Cover Page for Statistical Analysis Plan

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Official title of study:	A trial comparing NNC0148-0287 C (insulin 287) versus insulin glargine U100, both in combination with metformin, with or without DPP4 inhibitors and with or without SGLT2 inhibitors, in basal insulin treated subjects with type 2 diabetes mellitus
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16.1.9 Documentation of statistical methods

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

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Statistical Analysis Plan

Trial ID: NN1436-4466

A trial comparing NNC0148-0287 C (insulin 287) versus insulin glargine U100, both in combination with metformin, with or without DPP4 inhibitors and with or without SGLT2 inhibitors, in basal insulin treated subjects with type 2 diabetes mellitus

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List of abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis of co-variance
CGM	continuous glucose monitoring
CI	confidence interval
DPP4i	dipeptidyl peptidase 4 inhibitors
EASD	European Association for the Study of Diabetes
FAS	full analysis set
FPG	fasting plasma glucose
IWRS	interactive web response system
LLOQ	lower limit of quantification
MCMC	Markov Chain Monte Carlo
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SGLT2i	sodium-glucose cotransporter 2 inhibitors
SMPG	self-measured plasma glucose
T2DM	type 2 diabetes mellitus

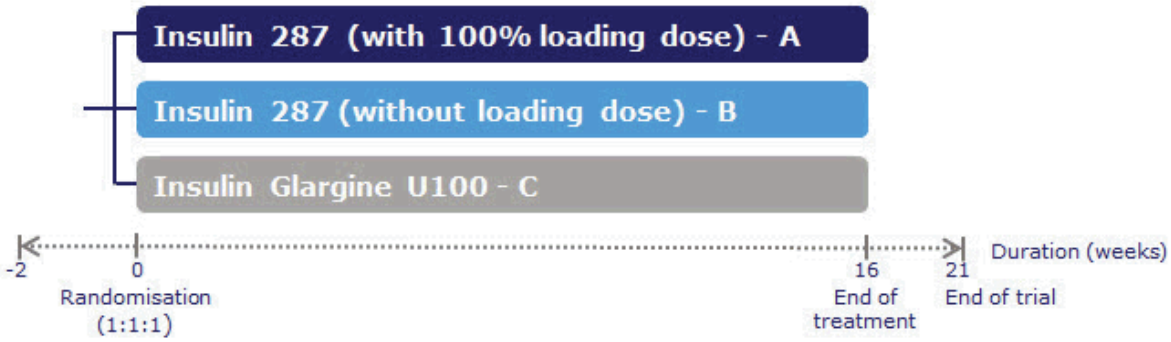
1 Introduction

1.1 Trial information

This is a 16 weeks exploratory, multicentre, randomised, open label, active-controlled, parallel-group trial with 3 arms investigating the effect on glycaemic control and safety of treatment with once weekly insulin 287 using 2 different switch approaches (either 'unit to unit switch with an additional 100% loading dose' approach, referred in the trial design as arm A or 'unit to unit switch' approach, referred in the trial design as arm B) versus once daily insulin glargine U100 (arm C) in basal insulin analogue treated subjects with type 2 diabetes mellitus (T2DM) inadequately controlled on basal insulin analogue with metformin, with or without dipeptidyl peptidase 4 inhibitors (DPP4i) and with or without sodium-glucose cotransporter 2 inhibitor (SGLT2i).

The overall trial design and visit schedule are outlined in Figure 1-1 and trial flowchart (see protocol Section 2) respectively.

Figure 1-1 Trial design



The trial duration is approximately 23 weeks and consists of 2 weeks of screening period, 16 weeks of randomised treatment period, and 5 weeks of follow-up period. From screening visit (after signed informed consent; visit 1) until randomisation, all subjects will be required to measure daily pre-breakfast self-measured plasma glucose (SMPG) and have a 10 day baseline continuous glucose monitoring (CGM) profile collected. At visit 2, after the screening period, all eligible subjects will be randomised (1:1:1), to receive once weekly insulin 287 using one of the 2 switch approaches (arm A and B) or once daily insulin glargine U100 (arm C). The randomisation will be stratified based on pre-trial insulin treatment regimen and based on whether subjects are treated with SGLT2i.

During the 16 weeks treatment period, subjects will have weekly contact with the site through either site visits (9 visits) or phone contacts (6 phone contacts). To evaluate the effect on glycaemic

control, subjects will have CGM profiles collected during the 16 weeks treatment period. The CGM will be blinded for both subjects and investigator.

After 16 weeks of treatment subjects will come in for their end of treatment visit (V18). The end of treatment visit will be one week after the last dose of insulin 287 and on the day of or the day after the last dose of insulin glargine U100. This will be followed by 2 follow up visits (V19 and V20). The last follow up visit (V20) is scheduled to take place 6 weeks after the last dose of once weekly insulin 287 and 5 weeks after the last dose of once daily insulin glargine U100. This will allow for appropriate wash-out of trial drug, following at least 5 half-lives of insulin 287.

