Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03078478
Sponsor trial ID:	NN1250-4252
Official title of study:	A trial comparing the efficacy and safety of insulin degludec and insulin glargine 300 units/mL in subjects with type 2 diabetes mellitus inadequately treated with basal insulin with or without oral antidiabetic drugs
Document date:	21 May 2019

16.1.9 Documentation of statistical methods

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

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Statistical Analysis Plan
Trial ID: NN1250-4252
UTN: U1111-1184-8175
EudraCT No.: 2016-002801-20

CONFIDENTIAL

Date: 12 March 2019
Version: 3.0
Status: Final
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Novo Nordisk

Statistical Analysis Plan

Trial ID: NN1250-4252

A trial comparing the efficacy and safety of insulin degludec and insulin glargine 300 units/mL in subjects with type 2 diabetes mellitus inadequately treated with basal insulin with or without oral antidiabetic drugs

Trial phase: 3b

Author:

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis of covariance
BG	blood glucose
FAS	full analysis set
FPG	fasting plasma glucose
HbA_{1c}	glycosylated haemoglobin
IDeg	insulin degludec
IGlar	insulin glargine
ITT	intention-to-treat
MACE	major adverse cardiovascular events
MMRM	mixed model for Repeated Measurement
OAD	oral antidiabetic drug
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
TEAE	treatment-emergent adverse event
TID	three times daily
T2DM	type 2 diabetes mellitus

1   Introduction

1.1   Trial information

Objectives and endpoints

The primary objective

- To compare the effects of IDeg OD and IGlar 300 U/mL OD on hypoglycaemia in subjects with T2DM, inadequately treated with basal insulin with or without OADs.

The secondary objectives

To compare IDeg and IGlar 300 U/mL in terms of basal insulin requirement.
To compare IDeg and IGlar 300 U/mL in terms of safety and parameters of glycaemic control.

Primary endpoint

- Number of severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes during maintenance 2 (36 weeks)

Confirmatory secondary endpoints

- Basal insulin dose (U) at end of maintenance 2 (up to 88 weeks)

- Number of nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes during maintenance 2 (36 weeks)

- Number of severe hypoglycaemic episodes during maintenance 2 (36 weeks)

1.1.1 Other endpoints and assessments

Other efficacy endpoints

- Change in HbA_{1c} from baseline to end of maintenance 2 (up to 88 weeks)
- Change in fasting plasma glucose (FPG) from baseline to end of treatment (up to 88 weeks)
- FPG $\leq$ 7.2 mmol/L (130 mg/dL) at end of treatment (up to 88 weeks) (yes/no)
- FPG $\leq$ 5 mmol/L (90 mg/dL) at end of treatment (up to 88 weeks) (yes/no)
- HbA_{1c} < 7% (53 mmol/mol) at end of maintenance 2 (up to 88 weeks) and no severe or BG confirmed symptomatic hypoglycaemic episodes during maintenance 2 (36 weeks) (yes/no)
- HbA_{1c} < 7% (53 mmol/mol) at end of maintenance 2 (up to 88 weeks) and no nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes during maintenance 2 (36 weeks) (yes/no)
- Change in mean pre-breakfast self-measured plasma glucose used for titration from baseline to end of treatment (up to 88 weeks)

Other safety endpoints

- Hypoglycaemia
  - Number of severe or BG confirmed symptomatic hypoglycaemic episodes from randomisation until end of maintenance 2 (up to 88 weeks)
  - Number of nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes from randomisation until end of maintenance 2 (up to 88 weeks)
  - Number of severe hypoglycaemic episodes from randomisation until end of maintenance 2 (up to 88 weeks)
- Number of adverse events from randomisation until end of maintenance 2 (up to 88 weeks)
- Change in body weight from baseline to end of treatment (up to 88 weeks)

Safety assessments

- Change in clinical evaluations from baseline to end of treatment (up to 88 weeks) in terms of:
  - Vital signs (including blood pressure and pulse)
    - Dilated fundoscopy or fundus photography
    - Electrocardiogram (ECG)
- Change in central laboratory assessments from baseline to end of treatment (up to 88 weeks) in terms of
  - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, leucocytes)
  - Biochemistry (creatinine, alanine aminotransferase , aspartate aminotransferase , alkaline phosphatase , sodium, potassium, albumin, total bilirubin)

Trial design:

This is a up to 88-week, randomised (1:1), open-label, parallel, multi-centre, multi-national, treat-to- target, active controlled trial comparing the efficacy and safety of insulin degludec 200 units/mL with insulin glargine 300 units/mL both administered once daily ± oral anti-diabetic drugs in subjects with type 2 diabetes mellitus previously treated with basal insulin once or twice daily ± oral anti-diabetic drugs excluding sulfonylureas/glinides. Type and dose of any pre-trial oral anti-diabetic treatment should remain unchanged throughout the trial.

Within each treatment arm, subjects will be randomised 1:1 to morning (from waking up to breakfast) or evening dosing (from main evening meal to bedtime). The dosing time will be kept throughout the entire treatment period.

