Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03377699
Sponsor trial ID:	NN1250-4300
Official title of study:	A trial comparing the effect and safety of insulin degludec versus insulin detemir, both in combination with insulin aspart, in the treatment of pregnant women with type 1 diabetes
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*Document date refers to the date on which the document was most recently updated.
Note: The date in the header of Page 2 is the date of compilation of the documents and not of an update to content.

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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EXPECT
Trial ID: NN1250-4300

Statistical Analysis Plan

A trial comparing the effect and safety of insulin degludec versus insulin detemir, both in combination with insulin aspart, in the treatment of pregnant women with type 1 diabetes

Trial Phase: 3b

Author
Name: [redacted]
Department: Biostatistics and Programming, GD-GBS

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Version history

This Statistical Analysis Plan (SAP) for trial NN1250-4300 is based on the final protocol version 4.0 dated 17DEC2020.

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	See ETMF	Not Applicable	Original version
2	See ETMF	Flowchart removed	Flowchart should not be included

1 Introduction

1.1 Objectives and endpoints

1.1.1 Objectives

Primary objective

To compare the effect on glycaemic control of IDeg once daily (OD) plus IAsp 2-4 times daily with meals and IDet OD or twice daily (BID) plus IAsp 2-4 times daily with meals in a population of pregnant women with T1DM.

Secondary objectives

- To compare the effect on maternal safety of IDeg OD plus IAsp 2-4 times daily with meals and IDet OD/BID plus IAsp 2-4 times daily with meals in a population of pregnant women with T1DM.
- To compare the effect on pregnancy outcome of IDeg OD plus IAsp 2-4 times daily with meals and IDet OD/BID plus IAsp 2-4 times daily with meals in a population of pregnant women with T1DM.

1.1.2 Endpoints

1.1.2.1 Primary endpoint

Last planned HbA_{1c} prior to delivery after gestational week (GW) 16.

This primary endpoint was chosen as it was not considered feasible to collect an HbA_{1c} sample at delivery. Therefore, the primary endpoint is evaluated at last planned visit prior to delivery after GW 16. Gestational week 16 has been chosen as the earliest assessment of the primary endpoint, as some subjects, e.g. those randomised as pregnant, may not attend a site visit prior to GW 16.

1.1.2.2 Secondary endpoints

Supportive secondary endpoints

Supportive maternal efficacy endpoints

- $HbA_{1c} \leq 6.0\%$ (42 mmol/mol) from last planned HbA_{1c} prior to delivery after GW 16 (yes/no)
- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) from last planned HbA_{1c} prior to delivery after GW 16 (yes/no)
- Last planned average post-prandial glucose (PPG) prior to delivery after GW 16
    - Average of three main meals

- Last planned fasting plasma glucose (FPG) prior to delivery after GW 16

Supportive maternal safety endpoints

The pregnancy period is defined as the period from the first day of pregnancy (date of conception) or randomisation (whichever comes last) to the date of delivery. The first day of pregnancy is calculated from the estimated gestational age from the ultrasound scan made before or at randomisation (visit 2) for subjects randomised pregnant and before or at visit 55 for subjects randomised non-pregnant and becoming pregnant in the conception period of the trial. For subjects with delivery prior to the ultrasound scan, the first day of pregnancy is determined by the investigator based on the estimated gestational age at time of delivery.

Two different baselines will be applied; a treatment baseline and a pregnancy baseline. For all subjects the treatment baseline is defined as the latest available measurement at or before randomisation (visit 2). For subjects randomised pregnant the pregnancy baseline is derived from the treatment baseline, and the two baseline values will be identical. For subjects randomised non-pregnant and becoming pregnant in the conception period of the trial, the pregnancy baseline corresponds to data from visit 55.

