

Cover Page for Statistical Analysis Plan

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16.1.9 Documentation of statistical methods

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Statistical Analysis Plan

Trial ID: NN1218-3854

Efficacy and Safety of Continuous Subcutaneous Insulin Infusion of Faster-acting Insulin Aspart compared to NovoRapid[®] in Adults with Type 1 Diabetes

Onset[®] 5

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

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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
CSII	continuous subcutaneous insulin infusion
CTR	clinical trial report
CV	coefficient of variation
ECG	electrocardiogram
FAS	full analysis set
FPG	fasting plasma glucose
HDL	high density lipoprotein
ICH	international council on harmonisation
IG	interstitial glucose
IMP	investigational medicinal product
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
T1DM	type 1 diabetes mellitus
TEAE	treatment emergent adverse event

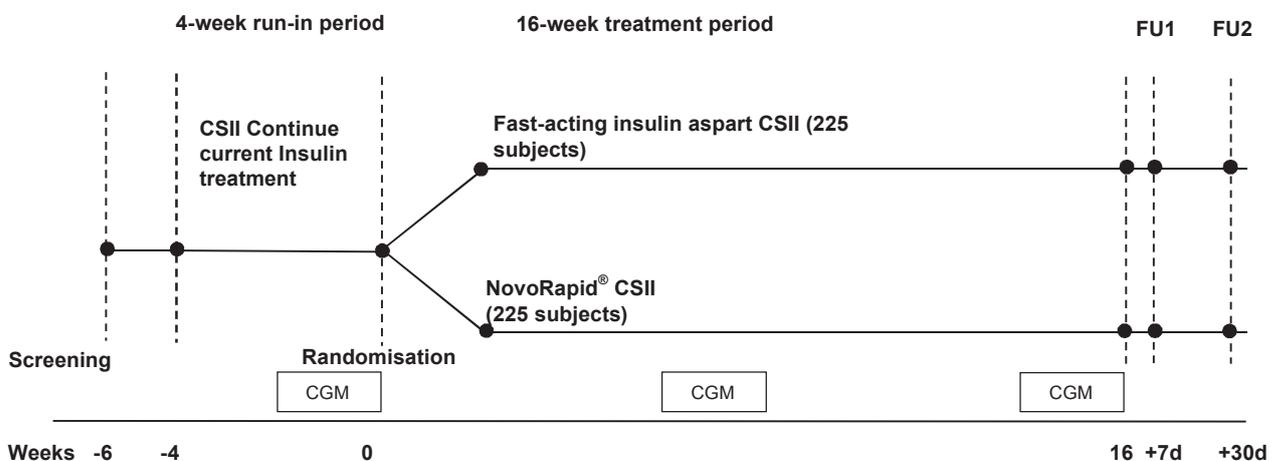
1 Introduction

1.1 Trial information

This is a double-blind, randomised, multicentre, multinational, active controlled, treat-to-target, parallel group trial with a 4-week run-in and a 16-week treatment period comparing the effect and safety of continuous subcutaneous insulin infusion (CSII) of fast-acting insulin aspart versus NovoRapid® in adult subjects with type 1 diabetes mellitus (T1DM). Subjects entering the trial will stay on their own insulin pump.

The total duration of the trial is approximately 26 weeks split into the following periods (see [Figure 1-1](#)):

- ≤ 2-week for screening period
- A 4-week run-in period primarily for reinforcement of subject training in trial procedures, diabetes education and collecting baseline assessments
- A 16-week double-blinded treatment period
- A 7-day and 30-day follow-up period



Note: Prior to randomisation and after end of treatment subjects are on marketed product.

Baseline is defined as randomisation.

Figure 1-1 Trial design

Up to 50% of the eligible subjects will be allowed to wear their own real-time continuous glucose monitoring (CGM) device during the entire course of the trial. The remaining enrolled Subjects will not be allowed to wear a CGM device except for three pre-specified periods. During these periods a

blinded CGM device will be handed out to all subjects by the Investigator, including subjects wearing their own CGM. Randomisation is stratified according to the use of own real-time CGM.

The primary objective is to confirm the effect of continuous subcutaneous insulin infusion (CSII) treatment with fast-acting insulin aspart in terms of glycaemic control by comparing it to CSII treatment with NovoRapid[®], in adults with Type 1 Diabetes Mellitus (T1DM), using a non-inferiority approach.

The secondary objectives are to confirm superiority of CSII treatment with fast-acting insulin aspart compared to CSII treatment with NovoRapid[®] in adults with T1DM, in terms of:

- Postprandial glucose regulation (meal test)
- Overall glycaemic control (HbA_{1c})
- Postprandial glucose excursions (1,5-anhydroglucitol)
- Time spent in low interstitial glucose (CGM)

To compare the effect and safety of CSII treatment with fast-acting insulin aspart vs. CSII treatment with NovoRapid[®] in adults with T1DM.

For further details see the trial protocol.

1.2 Scope of the statistical analysis plan

This statistical analysis plan (SAP) is based on the statistical considerations of NN1218-3854 as planned in the trial protocol *Efficacy and Safety of Continuous Subcutaneous Insulin Infusion of Faster-acting Insulin Aspart compared to NovoRapid[®] in Adults with Type 1 Diabetes*, version 4.0 (dated 04 February 2016). It contains a more detailed description for deriving and calculation of endpoints. Furthermore, it details changes to the statistical considerations presented in the protocol.

The changes to the statistical considerations proposed in this SAP and the reasons for the changes 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 randomisation (Visit 6). In case a measurement is not available at randomisation, the most recent measurement prior to randomisation 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 discontinuation of randomised treatment.
- **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 randomised NovoRapid[®]/fast-acting insulin aspart. The on-treatment observation period includes data collected up to and including 7 days after discontinuation of randomised treatment.

