Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04588259
Sponsor trial ID:	NN1218-4357
Official title of study:	Efficacy and Safety of Fast-acting Insulin Aspart Compared to NovoRapid® both in Combination with Insulin Degludec with or without Metformin in Adults with Diabetes
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Note: The date in the header of page 2 is the date of the compilation of the documents and not of an update to content.

9.1.9 Documentation of statistical methods

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Statistical Analysis Plan

Trial ID: NN1218-4357

Efficacy and Safety of Fast-acting Insulin Aspart Compared to NovoRapid® both in Combination with Insulin Degludec with or without Metformin in Adults with Diabetes

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

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Biostatistics Insulin & Devices 3

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Version History

This Statistical Analysis Plan (SAP) for study NN1218-4357 is based on the protocol version 5.0 dated 30 Nov 2020.

SAP Version	Date	Change	Rationale
1.0	26Sep2022	Not Applicable	Original version

List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
ECG	electrocardiogram
FAS	full analysis set
FPG	fasting plasma glucose
HbA_{1c}	glycosylated haemoglobin
HDL	high-density lipoprotein
LDL	low-density lipoprotein
LLoQ	lower limit of quantification
MAR	missing at random
MMRM	mixed model for repeated measurements
PG	plasma glucose
PK	pharmacokinetics
SAE	serious adverse event
SMPG	self-measured plasma glucose
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse events
UTN	Universal Trial Number

1 Introduction

1.1 Objectives, Endpoints, and Estimands

Primary Objective

To confirm the effect in terms of glycaemic control of treatment with faster aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in Chinese adults with T1DM or T2DM inadequately treated with a basal-bolus or a premix regimen, using a non-inferiority approach

Secondary objective

To compare the safety of faster aspart to NovoRapid® both in combination with insulin degludec with or without metformin in Chinese adults with T1DM or T2DM inadequately treated with a basal-bolus or a premix regimen

Primary estimand

The primary estimand is defined as the treatment difference in change from baseline in HbA1c 16 weeks after randomisation between treatment with faster aspart and treatment with NovoRapid® both in combination with insulin degludec with or without metformin in adult subjects with T1DM or T2DM on basal-bolus regimen with a basal optimisation if all had adhered to randomised treatment. This estimand aims to reflect the treatment effect for subjects that are actually able to take the drug during the intended treatment period.

Primary endpoint

• Change from baseline (week 0) in HbA1c to 16 weeks after randomisation

Secondary endpoints

Supportive secondary efficacy endpoints

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

• Change from baseline in 30-minutes, 1-hour, 2-hour and 3-hour PPG to 16 weeks after randomisation (meal test)

• Change from baseline in FPG to 16 weeks after randomisation

• If a subject achieves HbA1c target 16 weeks after randomisation:

  • HbA1c < 7.0%

  • HbA1c < 7.0% without severe hypoglycaemia

• Change from baseline in 7-9-7-point SMPG to 16 weeks after randomisation:

• Mean of the 7-9-7-point profile

• 1-hour PPG and PPG increment (mean, breakfast, lunch, main evening meal)

• Fluctuation in 7-9-7-point profile

• If a subject achieves PPG target (overall mean of daily PPG measurements in SMPG) 16 weeks after randomisation:

  • Overall PPG (1-hour) ≤7.8 mmol/L

  • Overall PPG (1-hour) ≤7.8 mmol/L without severe hypoglycaemia

• Insulin dose (Units/day and Units/kg/day; total basal, total bolus and individual meal insulin dose) 16 weeks after randomisation.

Supportive secondary safety endpoints

• Number of treatment emergent adverse events during the 16 weeks after randomisation

• Number of treatment emergent injection site reactions during the 16 weeks after randomisation

• Number of treatment emergent hypoglycaemic episodes classified both according to the ADA definition and Novo Nordisk definition during the 16 weeks after randomisation
• Overall

• Daytime and nocturnal hypoglycaemic episodes (00:01-05:59 – both inclusive)