- Number of hypoglycaemic episodes during the pregnancy period (from first day of pregnancy (date of conception) or randomisation (whichever comes last) to delivery)

- Development of sight-threatening retinopathy defined as proliferative retinopathy or maculopathy from treatment baseline as well as from pregnancy baseline to the end of treatment visit (yes/no)

- Number of adverse events during the pregnancy period (from first day of pregnancy (date of conception) or randomisation (whichever comes last) to delivery)

- Pre-eclampsia defined as new-onset hypertension (blood pressure $\geq$ 140 mmHg systolic or $\geq$ 90 mmHg diastolic, based on at least 2 measurements taken at least 4 hours apart) occurring from GW 20 to delivery and simultaneous proteinuria (defined as $\geq$ 300 mg protein in a 24 hours urine sample, a protein-to-creatinine ratio of $\geq$ 300 mg/g in a urine sample or a urine dipstick protein of 1+) or presence of eclampsia, HELLP syndrome, or other severe organ involvement (yes/no)

- Mode of delivery, e.g. vaginal, operative vaginal, planned caesarean section or unplanned caesarean section, induced or spontaneous delivery

- Change in body weight from pregnancy baseline to last planned visit before delivery (kg)

Supportive pregnancy outcome endpoints

- Birth weight (g)
- Pre-term delivery (delivery < 37 completed GWs) (yes/no)
- Early foetal death (delivery < 20 completed GWs) (yes/no)
- Perinatal mortality (death of foetus/infant between ≥ 20 completed GWs before delivery and < 7 completed days after delivery) (yes/no)
- Neonatal mortality (death of infant between ≥ 7 completed days after delivery and < 28 completed days after delivery) (yes/no)
- Presence of major abnormalities (classified according to EUROCAT) (yes/no)
- Live born infants (yes/no)
- Number of adverse events in the infant from day of delivery to final follow-up
- Neonatal hypoglycaemic episodes defined as plasma glucose ≤ 1.7 mmol/L (31 mg/dL) during the first 24 hours after birth or ≤ 2.5 mmol/L (45 mg/dL) between 24 hours and 48 hours after birth (yes/no)

1.1.2.3 Exploratory endpoints

Cord blood IDeg levels in live born infants.

1.1.2.4 Other assessments

- Change in clinical evaluations from treatment baseline as well as from pregnancy baseline to the end of treatment visit in terms of:
  - Vital signs (including blood pressure and pulse)
  - Physical examinations
- Change in central laboratory assessments from treatment baseline as well as from pregnancy baseline to the end of treatment in terms of:
  - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, leucocytes)
  - Biochemistry (creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), sodium, potassium, albumin, total bilirubin)
- Basal insulin dose from pregnancy baseline to the end of treatment visit

1.2 Trial design

- Trial population :

  Number of subjects planned to be screened: 306

  Number of subjects planned to be randomised: 214

  It is expected that approximately ⅓ of the subjects are to be randomised as non-pregnant and ⅔ of the subjects are to be randomised as pregnant.

- Trial phase : 3b

- Trial design :This is a randomised (1:1), open-label, parallel, multi-centre, multi-national, treat-to-target (TTT), comparing the effect and safety of IDeg OD plus IAsp 2-4 times daily with meals with IDet OD/BID plus IAsp 2-4 times daily with meals in pregnant women with T1DM.

- Subjects will be randomised either non-pregnant with the intention to become pregnant or pregnant from GW 8-13 + 6 days.

- Stratification : Randomisation will be stratified according to the pregnancy status at time of randomisation as well as planned continued use of the subject's own continuous glucose monitoring (CGM) device.