All 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 and analysed using the FAS.

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 interval (CI) 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 6) will only be summarised descriptively.

Subjects that prematurely discontinue from treatment or withdraw from trial will attend end of treatment visits called visit 22A and 22B. Data collected at these visits 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. The estimands will be defined in the next section.

Testing strategy and estimands

The primary objective, to confirm the effect of CSII treatment with fast-acting insulin aspart in terms of glycaemic control by comparing it to CSII treatment with NovoRapid[®], in adults with T1DM, will be assessed by the change from baseline in HbA_{1c} using a non-inferiority approach.

More specifically the upper limit of the 95% confidence interval for the difference between fast-acting insulin aspart and NovoRapid[®] 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 effect demonstrated.

The trial also aims to compare CSII treatment with fast-acting insulin aspart to NovoRapid[®] for a number of confirmatory secondary endpoints. The family-wise type I error rate will be controlled in the strong sense using a hierarchical (fixed sequence) testing procedure for the primary estimand. 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 a null hypothesis only will be considered for analyses where all previous null-hypotheses have been rejected in favour of fast-acting insulin aspart.

The steps in the hierarchical testing procedure are as follows:

Step 1 (Primary analysis): HbA_{1c} non-inferiority of fast-acting insulin aspart versus NovoRapid[®]

Step 2: 1-hour postprandial glucose (PPG) increment (meal test) superiority of fast-acting insulin aspart versus NovoRapid[®]

Step 3: HbA_{1c} superiority of fast-acting insulin aspart versus NovoRapid[®]

Step 4: 1,5-Anhydroglucitol superiority of fast-acting insulin aspart versus NovoRapid[®]

Step 5: time spent in low interstitial glucose (IG) (≤ 3.9 mmol/L [70 mg/dL]) superiority of fast-acting insulin aspart versus NovoRapid[®]

Primary estimand (de facto)

The primary estimand is defined as the treatment difference between Subjects randomised to CSII treatment with fast-acting insulin aspart and CSII treatment with NovoRapid[®] in adults with T1DM assessed by change from baseline in HbA_{1c} 16 weeks after randomisation for all randomised Subjects regardless of treatment discontinuation or use of ancillary therapies. This estimand is a de facto estimand addressing effectiveness.

The primary estimand assesses the expected benefit that a Subject can achieve if prescribed to CSII treatment with fast-acting insulin aspart as compared to CSII treatment with NovoRapid[®] in adults with T1DM. By not putting any restrictions on the randomised treatment adherence, this estimand aims at a difference as close as possible to the one that can be expected in real-world clinical practice, provided that the treatment adherence and use of ancillary therapies reflects clinical practice. Thereby the primary estimand provides a clinically relevant treatment difference for clinicians concerning the glycaemic effect of CSII treatment with fast-acting insulin aspart as compared to CSII treatment with NovoRapid[®] in the day to day life in adults with T1DM.

Secondary estimand (de jure)

Unlike the primary estimand, the secondary estimand is defined as the treatment difference in change from baseline in HbA_{1c} 16 weeks after randomisation between CSII treatment with fast-

acting insulin aspart and CSII treatment with NovoRapid[®] in adult Subjects with T1DM if Subjects continue on-treatment until 16 weeks. This estimand is a de jure estimand, addressing efficacy.

As an alternative to the primary estimand, this estimand provides a more hypothetical treatment difference, but may also be the most sensitive for a non-inferiority comparison, since the marketed product that Subjects discontinuing from randomised treatment are switched to may equalize the treatment effect.

The two estimands will be repeated for the endpoints:

- 1-hour PPG increment (meal test)
- 1,5-Anhydroglucitol
- time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) (CGM)

2.1 Sample size calculation

The primary objective of the trial is to confirm the effect of CSII treatment with fast-acting insulin aspart in terms of glycaemic control by comparing it to CSII treatment with NovoRapid[®] in adults with T1DM, using a non-inferiority approach. The non-inferiority margin of 0.4% (absolute) was chosen as described in section 5.2.1 of the protocol. The statistical evaluation will be done as described in section [2.3](#).

The trial also aims to confirm superiority of CSII treatment with fast-acting insulin aspart for a number of secondary confirmatory endpoints using the hierarchical testing procedure as described in section [2](#) (General considerations).

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

In previous exploratory trials where CSII treatment with faster aspart has been investigated, the completion rates have been high. Therefore it is expected that treatment discontinuation might be as low as 4% where trial discontinuation constitutes half of these.

The power for the non-inferiority step is based on a t-statistic under the assumption of a one-sided test of size 2.5 %. A mean treatment difference of -0.1% for the comparison between fast-acting insulin aspart and NovoRapid[®] is expected. As trials in this population where Subjects are using insulin pumps and where data from treatment withdrawn subjects is retrieved are limited, a conservative estimate of the standard deviation (SD) in change from baseline in HbA_{1c} of 0.8% was chosen.

For determination of power in the second step in the hierarchical testing, where change from baseline in 1-hour PPG increment 16 weeks after randomisation is compared between fast-acting insulin aspart and NovoRapid® a t-statistic with a two-sided test of size 5.0% is used, where the treatment difference is expected to be at least 0.9 mmol/L [16 mg/dL]. The SD=3.4 mmol/L [62 mg/dL] in change from baseline in 1-hour PPG increments 16 weeks after randomisation based on laboratory analysed plasma glucose (PG) in a standardised meal test is considered reasonable, based on prior trials.