The trial is conducted with a treat-to-target principle: the insulin dose is adjusted for each individual subject with the aim of achieving identical glycaemic targets for IDeg and IGlar 300 U/mL. This allows for a valid comparison of hypoglycaemia.

Due to an unusual data reporting pattern of hypoglycaemia and glycaemic values being linked to the glycaemic data collection system (the combined use of MyGlucoHealth with the electronic diary) it was decided on 14 February 2018 to apply a new data collecting system consisting of an Abbott BG-meter and a paper diary.

To accommodate changes in the data collection system and to ensure sufficient data collection with respect to the confirmatory endpoints a new maintenance period (maintenance 2) of 36 weeks duration was included in the trial. Following the protocol amendment, the total trial duration will be up to 94 weeks divided into the following periods:

- Screening up to two weeks
  - Screening (V1)
  - Randomisation (V2)
- Treatment period consisting of
  - A 16-week titration period
  - An up to 36-week maintenance 1 period
  - A 36-week maintenance 2 period
- 30 days post treatment follow-up period including two follow-up (FU) contacts
  - FU1 7-12 days after end of treatment
  - FU2 30-35 days after end of treatment

In case of premature treatment discontinuation, subjects will be encourage to remain in trial and come in for abbreviated visits according to the visit schedule until the planned time of V54/V93.

Further details

For further details on trial design and endpoints please see the NN1250-4252 protocol version 3.0.

1.2   Scope of the statistical analysis plan

This SAP is based on the NN1250-4252 protocol version 3.0.

Statistical Analysis Plan
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2   Statistical considerations

2.1   General considerations

The in-trial period will include information collected at or after the date of randomisation and until the date of:

- The last scheduled subject-site contact
- Withdrawal for subjects who withdraw their informed consent
- The last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up
- Death for subjects who die before any of the above

The on-treatment period represents the time period in which a subject is considered exposed to trial product. The period starts on day of the first dose of trial product and ends 7 days after last dose of trial product is taken, but no later than the end of the in-trial period.

Maintenance period 1 starts on the day of V18/V18A. For subjects not attending neither V18 nor V18A, but still in trial for more than 16 weeks, maintenance 1 instead starts 16 weeks (112 days) after randomisation.

Maintenance period 2 starts at the date of V57/V57A. Subjects not attending neither V57 nor V57A will not have a maintenance 2 period, regardless of duration in trial.

A subject is completing the trial if he/she attends V93 or V93A at the end of maintenance 2 period. It is considered completing trial on treatment if the subject attends V93 without premature discontinuation of trial product.

All efficacy endpoints will be summarised using the full analysis set (FAS) and safety endpoints excluding hypoglycaemic endpoints will be summarised using the safety analysis set (SAS). For hypoglycaemia, the SAS will be used when on-treatment data is used, and FAS is used for in-trial data.

All statistical analysis of efficacy and safety endpoints will be based on the FAS unless otherwise specified. Confirmatory analysis addressing the primary estimand will include on-treatment data and not available retrieved (V93A) data.

The primary objective is to compare the effects of IDeg OD and IGlar 300 U/mL OD on the rate of hypoglycaemia in subjects with type 2 diabetes mellitus, inadequately treated with basal insulin with or without oral anti-diabetic drugs. The primary estimand is the treatment difference between IDeg and IGlar 300 U/mL assuming that all randomised subjects adhered to the randomised treatment, and is thus referred as the on-treatment estimand. The on-treatment estimand addresses the treatment difference for subjects who can be long-term treated with either of the two insulins.

Data collected after premature treatment discontinuation will not be used when addressing the on-treatment estimand. With the aim of comparing a safety endpoint this estimand is considered the most relevant as it compares the occurrence of a safety endpoint that is caused by the drug during exposure to the drug. The confirmatory endpoints will additionally be investigated with a ITT estimand.

The secondary estimand is the treatment difference between IDeg and IGlar 300 U/mL regardless of whether subjects adhered to the randomised treatment throughout the trial, that is an ITT estimand. For this ITT estimand, data collected after premature discontinuation will be used.

In accordance with guidance[9] endpoints will be assessed at frequent visits and also for subjects who prematurely discontinue treatment. When an assessment is planned at randomisation visit, this value will be used as baseline value. If this value is missing the last recorded value before randomisation visit will be used. For assessments planned only at screening, the screening values will be used as baseline. If this value is missing, the first recorded visit after screening, but no later than the day of randomisation, will be used.

For patients not initiating maintenance period 2 on treatment a summary table of reasons for treatment discontinuation will be reported.

The severe hypoglycaemia episodes included in the statistical analysis are all events adjudicated with the outcome severe hypoglycaemia.

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ. Laboratory values above the upper limit of quantification (ULOQ) will be set to ULOQ+1.

The primary and secondary endpoints will be tested in a hierarchical order using the on-treatment estimand to control the family wise Type I error in the strong sense. Presentation of results from a statistical analysis will include the estimated treatment means as well as estimated mean treatment difference (or ratio) together with the two-sided 95% confidence interval and corresponding two-sided p-value.