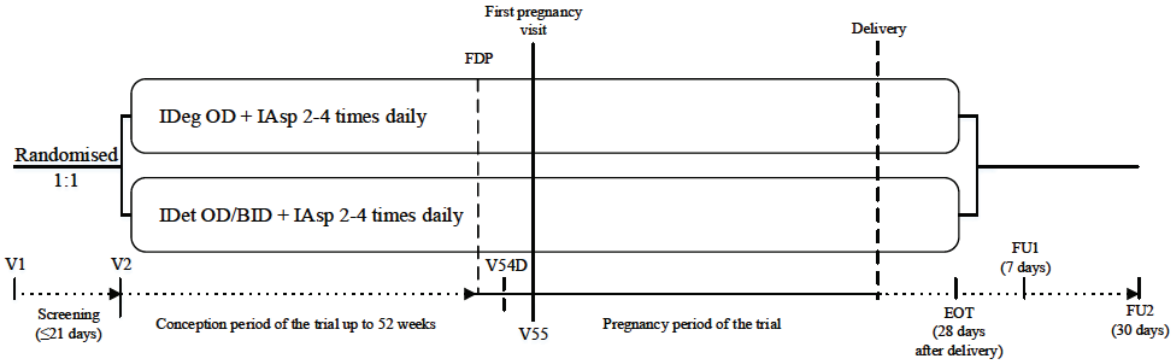
- Treatment : Eligible subjects will be randomised 1:1 in an open-label manner to one of the below treatment regimens:

    - IDeg OD + IAsp 2-4 times daily with meals, or
    - IDet OD/BID + IAsp 2-4 times daily with meals

- Trial duration : The duration of the trial depends on the time of conception relative to the time of enrolment and delivery as summarised schematically in Figure 1–1 and Figure 1–2. The total trial duration for the subject will depend on whether the subject is randomised non-pregnant or pregnant and will be maximum 25 months as summarised in Table 1–1.

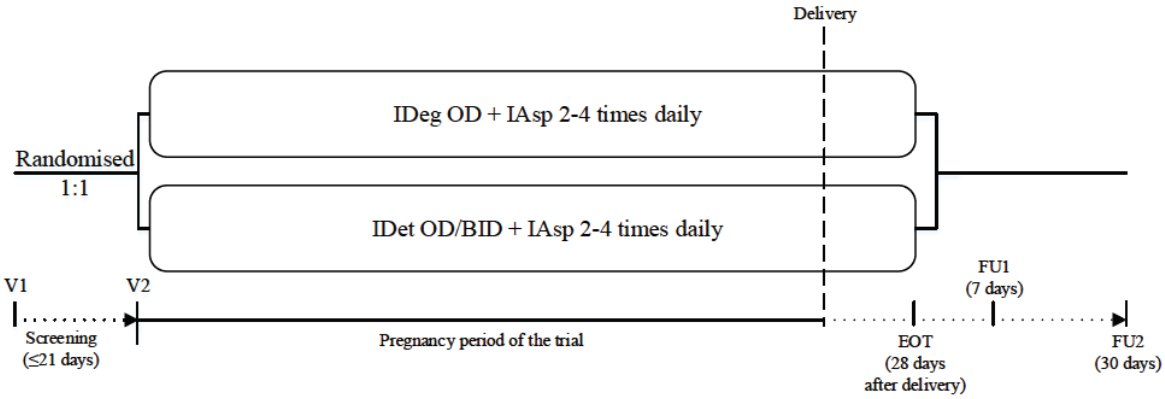
Table 1–1 Trial duration for subjects

Period	Non-pregnant subjects	Pregnant subjects
Screening	V1, up to three weeks before randomisation	
Randomisation	V2	
Treatment	Up to 53 weeks for conception. If the subject becomes pregnant, trial treatment furthermore continues throughout the pregnancy until end of treatment 28 days after delivery. If the subject does not become pregnant end of treatment will be 7 days after V54.	Throughout the pregnancy period. Trial treatment continues until end of treatment 28 days after delivery.
Follow-up period	The trial will end with two follow-up contacts (P91 and V92) 7 and 30 days after end of treatment respectively.	



