number of treatment emergent hypoglycaemic episodes
    - According to ADA/ISPAD classification
    - According to Novo Nordisk/ISPAD classification

- Number of treatment emergent hypoglycaemic episodes subdivided into daytime and nocturnal (23:00-7:00, both included)
    - According to ADA/ISPAD classification
    - According to Novo Nordisk/ISPAD classification

- Number of treatment emergent meal related (from start of meal until 1, 2, and 4 hours after start of meal and from 1 [exclusive] to 2 hours [inclusive], 2 [exclusive] to 3 hours [inclusive], 3 [exclusive] to 4 hours [inclusive], and from 2 hours [exclusive] to 4 hours [inclusive] after start of meal, respectively) hypoglycaemic episodes
    - According to ADA/ISPAD classification
    - According to Novo Nordisk/ISPAD classification

Data on treatment emergent hypoglycaemic episodes are presented in terms of the number of Subjects with at least one event (N), the percentage of Subjects with at least one event (%), the number of events (E) and the event rate per 100 years of exposure (R). Separate summaries are made by severity (the ISPAD criterion for severe hypoglycaemia[4]) considering all episodes, nocturnal and daytime episodes using Novo Nordisk and ADA classified episodes. Episodes will also be summarised overall and by category in relation to time since start of meal, as occurring within the following time intervals:
- During first 1, 2, and 4 hours after start of meal
- Between 1 (exclusive) to 2 hours (inclusive) after start of meal
- Between 2 (exclusive) to 3 hours (inclusive) after start of meal
- Between 3 (exclusive) to 4 hours (inclusive) after start of meal
- Between 2 hours (exclusive) to 4 hours (inclusive) after start of meal

Non-treatment emergent hypoglycaemic episodes will be listed.

The number of treatment emergent severe or BG confirmed hypoglycaemic episodes (all, daytime, nocturnal) will be analysed using a negative binomial regression model with a log -link function and the logarithm of the time period for which a hypoglycaemic epi sode is considered treatment emergent as offset. The model will include treatment, region and strata as factors, and will be based on the FAS. To the extent where data allow, separate analyses will be performed for severe episodes (all).

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- Number of treatment emergent adverse events (AEs)

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented based on system organ class and preferred terms.

A Treatment Emergent Adverse Event (TEAE) is defined as an event that has an onset date on or after the first day of exposure to randomised treatment, and no later than 7 days after the last day of randomised treatment.

TEAEs are summarised descriptively, whereas AE's not defined as treatment emergent are presented in listings, including AEs reported in the 30-day follow-up period. The summaries of TEAEs are made displaying the number of Subjects with at least one event, the percentage of Subjects with at least one event, the number of events and the event rate per 100 Subjects years of exposure. These summaries are done by seriousness, severity, relation to insulin treatment, relation to device, withdrawal due to AEs and outcome.

Furthermore summary tables based on system organ class and preferred term are made for
- All TEAEs
- Serious TEAEs
- Possibly or probably related TEAEs
- Severe TEAEs
- TEAEs with preferred term that are experienced by at least 5% of the Subjects in any treatment arm or by at least 5% of all Subjects

For AEs where additional information is recorded, this will be listed.

AEs occurring during the run-in period are considered non treatment emergent and will be summarised separately.

- Number of treatment emergent injection site reactions

Injection site reactions occurring during the trial, related to either basal and/or bolus insulin will be summarised and listed. No formal statistical analysis will be made.

- Change from baseline in clinical evaluations
  - Physical examination (head, ears, eyes, nose, throat, neck, respiratory system, cardiovascular system, gastrointestinal system incl. mouth, musculoskeletal system, central and peripheral nervous system, skin, Tanner stage)
    The physical examination parameters, and their change from baseline, will be summarised descriptively in shift tables. All findings will be listed.
  - Vital signs (blood pressure, pulse)

Vital signs include diastolic blood pressure, systolic blood pressure and pulse. The measurements and their change from baseline will be summarised descriptively.

- Change from baseline in body weight, height, body mass index (BMI) and SD-score of body weight and BMI (z-score)
  SD-scores are defined to be able to normalise the body weight in the various age groups. To estimate the growth of children, standardised weight is calculated for each year of age and for each sex. Thus, a child with a weight equal to the mean value for its age and sex has an SD score of 0, while a child with a weight 2 SDs above the mean value for its age and sex has an SD score of +2. The SD scores are derived from the age and sex of the Subjects and the body weight together with growth curves defined for a reference population. SD scores for BMI will be determined in a similar way as SD scores for weight by use of a suitable reference population based on age and sex. For all countries except Japan and India the reference values for the US will be used. The SD scores for Japanese Subjects will be based on country specific references whereas SD scores for Indian Subjects below 5 years of age will be based on World Health Organization (WHO) references and otherwise country specific references.
  The measurements and their change from baseline will be summarised descriptively. In addition, the endpoints will be analysed separately using a statistical model using multiple imputation similar to 1) including treatment, region and age group as factors and the corresponding baseline measurement as covariate. The analyses will be based on the SAS and the on treatment observation period.