The power calculation is done using proc power in SAS Version 9.4. Please refer to [Table 2-1](#) for assumption of the sample size calculation.

Table 2-1 Specifications assumed for sample size calculation

	Statistical test	Significance Level	Analysis Population	Non-inferiority Margin	SD	Mean Difference	Randomisation Scheme
Step 1	2-group t-test	One-sided 2.5%	FAS	0.4% (absolute)	0.8	-0.1	1:1
Step 2	2-group t-test	Two-sided 5.0%	FAS	NA	3.4	0.9	1:1

In [Table 2-2](#), the sensitivity of the sample size to the power in Step 1 and Step 2 is shown for three different sample sizes of FAS. Three different choices of the mean difference are used to calculate the power in Step 2.

Table 2-2 Sensitivity of sample size to power in step 1 and step 2

N Total FAS	N per arm FAS	Step 1			Step 2			
		Mean Diff	SD	Step 1 Power (%)	Null Diff	Mean Diff	SD	Step 2 Power (%)
300	150	-0.1	0.80	>99.9	0	0.8	3.4	52.8
		-0.1	0.80	>99.9	0	0.9	3.4	62.7
		-0.1	0.80	>99.9	0	1.0	3.4	71.9
450	225	-0.1	0.80	>99.9	0	0.8	3.4	70.2
		-0.1	0.80	>99.9	0	0.9	3.4	80.0
		-0.1	0.80	>99.9	0	1.0	3.4	87.6
600	300	-0.1	0.80	>99.9	0	0.8	3.4	82.0
		-0.1	0.80	>99.9	0	0.9	3.4	89.9
		-0.1	0.80	>99.9	0	1.0	3.4	94.9

In conclusion, a sample size of 450 Subjects in the FAS (225 Subjects per group) will ensure a power of >99.9% to conclude HbA_{1c} non-inferiority in the first step. This sample size gives 80.0% marginal power to conclude 1 hour PPG increment superiority in the second step.

Assuming a screening failure rate of 24% and run-in failure rate of 11%, 666 Subjects should be screened for inclusion in the trial.

2.2 Definition of analysis sets

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

- Full Analysis Set (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, excluding Subjects who:
 - Have violated any inclusion criteria
 - Have fulfilled any exclusion criteriaSubjects in the PP set will contribute to the evaluation “as treated”
- Safety Analysis Set includes all Subjects receiving at least one dose of the IMP or its comparator. Subjects in the safety analysis set will contribute to the evaluation “as treated”.

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

Before data are released for statistical review, a blinded review of all data will take place to identify serious non-adherence to the protocol 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 This will be performed using a fake randomisation.

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 (CTR).

2.3 Primary endpoint

The primary endpoint is the change from baseline in HbA_{1c} 16 weeks after randomisation.

Primary analysis

1) The primary estimand will be addressed by the below primary analysis based on all Subjects included in the 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, missing data will still occur. The primary analysis will be implemented as a statistical model using multiple imputations where the Subjects without any available HbA_{1c} measurements at scheduled visits will have their HbA_{1c} value 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, but 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 strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®] (insulin glulisine), Humalog[®] (insulin lispro) and region as factors, and baseline HbA_{1c} as a covariate is fitted to the change in HbA_{1c} from baseline to week 4 for each treatment group separately. The estimated parameters, and their variances, from these models are used to impute missing values at week 4 for Subjects in each treatment group, based on strata, previous insulin use, region and baseline HbA_{1c}.
- In the third step, for each of the 100 copies of the dataset, missing values at week 8 are imputed in the same way as for week 4. The imputations are based on an analysis of variance model with strata, previous insulin use and region as factors and baseline HbA_{1c} and change from baseline in HbA_{1c} at week 4 as covariates.
- This stepwise procedure is then repeated sequentially for week 12 and 16
- For each of the complete data sets, the change from baseline to week 16 is analysed using an analysis of variance model with treatment, strata, previous insulin use and region as factors, and baseline HbA_{1c} as a covariate.
- The estimates and standard deviations for the 100 data sets are pooled using Rubin's formula:

$$m_{MI} = \frac{1}{100} \sum_{i=1}^{100} m_i ,$$

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

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.

Non-inferiority of fast-acting insulin aspart will be considered confirmed if the upper boundary of the two-sided 95% CI 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 $H_A: D \leq 0.4\%$,

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

Note that as the anticipated number of Subjects discontinuing treatment, but not trial is low, imputations based on such Subjects will not be suitable.

Provided that the hierarchical testing allows, the evaluation of superiority will be based on the same statistical model, as the primary analysis 1). The associated sensitivity analysis that follows will investigate the robustness of non-inferiority and superiority (analysis 3b and 3c) as well.

Sensitivity analyses for the primary analysis addressing the primary estimand

All sensitivity analyses for the primary analysis addressing the primary estimand will use the in-trial observation period.

- 2) First the primary analysis in 1) will be repeated, but excluding all factors except from 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.
- 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. Therefore the statistical models using multiple imputation will be repeated with the following alterations:

- a) Imputations will be done from the treatment arm that the Subject was randomised to and a value of 0.4% (non-inferiority margin) is added to the change from baseline in HbA_{1c} at week 16 for Subjects randomised to fast-acting insulin aspart with an imputed value at week 16.²
- b) Missing values at week 16 will be imputed from the comparator arm (NovoRapid[®]). This will serve as a sensitivity analysis for the superiority analysis. It does not rely on the MAR assumption, but assumes that Subjects on fast-acting insulin aspart with an imputed value at week 16 switch to NovoRapid[®]. The imputation will be done such that the treatment effect diminishes gradually (conditional imputation).
- c) Missing values at week 16 will be imputed from the comparator arm (NovoRapid[®]). This will serve as a supplementary sensitivity analysis for the superiority analysis. It does not rely on the MAR assumption, but assumes that Subjects on fast-acting insulin aspart with missing value at week 16 switch to NovoRapid[®]. The imputation will be done such that the treatment effect diminishes immediately (unconditional imputation).