If the subject becomes pregnant at any time during the 52 weeks conception period of the trial, their next visit will be the V54D visit (if applicable) or V55 visit. If the subject does not become pregnant in the conception period of the trial, the EOT visit will be completed 1 week after V54. Abbreviations: IDeg = insulin degludec, IDet = insulin detemir, IAsp = insulin aspart, OD = once daily, BID = twice daily, FDP = first day of pregnancy, V55 = pregnancy baseline visit, EOT = end of treatment (V90), FU1/FU2 = follow-up contacts 1 (P91) and 2 (V92).

Figure 1–1 Trial design for subjects who are non-pregnant at randomisation.



Abbreviations: IDeg = insulin degludec, IDet = insulin detemir, IAsp = insulin aspart, OD = once daily, BID = twice daily, V2 = pregnancy baseline visit, EOT = end of treatment (V90), FU1/FU2 = follow-up contacts 1 (P91) and 2 (V92).

Figure 1–2 Trial design for subjects who are pregnant at randomisation.

Further details are described in the protocol section 5.

2 Statistical hypotheses

Formally, let D be the mean treatment difference (IDeg-IDet) in 'Last planned HbA1c prior to delivery after GW 16'. The null-hypothesis of IDeg being inferior by 0.4% or more will be tested against the alternative hypothesis of NI (IDeg inferior by less than the NI-limit) as given by:

$$H_0: D \geq 0.4\% \text{ against } H_A: D < 0.4\%$$

Non-inferiority will be considered confirmed if the upper bound of the two-sided 95% CI for D (mean treatment difference in HbA1c) is strictly below 0.4%. This is equivalent to using a one-sided test of size 2.5%.

3 Sample size determination

Refer protocol section 17.1.

4 Analysis sets

Table 4–1 Overview of subject analysis sets

Subject Analysis Set	Description
Full analysis set for all women (FAS_{all})	Includes all randomised women. Subjects in the FAS_{all} will contribute to the evaluation "as randomised".
Safety analysis set for all women (SAS_{all}):	Includes all randomised women exposed to at least one dose of trial product. Subjects in the SAS_{all} will contribute to the evaluation "as treated".

Table 4–2 Overview of defined analysis sets

Defined Analysis Set	Description
Full analysis set for pregnant women ($FAS_{pregnant}$)	Includes all randomised women who are pregnant during the trial. Subjects in the $FAS_{pregnant}$ will contribute to the evaluation "as randomised".
Per protocol analysis set for pregnant women ($PP_{pregnant}$)	Includes subjects from $FAS_{pregnant}$ who: • Have not violated any inclusion criteria • Have not fulfilled any exclusion criteria • Are exposed to trial drug at least the first four weeks after randomisation or, in case of termination of pregnancy within the first four weeks after randomisation, until time of termination of pregnancy. Subjects in the $PP_{pregnant}$ analysis set will contribute to the analysis according to the treatment received prior to potential discontinuation of randomised treatment. This will be referred to as contributing to the evaluation "as treated".
Safety analysis set for pregnant women ($SAS_{pregnant}$)	Includes all randomised women exposed to at least one dose of trial product and who are pregnant during the trial. Subjects in the $SAS_{pregnant}$ will contribute to the evaluation "as treated".

The primary endpoint and secondary efficacy endpoints are analysed using full analysis set for all pregnant women.

Table 4–3 Overview of defined data selections and observation periods

Defined data selections or observation periods	Description
In-trial	This represents the time period where subjects are considered to be in the trial, regardless of discontinuation of trial product. The in-trial observation period starts at randomisation and ends at trial completion. The date of trial completion is the date of the final scheduled follow-up visit V92. For subjects not attending the follow-up visit V92, the date of trial completion will be the date of the last subject-investigator contact.
On-treatment	This represents the time period where subjects are considered treated with the trial product. It is a subset of the in-trial observation period, starting at the date of first dose of trial product and ending at the date of the last day on trial product.
Pregnancy period	It is defined as the period from first day of pregnancy (date of conception corresponding to the first day in GW 2) or randomisation (whichever comes last) to the date of delivery. The first day of pregnancy is based on the estimated gestational age from the US scan made before or at randomisation (visit 2) for subjects randomised pregnant and before or at visit 55 for subjects randomised non-pregnant and becoming pregnant in the conception period of the trial. For subjects with delivery prior to the US scan the first day of pregnancy is determined by the investigator based on the estimated gestational age at the time of delivery.
Pre-pregnancy period	It is defined for subjects randomised as non-pregnant. The period starts at randomisation (visit 2). Two different end-dates will be defined. For subjects who become pregnant the period ends at the day prior to first day of pregnancy. For subjects who do not become pregnant during the trial, the period ends at the same time as the in-trial period.
Post-pregnancy period	This starts the day after the delivery and ends at the same time as the in-trial period.