In the statistical models explanatory factors will be categorized as follows:
1. Treatment: IDeg, IGlar 300 U/mL
2. Pre-trial 0 OADs, 1OAD, ≥2 OADs
3. Region: Europe , North America
4. Sex: male, female
5. Dosing time: morning, evening

2.2 Power calculation

The power is based on the primary objective and the primary endpoint, number of hypoglycaemic episodes during maintenance treatment.

For the power calculations it is assumed that the true treatment rate ratio (RR) is 0.75 corresponding to a 25% reduction in rate of hypoglycaemia in maintenance period with IDeg OD compared to

IGlar 300 U/mL OD. Sample size is determined based on a negative binomial model with log-offset equal to exposure time in maintenance. The observed rate of severe or BG confirmed symptomatic hypoglycaemia for IDeg is assumed to be 1.8 per patient years of exposure (PYE) and the dispersion parameter in the negative binomial distribution is assumed to be 3.1. Furthermore it is assumed that 4% of subjects will withdraw before starting the maintenance period and therefore have no on-treatment data for the maintenance period. For these 4% the treatment ratio is set to 1. Rate assumptions are based on experience from SWITCH 2 (NN1250-3998), which has similar inclusion criteria. Dispersion parameter assumptions are based on experience from the Degludec phase 3a and 3b program. Assumptions concerning withdrawal are similarly based on actual withdrawal rate of the trial during titration and maintenance 1.

The power equals 79% with the number of randomised subjects and the assumptions above.

Table 2–1   Power for the on-treatment estimand for combinations of RR and event rates

		Yearly event rate		
		1.5	1.8	2.0
RR	Adjusted RR	Primary	Primary	Primary
0.80	0.812	55%	57%	58%
0.75	0.765	77%	79%	79%
0.70	0.718	92%	93%	93%

The marginal power for detecting a difference between IDeg OD and IGlar 300 U/mL OD with 805 subjects per treatment arm assuming a one-sided t-test at the 2.5% significance level for the confirmatory secondary dose endpoints is shown below. The assumptions are based on data from NN1250-3998 with respect to hypoglycaemic episodes and the phase 3a+b program for the dose-difference.

Table 2–2   Marginal power for confirmatory secondary endpoints

Endpoint	Assumptions				
	True ratio	Adjusted RR	CV/ Over dispersion	Rate in IDeg treatment arm	Power
Insulin dose (U)	0.90	0.906	0.65	-	92%
Number of nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes during maintenance 2	0.7	0.718	3.1	0.55	82%
Number of severe hypoglycaemic episodes during maintenance 2	0.6	0.624	3.1	0.03	31%

2.3   Definition of analysis sets

Full analysis set (FAS): includes all randomised subjects. In exceptional cases, subjects may be eliminated from the full analysis set. In such cases the elimination will be justified and documented. In the statistical evaluation of the full analysis set subjects contribute "as randomised".

Safety analysis set (SAS): includes all subjects receiving at least one dose of the investigational product or comparator. Subjects in the safety set will contribute to the evaluation "as treated".

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

Before data are released for statistical analysis, a review of all data will take place to identify protocol deviations that could potentially affect the results. In exceptional cases a decision to exclude any subject or observation from the statistical analysis can be made. This is the joint responsibility of the members of the study group. The subjects or observations to be excluded, and the reasons for their exclusion must be documented before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

2.4   Primary endpoint

2.4.1   Primary statistical analysis for the on-treatment estimand

The on-treatment estimand will be estimated based on information from maintenance 2 collected when subjects use randomised treatment including a 7-day follow-up period (on-treatment data). Subjects that discontinue randomised treatment during maintenance 2 will contribute with the available on treatment data from maintenance 2. For subjects that discontinue randomised treatment during the titration period or maintenance 1, the number of events in maintenance 2 will be imputed based on data from the same arm from maintenance 2 for subjects that discontinued randomised treatment during maintenance 2. Missing data within each group will be imputed as follows:

- First 1000 samples from the posterior distribution of model parameters will be extracted. The model will be fitted to the on-treatment maintenance 2 data for subjects that discontinued randomised treatment during maintenance 2. This will be done using a Bayes Poisson log-link model dosing time as a factor, age as covariate, and log of exposure time as offset.
- For each sample of model parameters, the total number of hypoglycaemia events for subjects that discontinued randomised treatment in the titration period or maintenance 1 will be imputed as a random number of events from a Poisson distribution using the sampled parameters.

Having 1000 complete data sets that have maintenance 2 data for all randomised subjects, the mean treatment ratio will be estimated using a negative binomial model with all the factors described in section 2.1, age as covariate and log exposure time as offset. The estimates and standard deviations will be pooled to one estimate and associated standard deviation using Rubin's formula. From these the 95% confidence intervals for the treatment ratio and the associated p-value will be calculated.