Analyses addressing the secondary estimand

All analyses addressing the secondary estimand will use the on-treatment observation period.

- 4) The secondary estimand will be analysed using the same statistical model using multiple imputations as the primary analysis in 1) except using the on-treatment observation period.
- 5) A tipping point analysis based on a statistical model using multiple imputation model similar to 1), using the on-treatment 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 are given a penalty. 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 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 16 in the fast-acting insulin aspart group. This is done repeatedly, gradually increasing the penalty until the conclusion from the non-inferiority analysis no longer holds. This will serve as a sensitivity analysis for the non-inferiority analysis and the specific value of the penalty that changes the conclusion will be used to evaluate the robustness of the conclusion of the non-inferiority analysis.

- 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) in the fast-acting insulin aspart group 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.
- 7) The same statistical model using multiple imputations as the 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 might have deviated from the inclusion and exclusion criteria and will serve as sensitivity analysis for the non-inferiority analysis.

2.4 Secondary endpoints

2.4.1 Confirmatory secondary endpoints

If the effect of CSII treatment with fast-acting insulin aspart can be confirmed in the primary analysis, the trial also aims to confirm the superiority of CSII treatment with fast-acting insulin aspart, for a number of secondary confirmatory endpoints.

The steps used in the hierarchical testing procedure are as follows:

Step 1 (Primary analysis): HbA_{1c} non-inferiority of fast-acting insulin aspart versus NovoRapid[®]

Step 2: 1-hour PPG increment (meal test) superiority of fast-acting insulin aspart versus NovoRapid[®]

Step 3: HbA_{1c} superiority of fast-acting insulin aspart versus NovoRapid[®]

Step 4: 1,5-anhydroglucitol superiority of fast-acting insulin aspart versus NovoRapid[®]

Step 5: time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) superiority of fast-acting insulin aspart versus NovoRapid[®]

The primary estimand for the primary endpoint will be repeated for the confirmatory secondary endpoints, change from baseline in 1-hour PPG increment (meal test), change from baseline in 1,5-anhydroglucitol and change from baseline of time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) during CGM 16 weeks after randomisation. The analyses related to these estimands are defined below and will be used for the decisions to continue or not, throughout the hierarchical testing procedure. These analyses will be based on the FAS and use the in-trial observation period.

The secondary analysis 4) will also be repeated for the confirmatory secondary endpoints. The analysis will be based on the FAS and using the on-treatment observation period.

Change from baseline in 1-hour PPG increment 16 weeks after randomisation (meal test) (Step 2)

As the second step of the hierarchical testing procedure, change from baseline in 1-hour PPG increment 16 weeks after randomisation will be tested for superiority of fast-acting insulin aspart compared to Novo Rapid[®].

The 1-hour PPG increment will be analysed based on the laboratory measured values in the meal test, and is derived as the 1-hour PPG measurement minus the pre-prandial PG.

The 1-hour PPG increment endpoint will be analysed using the FAS and the in-trial observation period based on a multiple imputation technique where the change from baseline in 1-hour PPG increment at week 16 for subjects with missing value are imputed based on data from subjects in the NovoRapid[®] arm with non-missing values at week 16. Multiple copies (100 copies) of the full dataset will be generated by imputing missing values based on estimated parameters as follows:

- An analysis of variance model with strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors and baseline 1-hour PPG increment as covariate is fitted to the change from baseline in 1-hour PPG increment at week 16 for the NovoRapid[®] group only. The estimated parameters, and their variances, from this model are used to impute missing values using stochastic simulation at week 16 for subjects in both treatment groups in order to generate 100 complete datasets.
- For each of the complete data sets, the change from baseline to week 16 is analysed using an analysis of variance model with treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors, and baseline 1-hour PPG increment as covariate. The estimates and standard deviations for the 100 data sets are pooled to one estimate and associated standard deviation using Rubin's formula. From this, the pooled estimate and 95% confidence interval for the treatment difference are calculated.

The superiority will be assessed by comparing the upper limit of the 95% CI to 0. If the upper 95% CI is below 0 then superiority will be confirmed.

Change from baseline in HbA_{1c} 16 weeks after randomisation (Step 3)

The third step in the hierarchical testing is to confirm superiority of fast-acting insulin aspart compared to NovoRapid[®] with respect to HbA_{1c} 16 weeks after randomisation.

The confidence interval from the primary analysis 1) will be used to determine superiority. Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference (fast-acting insulin aspart minus NovoRapid[®]) is below 0%.

Change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation (Step 4)

Step 4 in the hierarchical testing procedure is to confirm superiority of change from baseline in 1,5-anhydroglucitol 16 weeks after randomisation with fast-acting insulin aspart compared to NovoRapid[®].

The change from baseline in 1,5-anhydroglucitol will be analysed using a model similar to 1), but with baseline 1,5-anhydroglucitol as a covariate.

Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference (fast-acting insulin aspart minus NovoRapid[®]) is below 0.

Change from baseline of time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) during CGM 16 weeks after randomisation (Step 5)

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 [70 mg/dL] from the first valid sensor value divided by the actual duration of the profile. To report the endpoint in minutes per 24 hours the ratio is multiplied by 1440.

Step 5 of the hierarchical testing procedure is to confirm superiority of change from baseline of time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) during CGM 16 weeks after randomisation with fast-acting insulin aspart compared to NovoRapid[®].