The above definitions form the basis for combinations of periods. The on-treatment pregnancy period is e.g. the intersection between the on-treatment period and the pregnancy period.

5 Statistical analyses

5.1 General considerations

Results from a statistical analysis will at a minimum be presented by the estimated treatment contrasts for the comparison between IDeg and IDet with associated two-sided 95% confidence intervals (CI) and p-values corresponding to two-sided tests of no difference.

Non-inferiority will be considered confirmed if the upper bound of the CI is strictly below 0.4%. The p-value corresponding to a two-sided test of no difference will also be reported.

The full analysis set for all pregnant women (**$FAS_{pregnant}$**) who contribute to the analysis will be used in the analysis of efficacy endpoints. For further details of how the subjects will be determined whether they contribute to the statistical analysis or not refer to 6.3.1.1. For the safety endpoints, the safety analysis set for all pregnant women (**$SAS_{pregnant}$**) will be used. The definition of analysis sets are given in section 4.

The treatment baseline value will be used in the statistical models and is defined as the latest available measurement at or before randomisation. For all subjects the treatment baseline value hence corresponds to the value obtained at the randomisation visit (visit 2) if available, or at the screening visit (visit 1). If neither of these measurements have been obtained the treatment baseline will be left missing. For subjects randomised pregnant the pregnancy baseline is derived from the treatment baseline, and the two baseline values will be identical, corresponding to the values obtained at visit 2 or visit 1.

When summarising change from baseline for effect and safety variables assessed during or after the pregnancy period, both treatment baseline and pregnancy baseline variables will be applied. First the treatment baseline described above to illustrate changes since initiation of treatment, second the pregnancy baseline to illustrate changes since early pregnancy.

Primary and secondary estimands

Primary estimand ("treatment policy" estimand):

- Treatment difference in last planned HbA_{1c} prior to delivery after GW 16 between IDeg OD plus IAsp 2-4 times daily with meals and IDet OD/BID plus IAsp 2-4 times daily with meals for all randomised pregnant women regardless of actual treatment received.

The primary estimand assesses the average glycaemic difference prior to delivery after GW 16 in a population of pregnant women with T1DM, resulting from initiation of a treatment regimen with IDeg OD plus IAsp 2-4 times daily with meals including potential additional therapy as compared

to initiation of a treatment regimen with IDet OD or BID plus IAsp 2-4 times daily with meals including potential additional therapy. Generalisation of this estimand depends among other things on the extent to which the treatment adherence and the potential use of additional therapy reflect clinical practice, and whether the trial population can be considered a representative sub-sample of the target population.

Secondary estimand ("If all subjects had adhered" estimand):

- Treatment difference in last planned HbA_{1c} prior to delivery after GW 16 between IDeg OD plus IAsp 2-4 times daily with meals and IDet OD/BID plus IAsp 2-4 times daily with meals for all randomised pregnant women if all subjects adhered to treatment.

The secondary estimand assesses the glycaemic benefit a pregnant woman with T1DM is expected to achieve prior to delivery after GW 16 if adhering to a treatment regimen with IDeg OD plus mealtime IAsp as compared to adhering to a treatment regimen with IDet OD or BID plus mealtime IAsp. Generalisation of this estimand depends among other things on the extent to which the compliance to trial product administration in this trial reflects clinical practice. Only data collected prior to discontinuation of trial product will be included in the analysis.