If a subject is prematurely discontinued from trial treatment, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to end of treatment visit (V18) and to come in for the follow up visits V19 and V20. Subjects should be asked to continue wearing CGM (changed weekly) throughout the remaining weeks finalised by a last visit (V18A) 16 weeks after randomisation. End of treatment assessments for withdrawn or prematurely discontinued subjects are reallocated to the nearest planned visit where the assessments were supposed to be taken, if this scheduled visit is at most 7 days apart and no assessment already exists at this visit.

1.2 Primary objective

To compare the effect on glycaemic control of treatment with once weekly insulin 287 using the two different switch approaches versus once daily insulin glargine U100 both in combination with metformin ± DPP4i ± SGLT2i in basal insulin analogue treated T2DM subjects.

1.3 Secondary objective

To compare the safety and tolerability of once weekly insulin 287 using 2 different switch approaches versus once daily insulin glargine U100 both in combination with metformin ± DPP4i ± SGLT2i in basal insulin analogue treated T2DM subjects.

1.4 Primary estimand

The primary estimand is defined as the mean difference in ‘time in target range 3.9-10.0 mmol/L (70–180 mg/dL)’ during the last 2 weeks of treatment (week 15 and 16) between each of the 2 different switch approaches of once weekly insulin 287 and once daily insulin glargine U100 for all randomised subjects, if all subjects had adhered to the randomised insulin treatment and had 70% of the planned continuous glucose monitoring (CGM) measurements recorded.

The following intercurrent events for the primary estimand will be handled by the hypothetical strategy: initiation of insulin treatment other than the randomised treatment, discontinuation of randomised insulin treatment, withdrawal from the trial, and recording of less than 70% of planned CGM measurements in the last two weeks of treatment. Other intercurrent events will be handled by

the treatment policy strategy. This estimand aims to reflect the estimated treatment effect for subjects that had adhered to the planned insulin treatment during the planned treatment period.

1.5 Scope of the statistical analysis plan

This statistical analysis plan (SAP) is based on the protocol *A trial comparing NNC0148-0287 C (insulin 287) versus insulin glargine U100 both in combination with metformin, with or without DPP4 inhibitors and with or without SGLT2 inhibitors, in basal insulin treated subjects with type 2 diabetes mellitus*, version 2.0 (dated 01 February 2019).
It clarifies the statistical analyses described in the protocol with additions and corrections, which are described in Section 3.

2 Statistical considerations

2.1 Sample size determination

The sample size calculation is based on the width of the 95% confidence interval (CI). Data from insulin degludec treated subjects in trial NN9068-3697 showed a standard deviation (SD) of 2.5 hour for a 24h period after 26 weeks of treatment and for time in range defined as 3.9-10.0 mmol/L (70–180 mg/dL). NN9068-3697 was conducted in insulin naïve subjects with T2DM and used older CGM devices (iPro1 and iPro2). Another trial in type 1 diabetes mellitus (T1DM) subjects NN1250-3874 with insulin glargine U100 as comparator used the Dexcom SEVEN® PLUS CGM device which is considered more representative for the present trial as there have been notable improvements in the CGM-devices. In this trial a SD of 3.0 hour in the last maintenance period was observed for time in range defined as 3.9-10.0 mmol/L (70–180 mg/dL). However, the titration periods were only four weeks in NN1250-3874. The SD for the current trial is assumed to be 3.0 based on observations from these two trials. Table 2-1 shows the width of the 95% confidence interval for any pairwise comparison that can be obtained with 80% probability for a range of sample sizes and assumed values of SD.

Table 2-1 Width of the 95% CI for various SD and number of subjects per treatment arm

	Number per treatment arm		
SD	40	50	60
2.5	2.4	2.1	1.9
3.0	2.9	**2.5**	2.3
3.5	3.3	3.0	2.7

CI: confidence interval. SD: standard deviation.

With 50 subjects randomised to each treatment arm in a 1:1:1 manner, the width of the 95% for any pairwise comparison is 2.5h/24h with a probability of 80%. Two-and-a-half hour corresponds to approximately 10%-points for percent time in range.

2.2 Definition of analysis sets

The following analysis sets will be defined:

Full analysis set (FAS): includes all randomised subjects. Subjects in the FAS will contribute to evaluation "as randomised".

Safety analysis set (SAS): includes all subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation based on the trial product received for the majority of the period they were on treatment. Any dose deviation will be ignored. This implies that subjects will contribute as randomised unless the subject receives insulin glargine instead of insulin 287 or vice versa.