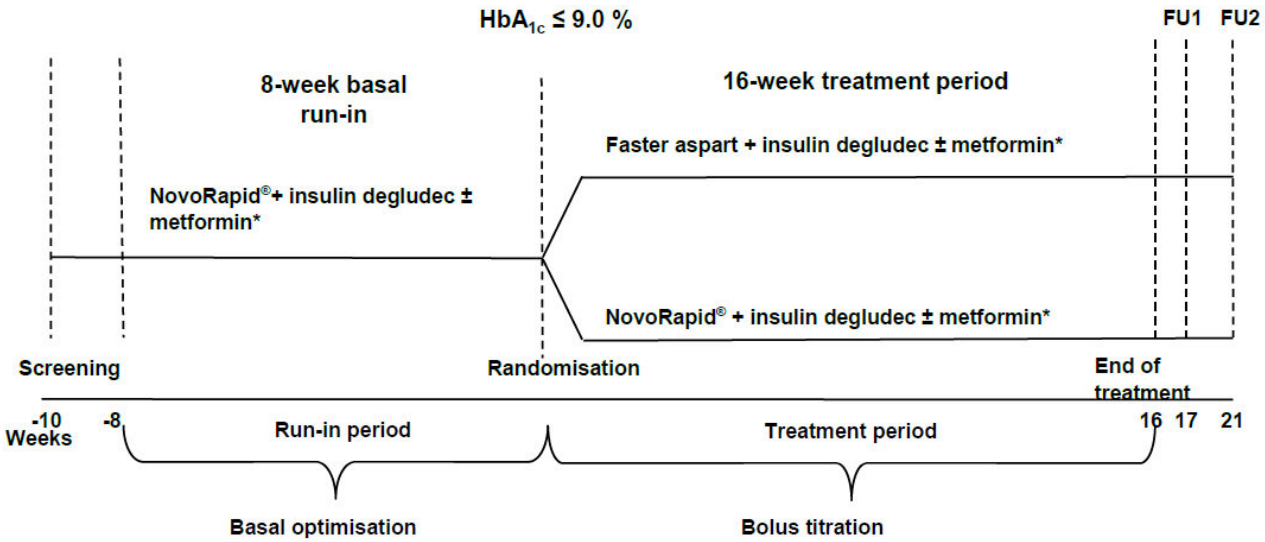
• Hypoglycaemic episodes from start of meal until 30 minutes, 1, 2, 4 hours and from 2 hours (exclusive) to 4 hours (inclusive) after start of meal

1.2 Study Design

1.2.1 Trial information

This is a phase 3a, 16-week, multicentre, 1:1 randomised, double-blind, active controlled, treat-to-target, two-arm parallel group, non-inferiority trial with an 8-week run-in period comparing the effect and safety of faster aspart to NovoRapid® both in combination with insulin degludec with or without metformin in subjects with T1DM or T2DM inadequately treated with a basal-bolus or a premix regimen.

Figure 1-1 Trial design



*Treatment with metformin is only applicable for subjects with T2DM treated with metformin prior to the trial.

The trial design is summarised in Figure 1-1.

The total duration of the trial is approximately 30 weeks divided into the following periods:

• An approximately 2-week screening period

• An 8-week run-in period primarily for optimisation of the basal insulin treatment

• A 16-week treatment period

• A 30-day follow-up period: FU1; 7 days after end of treatment and FU2; 30 days after end of treatment

The trial includes a screening visit to assess subject's eligibility and additional weekly visits/phone contacts during the trial. After screening, all eligible subjects will be enrolled in an 8-week run-in period. All subjects eligible for the trial will receive novorapid and the basal insulin degludec with or without metformin once daily. After the run-in period, subjects eligible for randomisation (HbA_{1c} ≤ 9.0% measured at visit 9) will be randomised (1:1) to receive double blinded treatment with either faster aspart or NovoRapid® both in combination with once daily insulin degludec with or without metformin. To aim for an even distribution of treatment groups within T1DM and T2DM, the randomisation will be stratified according to the type of diabetes.

All subjects will have a standardised meal test at baseline (V10 before randomisation) and at end of treatment (V26/V26A). The meal test is described in more details in the protocol Section 8.3.1.

After the 16-week treatment period, the subject will have a 30-day safety follow-up period.

For further details see the trial protocol.

2 Statistical Hypothesis

The primary endpoint is relative change from baseline (week 0) in HbA1c to 16 weeks after randomisation.