5.2 Subject disposition

Refer TFL of section 14.1.

5.3 Primary endpoint analysis

5.3.1 Definition of primary endpoint

The primary endpoint is the last planned HbA_{1c} prior to delivery after GW 16.

For subjects who have discontinued treatment and where retrieved last planned HbA_{1c} prior to delivery after GW 16 data are not available, it may not be known whether time of delivery is after GW 16. In this case time of delivery will be assumed to be after GW 16 and last planned HbA_{1c} prior to delivery after GW 16 will hence be imputed.

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5.3.2 Main analytical approach

Table 5–1 Estimands under primary analysis

Objective	Estimand category	Estimand			
		Variable/Endpoint	Population of interest	Intercurrent event strategy	Population-Level Summary Measure
Primary Objective: To compare the effect on glycaemic control of IDeg once daily (OD) plus IAsp 2-4 times daily with meals and IDet OD or twice daily (BID) plus IAsp 2-4 times daily with meals in a population of pregnant women with T1DM.	Primary	Last planned HbA_{1c} prior to delivery after gestational week (GW) 16. (Primary endpoint)	Full analysis set for all pregnant women	Treatment policy strategy	Mean difference in the IDeg and IDet arm.
	Secondary	Last planned HbA_{1c} prior to delivery after gestational week (GW) 16. (Primary endpoint)	Full analysis set for all pregnant women	If all subjects had adhered	Mean difference in the IDeg and IDet arm.

5.3.2.1 Analysis of primary estimand

Available data from the in-trial period will be included regardless of whether trial product was discontinued or not.

The multiple imputation approach is done in three steps.

Imputation :

Step 1: Imputation of missing data will be done within four groups of subjects defined by randomised treatment arm and whether or not subjects discontinue treatment. It is hereby assumed that the likely values of what the missing data would have been if available, are best described by information from subjects who at the last scheduled visit prior to delivery are similar in terms of randomised treatment arm and whether or not treatment has been discontinued.

If there are 3 or less retrieved observations among discontinued subjects in a treatment group, it is infeasible to estimate a simple intercept model (including variance) and imputed separately by ontreatment and off-treatment. Instead, on-treatment factors will be included in the models. Hereby, separate means will be estimated for on-treatment and off-treatment observations, while only one joint variance is estimated. In the special case with no subjects off-treatment having HbA1c in one treatment group, an on-treatment factor will not be included in the this group but only in the other group (expecting that this group also has most missing values).

Missing data at the last scheduled visit prior to delivery after GW 16 are for each group imputed in the following steps:
An analysis of covariance (ANCOVA) will be fitted to the observed last values of last HbA1c prior to delivery after GW 16

- For subjects where HbA1c at the last scheduled visit prior to time of delivery is in the on-treatment period, the model will include region and the stratification factor as categorical fixed effects, and a pregnancy status at randomisation-by-baseline HbA1c interaction.
- For subjects where HbA1c at the last scheduled visit prior to time of delivery is not in the on-treatment period, the model will include pregnancy status at randomisation and a pregnancy status at randomisation-by-baseline HbA1c interaction. If this model cannot be fitted in case of very few retrieved observations among discontinued subjects, a model including pregnancy status at randomisation will be applied. If this model cannot be fitted either, a simple model including just the intercept will be fitted instead. If there are 3 or less retrieved observations among discontinued subjects in one or both treatment groups, this step will be skipped.
- With 3 or less retrieved observations among discontinued subjects in one of the treatment groups, the step below replaces the two steps above. For subjects with HbA1c at the last scheduled visit prior to time of delivery, the model will include on-treatment (Yes/No), region and the stratification factor as categorical fixed effects, and a pregnancy status at randomisation-by-baseline HbA1c interaction. In treatment groups having no subjects off-treatment with HbA1c, the on-treatment factor will not be included.