If the above imputation model cannot fit or leads to inflate the standard error of the treatment ratio on logscale by more than 15% compared to a negative binomial model fitted to the available on-treatment data during maintenance 2 without any imputation, an alternative model is used for the analysis: The imputation model will be a negative binomial model fitted to all available on-treatment data during maintenance 2 and including all factors described in section 2.1, age as covariate and log exposure time as offset. If this model cannot fit either, the imputation model is fit as a Poisson model to all available on-treatment maintenance 2 data, and if needed factors are left out from the imputation model in the following order:

- sex
- region
- previous OAD treatment

2.4.2   Sensitivity analyses for the on-treatment estimand

To investigate missing not at random scenarios, a tipping point analysis of the hypothesis that IDeg is superior to IGlar 300 U/mL will be performed for the on-treatment estimand. In this analysis the event rates for subjects that discontinued randomised treatment in the IDeg OD arm during either titration or maintenance 1 periods is gradually increased until the difference between the two treatments is no longer statistically significantly different. If the penalty found by this method is evaluated to be clinically plausible the sensitivity analysis does not support the primary analysis. If the penalty is not considered plausible the sensitivity analysis supports the primary analysis.

To investigate the potential influence of subjects with high number of events, the analysis of the on-treatment estimand will be repeated on data where the maximal number of events in maintenance 2 is truncated at three. The value three is based on data from SWITCH 2 (NN1250-3998) where three hypos correspond to the 95% percentile in the IDeg arm. Furthermore, a statistical sensitivity analysis is performed with a truncation at seven, to accommodate for the longer analysis period in the current trial (36 weeks instead of 16 weeks).

The primary analysis will be performed using only available on-treatment data during maintenance 2. Subjects without on-treatment data for maintenance 2 period will be excluded from this analysis, and thus no imputation is needed.

The primary analysis will be repeated, but considering the full maintenance period (maintenance 1 and maintenance 2). Missing data will be imputed for subjects that discontinued randomised treatment during titration period only, using on-treatment data for maintenance 1 and 2. This

analysis evaluates if including the data from the discontinued BG-meter challenge the overall conclusion of the trial.

The primary analysis will be repeated, with the exemption of imputation of hypoglycaemic episodes for subjects in IDeg arm actively refusing to reconsent to the extended trial period following the protocol amendment, defined as subjects discontinuing treatment after 15FEB2018 and either not reconsenting or not taking any doses of trial product later than the date of reconsenting. For these subjects, the imputation will be based on the usual statistical model fitted to all maintenance 2 data in the IGlar arm. This analysis evaluates if the conclusion of the primary analysis is different if non-consenters on IDeg arm are worse off than consenters.

The impact of protocol deviations and outliers may be investigated further in sensitivity analyses.

2.4.3 Statistical analysis for the ITT estimand

The ITT estimand will be estimated based on information from maintenance 2 collected regardless of whether subjects used randomised treatment or not, i.e. including data after premature discontinuation.

Missing data for withdrawn subjects prior to maintenance 2 will be imputed based on off-treatment data from the same arm from maintenance 2 . The imputations and the analysis will be made using the same method as for the on-treatment estimand. If the imputation model cannot fit or leads to inflate the standard error of the treatment ratio on logscale by more than 15% compared to a negative binomial model fitted to the available on- and off-treatment data during maintenance 2 without any imputation the analysis will not be performed.

2.4.4 Sensitivity analysis for the ITT estimand

A tipping point sensitivity analysis similar to the one for the on-treatment estimand will be performed. The penalty will only be added to withdrawn subjects in IDeg arm. Further sensitivity analyses may be performed.

2.5 Secondary endpoints

2.5.1 Confirmatory secondary endpoints

Provided that IDeg OD is superior to IGlar 300 U/mL OD for the primary endpoint using the on-treatment estimand, the confirmatory secondary endpoints will be tested for superiority of IDeg OD over IGlar 300 U/mL OD using the on-treatment estimand.

The confirmatory secondary endpoints are given below; the order of the endpoints defines the testing sequence. The hierarchical testing strategy will control the family wise type 1 error in the strong sense at 5% (two sided).

1. Basal insulin dose (U) at end of maintenance 2 (up to 88 weeks)
2. Number of nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes during maintenance 2 (36 weeks)
3. Number of severe hypoglycaemic episodes during maintenance 2 (36 weeks)

The hypoglycaemic endpoints will be analysed with the same analysis method as the primary endpoint including backup strategy and with similar sensitivity analysis.

Basal insulin dose at end of maintenance 2 will be analysed as follows: A basal insulin dose at every titration, maintenance and end of treatment visit mentioned in the flow chart will be calculated as a mean of the insulin doses in the 7 day period before the visits. For the on-treatment estimand these doses will be analysed on log-scale with an MMRM with the factors described in section 2.1 and age at baseline and logarithm of pre-trial insulin dose as covariate, all nested within visit. If this model does not converge visits and/or factors will be excluded from the analysis. Before transforming to log-scale, dose values of 0 will be assigned the value 0.5.