Non-inferiority 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 H0: $D > 0.4\%$ against HA: $D \leq 0.4\%$,

is less than or equal to 2.5%, where D is the mean treatment difference (faster aspart minus NovoRapid®).

Superiority will be based on the same 95% CI that was used for addressing the primary analysis. Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference is below 0%.

3 Analysis Sets

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

- 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 FAS, excluding subjects who:
  - Have violated any inclusion criteria
  - Have fulfilled any exclusion criteria

Subjects in the PP analysis set will contribute to the evaluation "as treated"

- Safety Analysis Set includes all subjects receiving at least one dose of randomised treatment. Subjects in the safety analysis set will contribute to the evaluation "as treated"

Randomised subjects, who are lost to follow-up, and where no exposure information of 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 by 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.

4 Statistical Analyses

4.1 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 (V10). In case a measurement is not available at randomisation, the most recent measurement prior to randomisation will be used as baseline.

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. The FAS is defined in Section 3.

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.

The primary objective of the trial is to confirm the effect in terms of glycaemic control of treatment with faster aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in Chinese adults with T1DM or T2DM inadequately treated with a basal-bolus or a premix regimen, using a non-inferiority approach.

More specifically the upper limit of the 95% confidence interval for the difference between faster 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.

4.2 Estimand

The estimand is defined as the treatment difference in change from baseline in HbA_{1c} 16 weeks after randomisation between faster aspart and NovoRapid® both in combination with insulin degludec with or without metformin in Chinese adults with T1DM or T2DM treated on basal-bolus regimen with a basal optimisation if all had adhered to randomised treatment. This estimand aims to reflect the treatment effect for subjects that are actually able to take the drug during the intended treatment period.

4.3 Primary endpoint analysis

4.3.1 Definition of Endpoint

The primary endpoint is change from baseline (week 0) in HbA_{1c} to 16 weeks after randomisation.

4.3.2 Main Analytical Approach

The estimand will be addressed by the primary analysis on all subjects included in the full analysis set and using the data collected from date of first dose of randomised NovoRapid®/faster aspart and to 7 days after the day of last dose of randomised NovoRapid®/faster aspart. Change from baseline in HbA_{1c} after 16 weeks of randomised treatment will be analysed using a mixed-effect model for repeated measurements (MMRM) where all calculated changes in HbA_{1c} from baseline at visits will be included in the analysis. This model will include treatment and stratification (T1DM/T2DM) as

fixed factors, HbA_{1c} at baseline as covariate and interactions between all fixed factors and visit. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. This approach relies on the assumption that data are missing at random (MAR). From this model, the treatment difference after 16 weeks will be estimated with a 95% confidence interval calculated.
Non-inferiority 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: $D \leq 0.4\%$,
is less than or equal to 2.5%, where D is the mean treatment difference (faster aspart minus NovoRapid®).
The trial also aims to confirm the superiority of treatment with faster aspart for the change from baseline HbA_{1c} 16 weeks after randomisation. Here superiority will be based on the same 95% CI that was used for addressing the primary analysis. Superiority will be confirmed if the upper boundary of the two-sided 95% confidence interval of the mean treatment difference is below 0%.

4.3.3 Additional analysis

Differences between the two populations will be investigated further by estimating the treatment differences separately for subjects with T1DM and T2DM. These treatment differences will be estimated based on the same data and a similar statistical model as the primary analysis but including interaction terms between treatment, stratification (T1DM and T2DM), and visit.

4.3.4 Sensitivity analysis for the primary analysis addressing the estimand

1) A tipping point analysis will be made based on the data and a similar statistical model as the primary analysis addressing the estimand but using multiple imputation. In this analysis observations for subjects with missing values are imputed based on the treatment arm they were randomised to and subjects in the faster 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 in the faster aspart groups evolve less favourably than predicted. As a first step imputations will be done without penalty assuming MAR. Second, the imputed values for week 16 in the faster aspart group will be added a penalty. 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.
2) A tipping point analysis using multiple imputation similar to 1) but with the modification that subjects discontinuing treatment due to non-eligibility (discontinuation due to criteria 1-4, protocol Section 6.6) in the faster aspart group will not have a penalty added. These analyses are motivated by the fact that data from subjects prematurely discontinuing randomised treatment due to non-eligibility can reasonably be assumed to be missing completely at random.
3) The same statistical model using MMRM and data as in the primary analysis, but restricted to the PP analysis set. 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.