- Change from baseline in laboratory assessments
    - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, and leucocytes)
    - Biochemistry (creatinine, , alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), sodium, potassium, albumin, and total bilirubin)
    - Lipid profile (total cholesterol, high density lipoprotein (HDL), low density lipoproteins (LDL))

Individual laboratory values will be compared to their relevant reference range (when existing) and flagged as being below or above the range. The measurements and their change from baseline will be summarised descriptively. Change from baseline will be summarised descriptively using both the actual values and the low/normal/high categorisation in shift tables.

Lipid endpoints (LDL, HDL, and total cholesterol) will be log-transformed and analysed separately using a statistical model using multiple imputation similar to 1) including treatment, region and strata as factors and the corresponding log-transformed baseline measurement as covariate. The

analyses will be based the FAS and the in trial observation period and repeated using the on treatment observation period. The treatment difference and associated 95% confidence intervals will be back-transformed providing results in terms of ratios of geometric means on the original scale. NovoRapid® will be used as reference.

- Change from baseline in anti-insulin aspart (specific and cross-reacting with human insulin) antibody development

The measurements and their change from baseline will be summarised descriptively. The correlation to other relevant variables such as insulin dose and HbA_{1c} are illustrated using graphs.

3   Changes to the statistical analyses planned in the protocol

Minor editorial corrections have been made throughout the document.

General considerations

As a consequence of the small number of Subjects below 3 years of age included in the trial, the text "Selected tables and figures will also be presented by strata (age)." is changed to Selected tables and figures will also be presented by age group, where age group refers to the following categorisation of age: $1 \leq$ age < 6 years, $6 \leq$ age < 12 years and $12 \leq$ age < 18 years.

Statistical analysis

In the sensitivity analysis 2) for change from baseline in HbA_{1c}, It has been clarified that baseline HbA1c is included in the model as a covariate.

The descriptions of sensitivity analyses have been revised to clarify that all Subjects without a measurement at week 26 (not subjects withdrawing from trial in general) should have their values imputed. The new description is aligned with the primary analysis.

In order to emphasize the difference between sensitivity analyses 3)-b and 3)-c the wording have been rearranged.

The tipping point analyses have been described in more detail and tipping point analysis 5) has been repeated for the in trial observation period in the additional sensitivity analyses 3)-d.

In the statistical analysis for percentage of Subjects reaching HbA_{1c} target, it has been clarified that Subjects without an HbA_{1c} measurement at week 26 will be handled as non-responders for analyses on both the in trial and on treatment observation periods.

In the statistical analysis for percentage of Subjects reaching HbA_{1c} target without severe hypoglycaemia, it has been clarified that Subjects without an HbA_{1c} measurement at week 26 will be handled as non-responders for analyses on both the in trial and on treatment observation periods.

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Fluctuation in 8-point

In the analysis of fluctuation of the 8-point self-measured plasma glucose (SMPG) profile "Change from baseline" has been removed. This is done because data are logarithmically transformed and change from baseline potentially include negative values.

CGM endpoints

The percentage of time spent with IG >13.9 mmol/L [250 mg/dL] and incidence of episodes with IG >13.9 mmol/L [250 mg/dL] has been added. Likewise mean, variation, and CV% has been added to further evaluate the effect and safety of fast-acting insulin aspart.

In order to align with previous trials the endpoints IG peak and time to IG peak will be analysed using an analysis of variance model including treatment, region and strata as factors and the corresponding baseline value as covariate. Consequently, the sentence "An additive model will be used to estimate the treatment means and treatment differences with a 95% confidence interval." has been deleted.

AEs where additional information is recorded

For AEs where additional information is recorded, this will only be listed.

Hypoglycaemic episodes

The endpoints treatment-emergent hypoglycaemic episodes occurring within 1 (exclusive) to 2 hours (inclusive), 2 (exclusive) to 3 hours (inclusive), 3 (exclusive) to 4 hours (inclusive) after start of the meal has been added to further investigate the safety of fast-acting insulin aspart.

Change from baseline in body weight, height, body mass index (BMI) and SD-score of body weight and BMI (z-score)

In order to align with previous trials, analyses of change from baseline in body weight, height, body mass index (BMI) and SD-score of body weight and BMI (z-score) will be based on the safety analysis set and the on treatment observation period.

It has been specified that for all countries except Japan and India the reference values for the US will be used to calculate SD-scores for weight and BMI. The SD scores for Japanese Subjects will be based on country specific references whereas SD scores for Indian Subjects below 5 years of age will be based on WHO references and otherwise country specific references.

Lipid endpoints

In order to align with previous trials, the analyses of lipid endpoints will be based on FAS and the in trial observation period and repeated using the on treatment observation period.

4 References

1. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. Stat Med. 1999;18(15):1905-42.

2. Koch GG. Comments on 'Current issues in non-inferiority trials' by Thomas R. Fleming, Statistics in Medicine, DOI: 10.1002/sim.2855. Stat Med. 2008;27(3):333-42.

3. Rewers MJ, Pillay K, de Beaufort C, Craig ME, Hanas R, Acerini CL, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and monitoring of glycemic control in children and adolescents with diabetes. Pediatr Diabetes. 2014;15 Suppl 20:102-14.

4. International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2014 Compendium. Pediatr Diabetes. 2014;15 Suppl. 20:1-290.

5. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95.

6. Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. J Clin Invest. 1987;79(3):777-81.