Insulin dose will also be analysed with the ITT estimand, i.e. including insulin dose collected after premature discontinuation. This is done using a pattern mixture model using multiple imputation to handle missing data. Imputation of missing data at end of trial will be done within the 4 groups of subjects defined by randomised treatment and whether subjects discontinued randomised treatment or not. Missing data within each group will be imputed as follows:

- An analysis of covariance model for insulin dose at visit 93 and 93A with the factors listen in 2.1 (except treatment) and pre-trial insulin dose and age at baseline as covariates will be fitted to the observed data.
- The estimated parameters will be used to impute 1000 values for insulin dose at visit 93/93A, creating 1000 complete datasets.

Having 1000 complete datasets, each of these will be analysed using an analysis of covariance model with all the factors listed in 2.1, pre-trial insulin dose and age at baseline as covariates. The estimates and standard deviations will be pooled to one estimate and associated standard deviation using Rubin's formula. From these the 95% confidence intervals for the treatment ratio and the associated p-value will be calculated.

2.6 Other endpoints and assessments

2.6.1 Efficacy endpoints

Supportive secondary efficacy endpoints will be summarised descriptively by visits and and supplemented by mean plots of observed values for the continuous endpoints.

2.6.2 Safety endpoints

Adverse events during the total treatment period (titration and maintenance periods)

AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities.

A treatment-emergent AE (TEAE) is defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment, or has onset date before the first day of exposure on randomised treatment and increases in severity during the treatment period and until 7 days after the last drug date. Major adverse cardiovascular events (MACEs, defined as all cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes) are considered treatment-emergent until 30 calendar days after the last day of randomised treatment.

AEs are summarised descriptively. AE data will be displayed 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).

Summaries are presented as an overview including all AEs, serious AEs, number of deaths, AEs by severity, AEs by relation to treatment and AEs leading to treatment discontinuation as summary tables based on system organ class and preferred terms for the following AEs:

- All TEAEs
- All AEs
- All TEAEs during maintenance 2
- Serious TEAEs
- TEAEs possibly or probably related to trial product
- 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

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Hypoglycaemic episodes

For the definition and classification of hypoglycaemic episodes refer to section 2.7.

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 severe or BG confirmed symptomatic hypoglycaemic episodes, severe hypoglycaemic episodes, and the Novo Nordisk interpretation of ADA classification of hypoglycaemia from 2018. The summaries are made for all and nocturnal (between 00:01 and 05.59 both inclusive) episodes respectively and for the total treatment period (titration and maintenance periods) and maintenance 2 only (36 weeks).

For both periods, hypoglycaemic episodes during the 7 days treatment-emergent period after last drug day will be included.

The number of severe or BG confirmed symptomatic hypoglycaemic events during total treatment period (up to 88 weeks) will be analysed statistically, addressing both the on-treatment and ITT estimand. Also nocturnal severe or BG confirmed symptomatic hypoglycaemic events as well as severe hypoglycaemic events during total treatment period will be analysed following these procedures.

The on-treatment estimand is estimated based on on-treatment data and a negative binomial model including the factors in section 2.1, age as covariate and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset. The model will use log as link function.

The ITT estimand is based on in-trial data. For withdrawn subjects, data after withdrawal will be imputed for a period lasting from the day after withdrawal up until 36 weeks after entering maintenance 2 period, and until 36 weeks after first reconsent of any subject in trial (i.e. until 09NOV2018) for subjects not entering maintenance 2. The imputation will follow the procedure described in section 2.4.1, using all off-treatment data to build the imputation model. Observed and imputed data are summarised by subject, and analysed through a negative binomial model including the factors in section 2.1, age as covariate and the logarithm of the total time period where hypoglycaemic episodes are either observed or imputed as offset. The model will use log as link function. If the imputation model cannot fit or leads to inflate the standard error of the treatment ratio on logscale by more than 15% compared to a negative binomial model fitted to the available on- and off-treatment data during total treatment period without any imputation the analysis will not be performed.

Body weight

Body weight (absolute value and change from baseline) will be summarised descriptively by visit.

2.6.3 Safety assessments

Clinical evaluation (ECG, vital signs, eye examination and physical examination) change from baseline

Vital signs, physical examination, eye examination and 12-lead ECG findings will be summarised, including:
- Summaries for each visit
- Shift tables from baseline to end of treatment

Laboratory assessments

Biochemistry and Haematology laboratory parameters will be summarised including:
- Summaries by visit
- Shift tables from baseline to end of treatment

2.7 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, and no later than the 7 days from last day on IMP.

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, the ADA 2013 classification of hypoglycaemia and the Novo Nordisk interpretation of ADA 2018 interpretation

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)[1]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

Novo Nordisk uses the following classification in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA 2013 classification[2]: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[2] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia.

Novo Nordisk interpretation of ADA 2018 definition of hypoglycaemia

Classification of hypoglycaemia		
Level	Glycaemic criteria	Description
Hypoglycaemia alert value (level 1)	< 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (level 2)	< 3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (level 3)	No specific glucose threshold	Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery
Notes: Novo Nordisk terms adapted from IHSG [3], ADA-2018[4], ISPAD[5], Type 1 diabetes outcomes program[6], ATTD[7]. Severe hypoglycaemia as defined by Seaquist[8].		