4.4 Secondary endpoints analyses

4.4.1 Supportive secondary endpoints

4.4.1.1 Efficacy endpoints

All endpoints except insulin dose in this section will be assessed using the FAS. Insulin dose will be presented using the safety analysis set.

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

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

Change from baseline in PPG and PPG increment endpoints 16 weeks after randomisation will be analysed based on the FAS using an ANOVA model including treatment and stratification (T1DM/T2DM) as factors, and with the corresponding baseline value as covariate.

Change from baseline in FPG to 16 weeks after randomisation

Change from baseline in FPG to 16 weeks after randomisation will be analysed based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to the primary analysis except with baseline FPG as covariate.

If a subject achieves HbA1c 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%) 16 weeks after randomisation.

This responder endpoint will be analysed based on a logistic regression model using treatment and stratification (T1DM/T2DM) as factors, and baseline HbA_{1c} as covariate. In the analysis, subjects who prematurely discontinue trial product and subjects with missing HbA_{1c} at 16 weeks will be included as non-responders.

HbA1c < 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%) 16 weeks after randomisation without treatment emergent severe hypoglycaemic episodes.

This responder endpoint will be analysed based on a logistic regression model using treatment and stratification (T1DM/T2DM) as factors and baseline HbA_{1c} as covariate. In the analysis, subjects

who prematurely discontinue trial product and subjects with missing HbA_{1c} at 16 weeks will be included as non-responders.

Change from baseline in endpoints derived from the 7-9-7-point SMPG profile to 16 weeks after randomisation

In general, analyses will be based on the entire 7-9-7-point SMPG profile.

PPG and PPG increments based on the 7-9-7-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 7-9-7-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 7-9-7-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 7-9-7-point SMPG profile

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

Change from baseline in the mean of the 7-9-7-point SMPG profile 16 weeks after randomisation will be analysed based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to the primary analysis except with the corresponding baseline value as covariate.

- Change from baseline in 1-hour PPG and PPG increment (mean, breakfast, lunch and main evening meal)

Change from baseline in 1-hour PPG and PPG increment endpoints 16 weeks after randomisation for mean over all three meals and the individual meals will be analysed separately based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to the primary analysis except with the corresponding baseline value as covariate.

- Fluctuation in 7-9-7-point SMPG profile

The fluctuation in the 7-9-7-point SMPG 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. It will be calculated using the linear trapezoidal technique.

Fluctuation in the 7-9-7-point SMPG profile will be logarithmically transformed and analysed based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to the primary analysis except with the corresponding log-transformed baseline value as covariate. Estimated treatment means and the estimated treatment differences with corresponding 95% CI will be back-transformed to the original scale, resulting in estimated geometric means, a treatment ration and a 95% CI for the treatment ratio.

If a subject achieves PPG target (based on overall mean of daily PPG measurements in 7-9-7-point SMPG profile) 16 weeks after randomisation:

Overall PPG (1-hour) £7.8 mmol/L

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 7-9-7-point SMPG profile.

This responder endpoint will be analysed based on a logistic regression model using treatment and stratification (T1DM/T2DM) as factors, and baseline overall mean 1-hour PPG as covariate. In the analysis, subjects who prematurely discontinue randomised treatment will be included as non-responders.

Overall PPG (1-hour) £7.8 mmol/L 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 and stratification (T1DM/T2DM) as factors, and baseline overall mean 1-hour PPG as covariate. In the analysis, subjects who prematurely discontinue randomised treatment will be included as non-responders.

Insulin dose (Units/day and Units/kg/day; total basal, total bolus, and individual meal insulin dose) 16 weeks after randomisation

The insulin doses will be summarised descriptively by treatment week according to regimen, by meal type in units and units/kg (separately for each mealtime dose). Insulin doses will be summarised using the safety analysis set.

Lipids-lipoproteins profile 16 weeks after randomisation

Lipid endpoints (total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride) will be logarithmically transformed and analysed separately based on all planned post baseline measurements until or at 16 weeks after randomisation using a model similar to the primary analysis except with the corresponding log-transformed baseline 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.

4.4.1.2 Safety Analysis

In terms of AEs, as a minimum, SAEs will be tabulated.