The change from baseline of time spent in low IG (≤ 3.9 mmol/L [70 mg/dL]) will be analysed with a model similar to 1), but with the corresponding baseline value as covariate.

2.4.2 Supportive secondary endpoints

2.4.2.1 Efficacy endpoints

All endpoints except insulin dose and insulin pump parameters 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 and insulin pump parameters will be presented using the safety analysis set and will therefore only use the on-treatment observation period.

Change from baseline in FPG to 16 weeks after randomisation

Change from baseline in FPG 16 weeks after randomisation will be analysed on all planned post-baseline measurements until or at 16 weeks with a model similar to 1) except with baseline FPG as covariate.

Percentage of Subjects reaching HbA_{1c} target 16 weeks after randomisation:

HbA_{1c} < 7.0%

A dichotomous (responder/non-responder) endpoint will be defined based on whether a Subject has met the HbA_{1c} target (HbA_{1c} <7.0% (53 mmol/mol)) 16 weeks after randomisation.

This responder endpoint will be analysed based on a logistic regression model using treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors, and baseline HbA_{1c} as covariate. In analysis of the in-trial observation period Subjects without an HbA_{1c} measurement at week 16 will be treated as non-responders. In the on-treatment observation period analysis Subjects who discontinue fast-acting insulin aspart/NovoRapid[®], withdraw from trial, and/or have no HbA_{1c} measurement at week 16 are included as non-responders.

HbA_{1c} <7.0 % without severe hypoglycaemia

A dichotomous (responder/non-responder) endpoint will be defined based on whether a Subject has met the HbA_{1c} target (HbA_{1c} <7.0% (53 mmol/mol)) 16 weeks after randomisation without treatment emergent severe hypoglycaemic episodes.

This responder endpoint will be analysed based on a logistic regression model using treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors and baseline HbA_{1c} as covariate. In the analysis of the in-trial observation period Subjects without an HbA_{1c} measurement at week 16 will be treated as non-responders. In the on-treatment observation period analysis Subjects who discontinue fast-acting insulin aspart/NovoRapid[®], withdraw from trial, or have no HbA_{1c} measurement at week 16 are included as non-responders.

Change from baseline in 30- min, 1- hour, 2- hour, 3- hour and 4- hour PPG and in 30- min, 2- hour, 3- hour and 4- hour PPG increment after 16 weeks after randomisation (meal test)

Laboratory measured PG from the meal test will be analysed for 30 minutes, 1-hour, 2-hours, 3-hours and 4-hours PPG separately. The corresponding PPG increments will be derived separately using each PPG measurement minus the pre-prandial PG.

Change from baseline in PPG and PPG increment 16 weeks after randomisation will be analysed separately using a model similar to the model used in hierarchical testing procedure step 2 for 1 -

hour PPG increment 16 weeks after randomisation (meal test) except with the corresponding baseline value as covariate.

Change from baseline in endpoints derived from the 7-7-9 point self-measured plasma glucose (SMPG) profile 16 weeks after randomisation

PPG and PPG increments based on the 7-7-9-point SMPG profiles will be derived separately for PG measurements made 1 hour after the meal. In the following section this distinction will be considered implicit and without further explanation.

Pre-prandial PG and PPG will be recorded by the Subjects as part of the 7-7-9 point SMPG profile prior to three defined visits. Individual mean mealtime PPG (post-breakfast, post-lunch, post-main evening meal) will be derived from the three profiles. Overall mean PPG will be derived from the individual derived mealtime PPG values.

PPG increment for each meal (breakfast, lunch, main evening meal) will be derived from the 7-7-9 point SMPG 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 1 hour PPG increments over all meals will be derived as the mean of all corresponding mean meal increments.

- Change from baseline in mean of the 7-7-9-point SMPG profile

The mean of the 7-7-9-point SMPG profile is defined as the area under the curve profile divided by the measurement time, and is calculated using the linear trapezoidal technique.

Change from baseline in the mean of the 7-7-9-point SMPG profile 16 weeks after randomisation will be analysed using a model similar to 1) except with the corresponding baseline value as covariate.

- Change from baseline in mean pre-prandial PG, PPG and PPG increment over all three meals

Change from baseline in mean pre-prandial PG, PPG and PPG increment 16 weeks after randomisation 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, PPG increment and pre-prandial PG (pre-breakfast, pre-lunch, pre-main evening meal)

Change from baseline in PPG, PPG increment and pre-prandial PG endpoints 16 weeks after randomisation for the individual meals will be analysed separately using a model similar to 1) except with the corresponding baseline value as covariate.

- Fluctuation in 7-7-9-point profile

The fluctuation in the 7-7-9-point profile is defined as:

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

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 7-7-9-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 value 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 in nocturnal SMPG measurements

Change from baseline in nocturnal SMPG measurements will be assessed by considering the differences between PG values available at bedtime, at 4 AM and the before breakfast value the following day: (4 AM PG value minus at bedtime PG value), (before breakfast PG value minus at bedtime PG value) and (before breakfast PG value minus 4 AM PG value).

Change from baseline in nocturnal SMPG measurements 16 weeks after randomisation will be analysed in the same way as mean of the profile is analysed, except with the corresponding baseline values as covariate. .

Percentage of subjects reaching PPG target (based on mean of PPG measurements in SMPG) 16 weeks after randomisation:

- Overall PPG (1 hour) ≤ 7.8 mmol/L [140 mg/dL]

A dichotomous (responder / non-responder) endpoint will be defined based on whether a Subject has reached an overall mean 1 hour PPG ≤ 7.8 mmol/L [140 mg/dL] 16 weeks after randomisation, where PPG is derived from the 7-7-9 point SMPG profile.