2.8 Health economics and/or patient reported outcomes

Health economics and/or patient reported outcomes will be analysed after the CTR.

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3   Changes to the statistical analyses planned in the protocol

Below substantial updates to section 17 in protocol version 3.0 is described. Linguistic updates for clarity are not described.

3.1   Update of specifying safety assessments

p.28 l.,89-409 is replaced by:

"Other safety endpoints

- *Hypoglycaemia*
    - o *Number of severe or BG confirmed symptomatic hypoglycaemic episodes from randomisation until end of maintenance 2 (up to 88 weeks)*
    - o *Number of nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes from randomisation until end of maintenance 2 (up to 88 weeks)*
    - o *Number of severe hypoglycaemic episodes from randomisation until end of maintenance 2 (up to 88 weeks)*
- *Number of adverse events from randomisation until end of maintenance 2 (up to 88 weeks)*
- *Change in body weight from baseline to end of treatment (up to 88 weeks)*

Safety assessments
- *Change in clinical evaluations from baseline to end of treatment (up to 88 weeks) in terms of:*
    - o *Vital signs (including blood pressure and pulse)*
    - o *Dilated fundoscopy or fundus photography*
    - o *Electrocardiogram (ECG)*
- Change in central laboratory assessments from baseline to end of treatment (up to 88 weeks) in terms of
    - o *Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, leucocytes)*
    - o *Biochemistry (creatinine, alanine aminotransferase , aspartate aminotransferase , alkaline phosphatase , sodium, potassium, albumin, total bilirubin)"*

Update leads to new subsection on reporting of safety assessments.

Rationale:

Vital signs, fundoscopy, ECG, haematology and biochemistry are standard safety assessments, which are not actual endpoints for this trial.

3.2 Update and clarification of definition of in trial and on treatment period, maintenance period 1 and 2, and completer definition:

p.81 l.1965-1970 is replaced by:

"*The in-trial period will include information collected at or after the date of randomisation and until the date of:*

- *The last scheduled subject-site contact*
- *Withdrawal for subjects who withdraw their informed consent*
- *The last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up*
- *Death for subjects who die before any of the above*

The on-treatment period represents the time period in which a subject is considered exposed to trial product. The period starts on day of the first dose of trial product and ends 7 days after last dose of trial product is taken, but no later than the end of the in-trial period.

Maintenance period 1 starts on the day of V18/V18A. For subjects not attending neither V18 nor V18A, but is still in trial for more than 16 weeks, maintenance 1 instead starts 16 weeks (112 days) after randomisation.

Maintenance period 2 starts at the date of V57/V57A. Subjects not attending neither V57 nor V57A will not have a maintenance 2 period, regardless of duration in trial.

A subject is completing the trial if he/she attend V93 or V93A at the end of maintenance 2 period. It is considered completing trial on treatment if the subject attends V93 without premature discontinuation of trial product."

Rationale:

Update to in-trial and on-treatment definition is aligned to project derivation rules. Specification of the maintenance periods.

3.3 Update of baseline value

p.82 l. 1993-1995:

"The baseline value is defined as the value from the randomisation visit. If this value is missing the last recorded value before randomisation visit will be used."

is updated to:

"When an assessment is planned at randomisation visit, this value will be used as baseline value. If this value is missing the last recorded value before randomisation visit will be used. For assessments planned only at screening, the screening values will be used as baseline. If this value is missing, the first recorded visit after screening, but no later than the day of randomisation, will be used."

Rationale:

Some assessments are planned only at screening visits and should be used as baseline under such circumstances.

3.4 Specifying tables on treatment discontinued/withdrawn subjects prior to maintenance 2

Before p. 81 l. 1996, the following paragraph is added:

"For patients not initiating maintenance period 2 on treatment a summary table of reasons for treatment discontinuation will be reported."

Rationale:

Prespecifying output to check for potential bias in early treatment discontinuations/withdrawals compared to all treatment discontinuations/withdrawals.

3.5 Handling of ULOQ values

In p. 82 l. 1998 the following is added:

"Laboratory values above the upper limit of quantification (ULOQ) will be set to ULOQ+1."

Rationale:

Include project derivation rule of handling of ULOQ values

3.6 Contribution in FAS

p. 84 l. 2036-2037 is replaced by:

"In the statistical evaluation of the full analysis set subjects contribute "as randomised"."

Rationale:

To align with project standard and ensure unambiguous definition of dosing time point.