Number of treatment emergent adverse events

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 exposure to 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 subject 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 and 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

Treatment emergent injection site reactions occurring during the trial will be summarised 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 exposure to randomised treatment, and no later than one day after the last day of exposure to randomised treatment.

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

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 4-1) and the ADA classification of hypoglycaemia (see Figure 4-2).

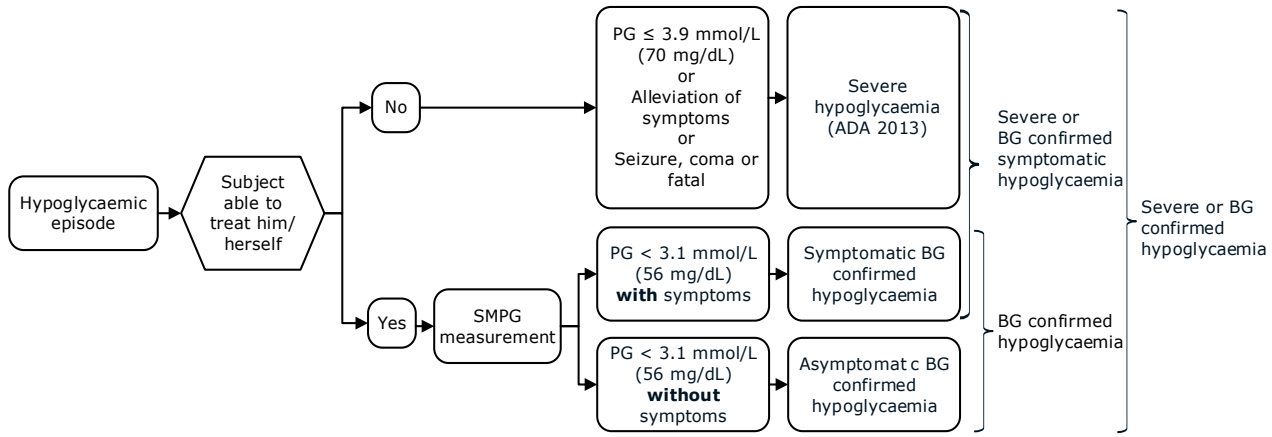
Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a PG level of 3.1 mmol/L (56 mg/dL).[2] Therefore, Novo Nordisk has included hypoglycaemia with PG levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see Figure 4-1) in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification.[3]
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[3] or BG confirmed by a PG value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.

Figure 4-1 Novo Nordisk classification of hypoglycaemia



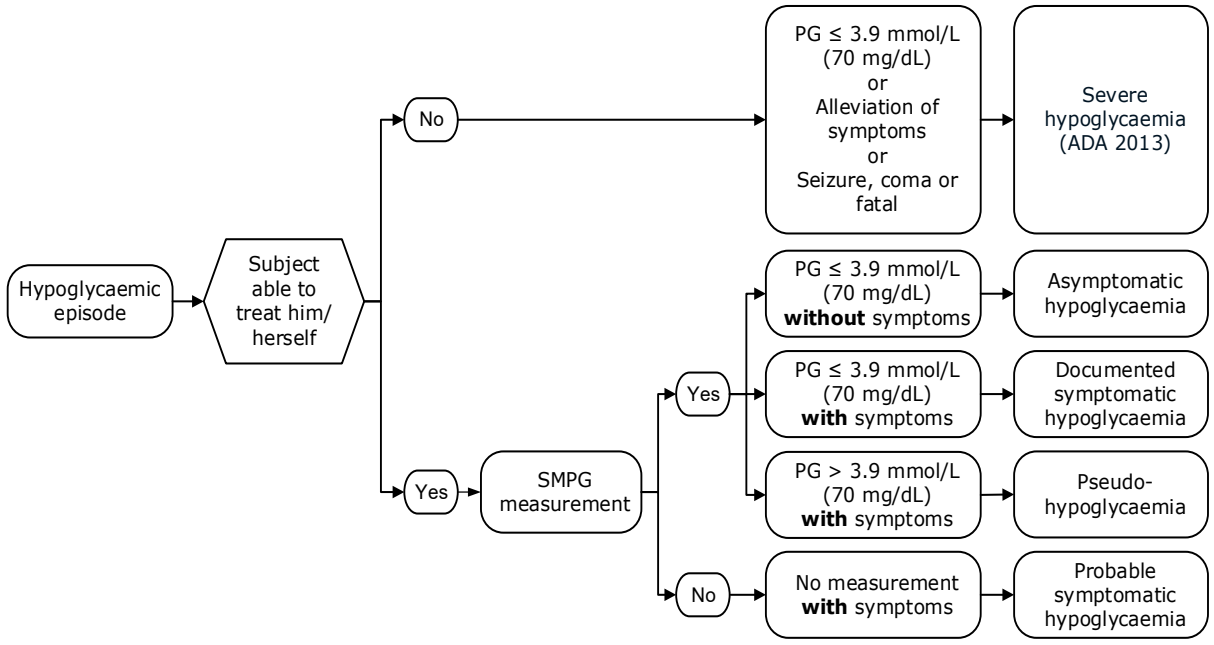
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