This responder endpoint will be analysed based on a logistic regression model using treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors, and baseline overall 1-hour mean PPG as covariate. In analysis of the in-trial observation period Subjects without an overall mean 1 hour PPG at week 16 will be treated as non-responder. In the on-treatment observation period analysis Subjects who discontinue fast-acting insulin aspart/NovoRapid[®], withdraw from trial, or have no 1-hour mean PPG measurement at week 16 will be included as non-responders.

- Overall PPG (1-hour) ≤ 7.8 mmol/L [140 mg/dL] without severe hypoglycaemia

A dichotomous (responder / non-responder) endpoint will be defined based on whether a Subject has reached an overall 1-hour PPG ≤ 7.8 mmol/L [140 mg/dL] 16 weeks after randomisation without any treatment emergent severe hypoglycaemic episodes.

This responder endpoint will be analysed based on a logistic regression model using treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]) and region as factors, and baseline mean 1-hour PPG as covariate. In analysis of the in-trial observation period Subjects without an overall mean 1 hour PPG at week 16 will be treated as non-responders. In the on-treatment observation period analysis Subjects who discontinue fast-acting insulin aspart/NovoRapid[®], withdraw from trial, or have no 1-hour PPG measurement at week 16 will be included as non-responders.

Change from baseline in lipids-lipoproteins profile 16 weeks after randomisation

Change from baseline in lipid endpoints (low density lipoprotein (LDL), high density lipoprotein (HDL), and total cholesterol) will be analysed separately using a model similar to 1). The lipid endpoints will be log-transformed before they are analysed including the corresponding baseline measurement which is included in the analysis as a covariate. 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.

Insulin dose (Units/day and Units/kg/day; total basal, total bolus, total daily insulin dose and individual meal insulin dose)

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). The total daily basal dose will be derived from the total daily dose and bolus doses including correction doses. Insulin doses will be summarised using the on-treatment observation period and using the safety analysis set.

Insulin delivery pump parameters

The insulin pump parameters including insulin carbohydrate ratio, glucose sensitivity factor and active insulin time will be summarised descriptively by treatment week. They will be summarised using the on-treatment observation period and using the safety analysis set.

Supportive secondary CGM-related endpoints

All following endpoints will be assessed 16 weeks after randomisation:

- Percentage of time spent with IG $\leq 2.5, 3.0, 3.5, 3.9$ mmol/L [45, 54, 63, 70 mg/dL] and IG $> 10.0, 12.0, 13.9$ mmol/L [180, 216, 250 mg/dL]
- Incidence of episodes with IG $\leq 2.5, 3.0, 3.5, 3.9$ mmol/L [45, 54, 63, 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 4.0-10.0mmol/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.

- Change from baseline in the area under the curve (AUC)_(3.9-IG) for IG \leq 3.9 mmol/L [70 mg/dL]

The AUC_(3.9-IG) is defined for each Subject at each CGM period as the AUC_(3.9-IG) when IG is below or equal to 3.9 mmol/L [70 mg/dL] from the first valid sensor value divided by the actual duration of the profile. The AUC will be calculated by the linear trapezoidal technique. If the profile has missing sensor values, then the AUC should be calculated for each profile part consisting of non-missing sensor values. The endpoint is then calculated as the sum of the AUCs for all profile parts divided by the sum of the duration of the profile parts for which AUC is calculated.

IG measurements during meal test will be excluded.

All CGM endpoints will be summarised descriptively by treatment.

Supportive secondary CGM and meal-characteristics endpoints

The following endpoints will be assessed 16 weeks after randomisation:

- Change from baseline in mean IG increment (0-30 min, 0-1 hour 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 30 min (1 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. All endpoints will be analysed separately, using a model similar to 1) except with the corresponding baseline value as covariate.

All CGM endpoints will be summarised descriptively by treatment.

Supportive secondary efficacy endpoints related to CGM and meal test

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

The following endpoints will be assessed 16 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 AUC IG using the linear trapezoidal technique and weighted by duration. From these endpoints the increments will also be calculated where an average of the IG concentrations immediately before the meal is subtracted from the weighted AUC. Each endpoint and derived increment will be analysed using an analysis of variance model including treatment, previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), region and strata as factors, and the corresponding baseline value as covariate.

The IG peak after start of meal will be derived as the IG maximum values within 4 hours after start of the meal-test meal.

Change from baseline in IG peak and time to IG peak 16 weeks after randomisation will be compared separately between treatments using an analysis of variance model including treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors, and the corresponding baseline value as covariate.

2.4.2.2 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.

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 seven days after the last day of randomised treatment.

TEAEs are summarised descriptively, whereas AEs 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 patient years of exposure. These summaries are done by seriousness, severity, relation to insulin treatment, relation to technical complaint, premature treatment discontinuation due to AEs, AEs leading to withdrawal from trial and outcome.

Furthermore, summary tables based on system organ class and preferred terms 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 infusion site reactions

Infusion site reactions occurring during the trial will be summarised using the on-treatment observation periods, and listed.

Classification of Hypoglycaemia

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of IMP administration after randomisation and no later than one day after the last day on IMP.

Nocturnal hypoglycaemic episodes: are episodes occurring between 00:01 and 05.59 both inclusive.