3.7 Changing imputation model in primary analysis from negative binomial to Poisson, fewer covariates and different backup strategy.

p. 85 l. 2051-2080 is replaced by:

*"**Primary statistical analysis for the on-treatment estimand**

The on-treatment estimand will be estimated based on information from maintenance 2 collected when subjects use randomised treatment including a 7-day follow-up period (on-treatment data). Subjects that discontinue randomised treatment during maintenance 2 will contribute with the available on treatment data from maintenance 2. For subjects that discontinue randomised treatment during the titration period or maintenance 1, the number of events in maintenance 2 will be imputed based on data from the same arm from maintenance 2 for subjects that discontinued randomised treatment during maintenance 2. Missing data within each group will be imputed as follows:

- *First 1000 samples from the posterior distribution of model parameters will be extracted. The model will be fitted to the on-treatment maintenance 2 data for subjects that discontinued randomised treatment during maintenance 2. This will be done using a Bayes Poisson log-link model dosing time as a factor, age as covariate, and log of exposure time as offset.*
- *For each sample of model parameters, the total number of hypoglycaemia events for subjects that discontinued randomised treatment in the titration period or maintenance 1 will be imputed as a random number of events from a Poisson distribution using the sampled parameters.*

Having 1000 complete data sets that have maintenance 2 data for all randomised subjects, the mean treatment ratio will be estimated using a negative binomial model with all the factors

described in section 2.1, age as covariate and log exposure time as offset. The estimates and standard deviations will be pooled to one estimate and associated standard deviation using Rubin's formula. From these the 95% confidence intervals for the treatment ratio and the associated p-value will be calculated.

If the above imputation model cannot fit or leads to inflate the standard error of the treatment ratio on logscale by more than 15% compared to a negative binomial model fitted to the available on-treatment data during maintenance 2 without any imputation, an alternative model is used for the analysis: The imputation model will be a negative binomial model fitted to all available on-treatment data during maintenance 2 and including all factors described in section 2.1, age as covariate and log exposure time as offset. If this model cannot fit either, the imputation model is fit as a Poisson model to all available on-treatment maintenance 2 data, and if needed factors are left out from the imputation model in the following order:

- *sex*
- *region*
- *previous OAD treatment*

,,

Rationale:

Due to a low number of subjects discontinuing treatment during maintenance 2, the imputation model specified in the protocol is unstable and leads to an extreme number of imputed hypos in several instances (subjects having in the magnitude of millions or billions of hypos in a 36 week period). The instability of the model persists when the simplest imputation model, containing only dosing time and age as factors/covariates, is applied. To ensure the scientific integrity in the reality of sparse data the imputation model is simplified.

In case the subjects discontinuing treatment during maintenance 2 is far from equally distributed across the trial arms, there is a risk that also the simplified Poisson imputation leads to unstable results. As the backup model in the original protocol has proven not always to be able to fit, an alternative is introduced for the on-treatment estimands with imputations.

3.8 Clarification of handling of treatment emergent hypoglycaemic episodes during follow-up period

After p. 88 l. 2179 is added:

"*For both periods, hypoglycaemic episodes during the 7 days treatment-emergent period after last drug day will be included.*"

Rationale:

Clarification to align with project derivation rules.

3.9 Sensitivity analyses for primary analysis on-treatment estimand:

p.85 after l. 2092 is added:

- *"Furthermore, a statistical sensitivity analysis is performed with a truncation at seven, the current observed 95% percentile in the blinded uncleaned data.*

- *The primary analysis will be performed using only available on-treatment data during maintenance 2. Subjects without on-treatment data for maintenance 2 period will be excluded from this analysis, and thus no imputation is needed.*

- *The primary analysis will be repeated, but considering the full maintenance period (maintenance 1 and maintenance 2). Missing data will be imputed for subjects that discontinued randomised treatment during titration period only, using on-treatment data for maintenance 1 and 2. This analysis evaluates if including the data from the discontinued BG-meter challenge the overall conclusion of the trial.*

- *The primary analysis will be repeated, with the exemption of imputation of hypoglycaemic episodes for subjects in IDeg arm actively refusing to reconsent to the extended trial period following the protocol amendment defined as subjects discontinuing treatment after 15FEB2018 and either not reconsenting or not taking any doses of trial product later than the date of reconsenting. For these subjects, the imputation will be based on the usual statistical model fitted to all maintenance 2 data in the IGlar arm. This analysis evaluates if the conclusion of the primary analysis is different if non-consenters on IDeg arm are worse off than consenters."*

Rationale:

Additional sensitivity analyses are needed to evaluate the impact of the protocol amendment for the on-treatment estimand of the primary analysis. As the truncation value in the sensitivity analysis is selected based on a 16 weeks maintenance period, an extra truncation analysis is added.

3.10 Omitting backup strategy for ITT estimand

After p 86 l. 2100 the following is added:

"If the imputation model cannot fit or leads to inflate the standard error of the treatment ratio on logscale by more than 15% compared to a negative binomial model fitted to the available on- and off-treatment data during maintenance 2 without any imputation the analysis will not be performed."

Rationale:

For ITT estimand it is not appropriate to include on-treatment data in the imputation model, and the statistical analysis is thus omitted if the imputations model is deemed unstable.

3.11   Sensitivity analyses for primary analysis ITT estimand:

p. 85 l 2101:

"The same sensitivity analysis as the sensitivity analyses for the on-treatment estimand will be performed."

is replaced by

"A tipping point sensitivity analysis similar to the one for the on-treatment estimand will be performed. The penalty will only be added to withdrawn subjects in IDeg arm. Further sensitivity analyses may be performed."