BG: blood glucose PG: plasma glucose SMPG: Self-measured plasma glucose

ADA classification[3] 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).

Figure 4-2 ADA classification of hypoglycaemia



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

PG: plasma glucose SMPG: Self-measured plasma glucose

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 during 0.5, 1, 2, and 4 hours after start of meal, and from 2 hours (exclusive) to 4 hours (inclusive) after start of meal, respectively.

The number of treatment emergent severe or BG confirmed hypoglycaemic episodes (all, daytime, nocturnal, 0.5, 1, 2, and 4 hours and from 2 hours (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 and stratification (T1DM/T2DM), as factors. To the extent where data allow, separate analysis will be performed for severe hypoglycaemic episodes.

Change from baseline in clinical evaluations 16 weeks after randomisation:

Physical examination

The physical examination parameters (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.

Vital signs

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

Electrocardiogram

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

Eye examination

Eye examination findings, including right eye ophthalmoscopy and left eye ophthalmoscopy, will be summarised descriptively including summaries of the change from baseline.

Change from baseline in clinical laboratory assessments 16 weeks after randomisation

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

- Haematology (haemoglobin blood, erythrocytes, haematocrit blood, leucocytes, thrombocytes)
- Biochemistry (AST serum, calculated creatinine clearance serum, sodium serum, potassium serum, creatinine serum, total protein serum, albumin serum, alkaline phosphatase serum, ALT serum, total bilirubin serum, GFR from creatinine adjusted for BSA)

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 both the actual values and the low/normal/high categorisation in shift tables.

Change from baseline in body weight and body mass index 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 based on all planned post baseline measurements until or at 16 weeks after randomisation using a statistical model similar to the primary analysis except with the corresponding baseline measurement as covariate.

4.5 Changes to Protocol-planned Analysis

No change to the protocol.

5 Sample size determination

The sample size is determined to ensure a sufficient power for the primary analysis. This is determined using a non-inferiority limit of 0.4%.
In the global phase 3a programme where treatment with faster aspart has been investigated, the completion rates have been high, i.e. approximately 88-94%. Therefore it will not be unexpected that treatment discontinuation might be as low as 10%.
It is expected that a larger portion of the trial population will constitute subjects with T2DM. For these calculations the proportion of subjects with T1DM is assumed to be at least 20%. Combining expected differences for T1DM and T2DM subjects and weighting by the proportion of expected T1DM subjects we will assume a treatment difference of -0.02% (i.e., in favour of faster aspart).
The power for the primary (non-inferiority) analysis is based on a *t*-statistic under the assumption of a one-sided test of size 2.5 %, a non-inferiority margin of 0.4% and SD of 1.2%. Using these values we get a power of 81.7% for the primary analysis with a sample size of 270. Adjusting further for a dropout rate of approximate 10%, 300 subjects will be randomised.
The power for non-inferiority for scenarios where SD = 1.0% or 1.2% and mean difference of 0.00% or -0.02% based on sample size 270 is shown in Table 5-1.

Table 5-1 The power for non-inferiority for different scenarios

Power for non-inferiority	Treatment difference = 0%	Treatment difference = -0.02%
SD = 1.0%	90.6%	93.0%
SD = 1.2%	77.9%	81.7%

The power calculation is done using proc power in SAS Version 9.4.

6 References

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