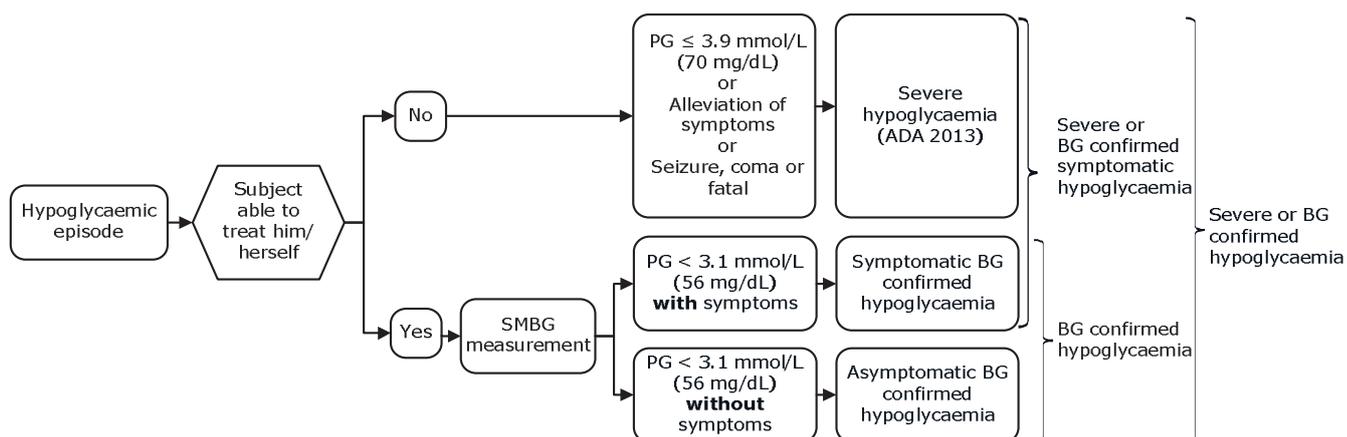
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see [Figure 2-1](#)) and the American Diabetes Association (ADA) classification of hypoglycaemia (see [Figure 2-2](#)).

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L [56 mg/dL].³ 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 ADA classification⁴
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification⁴ or BG confirmed by a PG value <3.1 mmol/L [56 mg/dL] **with or without** symptoms consistent with hypoglycaemia

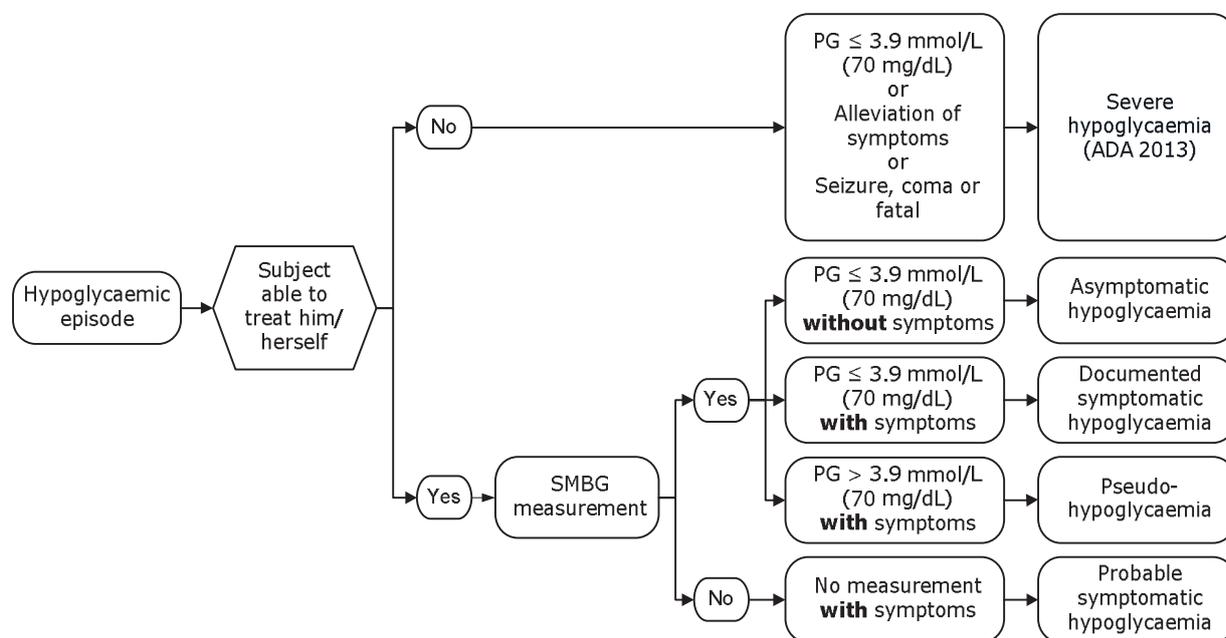


Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 2-1 Novo Nordisk classification of hypoglycaemia

ADA classification⁴ of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration
- 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 classification of hypoglycaemia

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 considering all episodes, nocturnal and daytime episodes using Novo Nordisk and ADA classified episodes. All episodes will also be summarised by category, including summaries in relation to time since start of meal, as occurring within the following time intervals:

- During first 1, 2 and 4 hours after the start of the 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 (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, 1 hour, 2 hour, 4 hour, 1 (exclusive) to 2 hours (inclusive), 2 (exclusive) to 3 hours (inclusive), 3 (exclusive) to 4 hours (inclusive), and 2 (exclusive) to 4 hours (inclusive) after start of the meal) will be analysed based on the FAS using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered

treatment emergent as offset. The model will include treatment, strata (two levels based on use of own CGM or not), previous insulin use (three levels: NovoRapid[®], Apidra[®], Humalog[®]), and region as factors. To the extent where data allow, separate analyses will be performed for all severe episodes.