Rationale: The sensitivity analysis addressing missing data patterns is considered the primary sensitivity analysis, other sensitivity analysis will be performed if necessary.

3.12   Clarification of primary analysis ITT estimand:

p 86 l. 2116: the following is deleted:

"for subjects that discontinued randomised treatment during maintenance 2"

Rationale:

Not intended statement in original protocol, as we want to impute base on all available off-treatment data.

3.13   Handling of zero doses

p.87, after l. 2122 to be added:

"*Before transforming to log-scale, dose values of 0 will be assigned the value 0.5*"

Rationale:

To ensure that zero doses does not count as missing in analysis.

3.14   Tables on adverse events

p.88, after l. 2157-2169 is replaced by:

"*Summaries are presented as an overview including all AEs, serious AEs, number of deaths, AEs by severity, AEs by relation to treatment and AEs leading to treatment discontinuation and as summary tables based on system organ class and preferred terms for the following AEs:*

- *All TEAEs*
- *All AEs*
- *All TEAEs during maintenance 2*
- *Serious TEAEs*
- *TEAEs possibly or probably related to trial product*
- *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*"

Rationale:

Streamlining which outputs are actually needed.

3.15   Analyse hypoglycaemic episodes during total treatment period

After page 88 l. 2179, the following is added:

"*The number of severe or BG confirmed symptomatic hypoglycaemic events during total treatment period (up to 88 weeks) will be analysed statistically, addressing both the on-treatment and ITT estimand, Also nocturnal severe or BG confirmed symptomatic hypoglycaemic events as well as severe hypoglycaemic events during total treatment period will be analysed following these procedures.*

The on-treatment estimand is estimated based on on-treatment data and a negative binomial model including the factors in section 2.1, age as covariate and the logarithm of the time period in which a

hypoglycaemic episode was considered treatment emergent as offset. The model will use log as link function.

The ITT estimand is based on in-trial data. For withdrawn subjects, data after withdrawal will be imputed for a period lasting from the day after withdrawal up until 36 weeks after entering maintenance 2 period, and until the 36 weeks after first of reconsent of any subject in trial (i.e. until 09NOV2018) for subjects not entering maintenance 2. The imputation will follow the procedure described in section 2.4.1, using all off-treatment data to build the imputation model. Observed and imputed data are summarised by subject, and analysed through a negative binomial model including the factors in section 2.1, age as covariate and the logarithm of the total time period where hypoglycaemic episodes are either observed or imputed as offset. The model will use log as link function. If the imputation model cannot fit or leads to inflate the standard error of the treatment ratio on logscale by more than 15% compared to a negative binomial model fitted to the available on- and off-treatment data during total treatment period without any imputation the analysis will not be performed."

Rationale:

Hypoglycaemic episodes are always clinical relevant, and though the data on hypoglycaemic episodes during titration and maintenance 1 periods is less reliable than during maintenance 2, for completeness the treatment difference during the full period should still be analysed statistically.

3.16   Presentation of lab data

p. 89 l. 2193:

Delete:

- *"Proportion of subjects with measurements outside reference range by treatment and visit*

- *Box plots by visit*

- *Listings of individual values outside reference ranges (abnormal values)"*

Rationale:

Limit number of outputs on lab data, as both insulins are approved with known safety profiles also regarding lab.

3.17 Omit antibodies from statistical section

p. 89. l. 2196:

Delete *"Anti-insulin antibodies will be summarised by visit."*

Rationale:

Antibodies will not be available to Biostat at time point of CTR.

3.18 Updated ADA hypo classification

in p.88 l. 2176-2177:

"*and the ADA classification of hypoglycaemia.*"

is replaced by

"and the Novo Nordisk interpretation of ADA classification of hypoglycaemia from 2018."

Instead of p.9l l 2217-2236 the following is added:

"Novo Nordisk interpretation of ADA 2018 definition of hypoglycaemia

Classification of hypoglycaemia		
Level	*Glycaemic criteria*	*Description*
Hypoglycaemia alert value (level 1)	*< 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)*	*Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy*
Clinically significant hypoglycaemia (level 2)	*< 3.0 mmol/L (54 mg/dL)*	*Sufficiently low to indicate serious, clinically important hypoglycaemia*
Severe hypoglycaemia (level 3)	*No specific glucose threshold*	*Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery*
Notes: Novo Nordisk terms adapted from IHSG [21], ADA-2018[22], ISPAD[23], Type 1 diabetes outcomes program[24], ATTD[25]. Severe hypoglycaemia as defined by Seaquist[26].		

"

Furthermore, figures describing the classification process are omitted, as incorrect due to the adjudication of severe hypoglycaemic events.

Rationale:

Include the more updated ADA 2018 hypoglycaemia definition in descriptive tables.

4 References

1. 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.

2. 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.

3. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2017;40(1):155-7.

4. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S55-S64.

5. Jones TW, Group IHGW. Defining relevant hypoglycemia measures in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2017.

6. Agiostratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, et al. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care. 2017;40(12):1622-30.

7. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017;40(12):1631-40.

8. 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.

9. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1). 2 Jul 2010.