2.3 Definitions of trial periods

The relevant observation periods are:

In-trial: The in-trial observation period starts at randomisation (as registered in IWRS) and ends at the date of:

- The last direct 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 (i.e. possibly an unscheduled phone visit)
- Death for subjects who die before any of the above

For subjects not randomised but exposed to trial product the in-trial period starts at the date of first dose of trial product.

Baseline assessments are always included in the in-trial observation period.

For adjudicated events it is the event adjudication committee (EAC) determined onset date that determines if the event belongs to the in-trial period.

On-treatment: The on-treatment period starts at the date of first dose of trial product as recorded on the eCRF, and ends at the first date of any of the following:

- The follow-up visit (FU2)
- The last date on trial product + 5 weeks for once daily insulin and +6 weeks for once weekly insulin
- The end-date for the in-trial observation period

Baseline assessments are always included in the on-treatment period.

For adjudicated events it is the EAC determined onset date that determines if the event belongs to the on-treatment period.

On-treatment without rescue medication: This observation period is a sub-set of the on-treatment observation period. The on-treatment without rescue medication or ancillary treatment starts at the date of first dose of trial product as recorded on the eCRF and ends at the first date of any of the following:

- Initiation of a non-randomised insulin treatment (rescue medication)
- The end date of the on-treatment period if no rescue medication was initiated.

The following will *not* be considered rescue medication:

- If a subject takes an insulin other than randomised treatment for a few days due to reasons not related to the effect of the randomised treatment, e.g.,
    - if a subject is hospitalised and it is against hospital policy to use trial products
    - if a temperature deviation leaves trial product unavailable for distribution and administration
- Insulin treatment initiated after end of treatment visit

Baseline assessments are always included in the on-treatment without rescue medication/ancillary treatment period.

The 'on-treatment without rescue medication' observation period will be the primary observation period for efficacy evaluations. Safety will be evaluated based on the on-treatment observation periods unless otherwise specified.

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period. Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude either a subject or single observation from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group.

Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion, will be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

2.4 Statistical analyses

All efficacy endpoints will be summarised using the full analysis set (FAS) and safety assessments will be summarised using the safety analysis set (SAS).

All statistical analyses of efficacy and safety endpoints will be based on the FAS unless otherwise specified.

Endpoints will be assessed at frequent visits also for subjects who prematurely discontinue treatment. 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.

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

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.

The statistical models will include baseline values of the endpoint value as a covariate as well as explanatory factors that are categorized as follows:

- Treatment: switch approach with 100% loading dose, switch approach without loading dose, insulin glargine U100
- Pre-trial insulin treatment: twice daily basal insulin analogue or once daily insulin glargine U300: yes or no
- SGLT2i use: yes or no

2.4.1 Primary endpoint

The primary endpoint is 'time in target range 3.9–10.0 mmol/L (70-180 mg/dL)' during the last 2 weeks of treatment (week 15 and 16) and will be calculated as 100 times the number of recorded measurements in glycaemic target range 3.9–10.0 mmol/L (70-180 mg/dL), both inclusive, divided by the total number of recorded measurements.

Following international consensus criteria[1] it will be required that at least 70% of the planned CGM measurements, during the last two weeks of treatment is available, for endpoint data to be included in the analysis.

Baseline 'time in target range 3.9–10.0 mmol/L (70-180 mg/dL)' will be computed in the same way as the primary endpoint. Subjects with less than 72 hours corresponding to 864 measurements of CGM during the screening period will not have a baseline computed and hence will be excluded from the analysis.

The primary estimand will be estimated based on the Full Analysis Set (FAS) using measurements obtained while subjects are adhering to randomised treatment without initiation of rescue medication. Measurements obtained after initiation of rescue treatment and endpoint data from which the required 70% of the planned CGM measurements during the last two weeks of treatment are not available will be regarded as missing. Missing endpoint data will be imputed from trial participants who are from the same randomised group, and who have completed and adhered to their randomised insulin treatment without initiation of a non-randomised insulin treatment i.e., data will be imputed based on the assumption that, within treatment groups, subjects with missing endpoint data will behave like subjects completing randomised treatment. Specifically, the imputations and analyses will be carried out as follows:

- First, one thousand (1000) copies of the dataset will be generated for time in range.

- Second, for each dataset copy, each assessment and each treatment group, an analysis of covariance (ANCOVA) model with baseline 'time in target range' as covariate will be fitted to the time in range values for subjects having completed their randomised treatment. The estimated mean, and variances, from the model will be used to impute missing values in the same treatment group.
- For each of the complete data sets, the primary endpoint will be analysed using an ANCOVA model with randomised treatment, pre-trial insulin treatment and SGLT2i use (yes/no) as fixed factors and baseline 'time in target range' as covariate. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule[2].

2.4.2 Supportive secondary efficacy endpoints

The secondary efficacy endpoints will be addressed in terms of the frame work of the primary estimand.