Number of unexplained episodes of hyperglycaemia (confirmed by SMPG)

The number of unexplained episodes of hyperglycaemia will be summarised in a frequency table. Unexplained hyperglycaemia is defined as a confirmed PG value ≥ 16.7 mmol/L (300 mg/dL) and is unexplained (i.e. no apparent medical, dietary, insulin dosage or pump failure reason). The percentage of Subjects with unexplained hyperglycaemia will be presented.

Unexplained hyperglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of IMP administration after randomisation and no later than one day after the last day on IMP.

Physical examination

The physical examination parameters (head, ears, eyes, nose, throat, neck, respiratory system, cardiovascular system, gastrointestinal system incl. mouth, musculoskeletal system, central and peripheral nervous system, skin), and their change from baseline, will be summarised descriptively. All findings will be listed.

Electrocardiogram

Electrocardiogram (ECG) findings will be summarised descriptively including summaries of the change from screening. Change from screening will be summarised as normal/abnormal not clinically significant/abnormal clinically significant categorisation in shift tables.

Vital signs (blood pressure, pulse)

Vital signs include diastolic blood pressure, systolic blood pressure and pulse. The measurements will be summarised descriptively using both the actual values as mean change.

Fundus photography/fundoscopy

Fundus photography/fundoscopy findings and the change from screening will be summarised descriptively.

Clinical laboratory assessments

Change from baseline 16 weeks after randomisation in central laboratory assessments:

- Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, and leucocytes)
- Biochemistry (total protein, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), sodium, potassium, albumin, and total bilirubin)
- Urinalysis (albumin/creatinine ratio, erythrocytes, protein, and ketones)

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.

Change from baseline in body weight and body mass index (BMI) 16 weeks after randomisation

The measurements will be summarised descriptively using the actual values as mean change.

Change from baseline in body weight will be analysed using a statistical model similar to 1), except with the corresponding baseline measurement as covariate. The analysis will be based on the safety analysis set and the on-treatment observation period.

Number of change-of-infusion-sets per week during 16 weeks after randomisation

For each Subject this is calculated as the total number of infusion sets used divided by the actual duration of the randomised treatment period in days, multiplied by seven. It will be summarised for each treatment using descriptive statistics.

Number of Subjects with at least one non-routine change categorised by reasons for change

The percentage of Subjects with at least one non-routine change will be presented, categorised by reasons for change, in a frequency table by treatment.

3 Changes to the statistical analyses planned in the protocol

General considerations

It has been clarified how data collected at visit 22A and 22B are handled.

Statistical analysis

It has been clarified that type 1 error will only be controlled for the primary estimand.

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

In the statistical analysis in the protocol it is not clear if missing values or values for subjects discontinuing treatment/withdraw from trial should be imputed. Some of the following changes have been implemented to account for this issue.

In the sensitivity analysis for change from baseline in HbA_{1c} it has been changed from subjects withdrawing from trial to subjects with an imputed value at week 16 to be aligned with the primary analysis.

In the statistical sensitivity analysis 3b) for change from baseline in HbA_{1c} copy reference has been changed to conditional imputation, and for 3c) jump to reference has been changed to unconditional imputation to clarified the method used.

It has been clarified that the statistical analysis 4) will be repeated as for the confirmatory secondary endpoints.

For change from baseline in 1-hour PPG increment (meal test) it has been clarified how the endpoint is derived, which is aligned with the other endpoints derived from the meal test. To align with the primary analysis it has been changed so values at week 16 are imputed for subjects with missing values instead of imputing values for subjects withdrawn from trial, and the imputations are based on subjects in the NovoRapid[®] arm with non-missing values instead of completers in the NovoRapid[®] arm.

For the statistical analysis of change from baseline of time spent in low IG (≤ 3.9 mmol/L) it has been clarified that the corresponding baseline value will be included as covariate.

In the statistical analysis for subjects reaching HbA_{1c} or PPG (SMPG) targets it has been clarified that subjects without an HbA_{1c} measurement or 1-hour mean PPG measurement at week 16 will be handled as non-responders in the on-treatment observation period analysis.

Change from baseline has been removed for fluctuation in the 7-7-9-point SMPG profile as it is analysed logarithmically transformed and change from baseline values could be negative.

CGM endpoints

Percentage of time spent with IG ≤ 3.9 mmol/L [70 mg/dL] has been added to align with the thresholds for IG for the endpoints incidence of episodes.

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 to further evaluate the effect and safety of fast-acting insulin aspart.

It has been clarified the variation in the IG profile will be presented by the fluctuation.

The change from baseline in $\Delta\text{AUC}_{\text{IG},0-15\text{min}}$, $\Delta\text{AUC}_{\text{IG},0-30\text{min}}$, $\Delta\text{AUC}_{\text{IG},0-1\text{h}}$, $\Delta\text{AUC}_{\text{IG},0-2\text{h}}$ and $\Delta\text{AUC}_{\text{IG},0-4\text{h}}$ are added to further evaluate the effect and safety of fast-acting insulin aspart.

It has been clarified that the endpoints related to CGM and meal test derived as AUCs will be weighted by the duration.

Adverse events

For adverse events summaries by relation to device has been change to relation to technical complaint to align with what is reported on the case report forms. Summaries for AEs leading to withdrawal from trial have been added to further investigate the safety of fast -acting insulin aspart.

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.

It has been clarified that separate statistical analysis will only be for all severe hypoglycaemic episodes as the number is expected to be very low.

Unexplained hyperglycaemic episodes

The treatment emergent definition for unexplained hyperglycaemic episodes has been clarified.

Assessments not collected at baseline

ECG and fundus photography/fundoscopy is not collected at baseline, hence change from screening will be summarised for these endpoints instead.

4 References

1. ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials: dated 05 February 1998.
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. 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.
4. 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.