2.4.2.1 HbA1c, fasting plasma glucose (FPG), and body weight – change from baseline to week 16

The supportive secondary efficacy endpoints addressing glycaemic control and body weight will be analysed using the same model as specified for the primary endpoint with the exception that baseline value of the endpoint will be used as covariate.

The missing data will be imputed in the following way:

- First, intermittent missing values will be imputed using a Markov Chain Monte Carlo (MCMC) method in order to obtain a monotone missing data pattern. The imputation is, as for the imputation of the primary analysis, done for each treatment arm separately and 1000 copies of the data set will be made.
- Next, a sequential conditional regression approach for imputing monotone missing values at planned visits will be implemented beginning with the first assessment after baseline and sequentially continuing to the last planned assessment. Models will be fitted for each treatment arm (using observed and imputed data). The models include the baseline and post-baseline values of the corresponding endpoint, prior to the visit in question as covariates.

2.4.2.2 Weekly insulin dose - during week 15 and 16

Insulin doses will be summarised by weekly averages and the actual average insulin dose during the last two weeks of treatment (week 15 and 16) will be log-transformed and analysed without a covariate reflecting baseline dose but otherwise using the same statistical model as specified for the primary endpoint.

The missing data on dose will be imputed in the same way as missing data on glycaemic control and body weight. However, the model in the sequential conditional regression approach will not include a baseline value, but all values (observed or imputed) prior to the visit in question as covariates.

2.4.2.3 HbA1c responders

Two variables of dichotomous outcome (responder=yes/non-responder=no) will be defined based on whether a subject has met a specific level of HbA1c < 7% (American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD)), respectively, <6.5% (American Association of Clinical Endocrinologists (AACE)) by treatment week.

Responders during the 'on treatment without rescue medication' period will be summarised and tabulated. No analysis will be performed.

2.4.3 Supportive secondary safety endpoints

2.4.3.1 Adverse events

A treatment-emergent AE is an event that has onset date (or increase in severity) during the on-treatment observation period. These will therefore be referred to as 'on-treatment AEs' hereafter. On-treatment AEs are summarised descriptively 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 (R). These summaries are replicated by outputs including all 'in-trial' AEs (i.e., AEs with onset date [or increase in severity] during the 'in-trial' observation period).

The most frequent AEs will be defined as preferred terms that are experienced by at least 5% of the subjects in any of the treatment arms.

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding.

2.4.3.2 Hypoglycaemic episodes

Hypoglycaemia endpoints will be summarized similarly to the treatment emergent AE's for the 'on-treatment observation' period as well as from baseline to the end of treatment visit based on the SAS.

2.4.4 Pharmacokinetic and/or pharmacodynamic modelling

Not applicable for this trial.

3 Changes to the statistical analyses planned in the protocol

Definition of 'as treated'

Arm A and B of the trial design differ only in dosage at the first visit and so constructing a rule for when subjects should be considered as treated in arm A, respectively, arm B was difficult. Also since dosage deviations happens not only at randomisation, but any subsequent visits it was decided to ignore dose deviations when defining 'as treated'.

This implies that 'as treated' coincides with 'as randomised' unless the subject receives insulin Glargine instead of insulin 287 or vice versa.

Requirements for baseline CGM measurements

Due to a very low number of subjects with 70% or more of planned CGM measurements during the screening period it was decided that only subjects with less than 72 hours corresponding to 864 measurements of CGM during the screening period will not have a baseline computed and hence will be excluded from the analysis. It is remarked that only 10 days of CGM measurements was planned during the screening period as only one devise per subject was distributed prior to baseline.

Definition of HbA1c responders

HbA1c responders have been defined in Section 2.4.2.3 since summary tabulations on this will be included in EoT.

Hypoglycaemic endpoint

Due to inconsistency between the protocol Section 4.2.2.2, stating that hypoglycaemic endpoints will be summarised based on 'from baseline to week 16 (end of treatment)', and protocol Section 10.3.1, stating that hypoglycaemic endpoints will be summarised based on the 'on treatment' observation period, further details were specified in Section 2.4.3.2 stating that the hypoglycaemic endpoints will be summarised on both observation periods.

Primary analysis

Phrasing in the definition of the primary analysis in Section 2.4.1 has been modified from the protocol for added clarity. This has no implications on the analysis.

Supportive secondary efficacy endpoint

Detailed phrasing in the definition of the imputation method for glycaemic control, body weight and insulin dose endpoints in Section 2.4.2.1 have been added.

Definition of 'on-treatment without rescue medication'

The definition of the 'on-treatment without rescue medication' observation period has been modified in order to be a true subset of the 'on-treatment' observation period as also indicated in the protocol. See Section 2.3. This has no implications on the analysis.

4 References

1. 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.
2. Little R, Rubin D. Statistical analysis with missing data. Sons. JW, editor. New York.: John Wiley & Sons. 1987.