The estimated parameters from the analysis of covariance together with the variances of the estimates will be used to simulate 1000 data sets with imputed last planned HbA1c prior to delivery after GW 16 data for subjects missing these. Each of the 1000 datasets use one set of estimated

mean parameters and estimate of the residual variation. For subjects who have discontinued treatment and where retrieved last planned HbA1c prior to delivery after GW 16 data are not available, it may not be known whether time of delivery is after GW 16. In this case time of delivery will be assumed to be after GW 16 and last planned HbA1c prior to delivery after GW 16 will hence be imputed.

Analysis:
Step 2: For each of the 1000 complete datasets, the mean difference in last planned HbA_{1c} prior to delivery after GW 16 will be analysed in both arms using the main ANCOVA model with treatment, region and the stratification factor as categorical fixed effects and a pregnancy status at randomisation-by-baseline HbA1c interaction.

Pooling:
Step 3: The estimates and standard errors from the 1000 datasets are pooled to one estimate and associated standard errors using Rubin's rule to draw inference. From these pooled estimates the 95% CI for the treatment difference is calculated.

The multiple imputations will be generated using Novo Nordisk trial number 12504300 as seed number.

Table 5-2 Factors and covariates for the main analysis of the primary endpoint for primary estimand

Factors and covariates at baseline	Type	Categories
Randomised treatment	Categorical fixed effect	IDeg, IDet
Region	Categorical fixed effect	Europe (Austria, Denmark, Greece, Ireland, Italy, United Kingdom and Serbia), North America (Canada), South America (Argentina and Brazil) and Asia/Oceania (Australia, Israel and Russia).
Stratification factor	Categorical fixed effect	Randomised as pregnant and planned continuous use of CGM, randomised as pregnant and no planned continuous use of CGM, randomised as non-pregnant and planned continuous use of CGM, randomised as non-pregnant

		and no planned continuous use of CGM
Pregnancy status at randomisation and treatment baseline HbA_{1c}	Interaction factor	Treatment baseline for HbA1c for randomised pregnant , Treatment baseline for HbA1c for randomised non-pregnant

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*Baseline refers to treatment baseline

The categorical fixed effects and interaction factors will be included in the model as main effects in an additive structure.

Non-inferiority will be considered confirmed if the upper bound of the CI is strictly below 0.4%. The p-value corresponding to a two-sided test of no difference will also be reported.

5.3.2.2 Analysis for secondary estimand

The secondary estimand will be estimated based on the FASpregnant using data from the last planned visit prior to delivery after GW 16. Imputation of missing data will now be done within two groups of subjects defined by randomised treatment arm. It is hereby assumed that the likely values of what the missing data would have been if available, are best described by information from subjects who at the last scheduled visit prior to delivery are similar in terms of randomised treatment arm and who have not discontinued treatment.

Missing data at the last scheduled visit prior to delivery after GW 16 are for each group imputed using multiple imputation approach in the following steps:

Data preprocessing:

Step 1 : Data retrieved outside of the on-treatment period will not be used in the analysis, but will be considered missing.

Imputation :

Step 2 : Impute the missing value by fitting enriched ancova model to the observed last values of last HbA_{1c} prior to delivery after GW 16. Imputation was done within randomised treatment arm and model will be fitted with the categorical fixed effects, factor and interaction term in the same order as mentioned in Table 5-3. Similar to the description above for the primary estimand the estimated parameters from the ANCOVA together with the variances of the estimates will be used to simulate 1000 data sets with imputed last planned HbA1c prior to delivery after GW 16 data for subjects missing these.

Analysis:

Step 3 : For each of the 1000 complete datasets, the mean difference in last planned HbA_{1c} prior to delivery after GW 16 will be analysed in both arms using the main ANCOVA model with factors and covariates as mentioned in Table 5-4.

Pooling :

Step 4 : The estimates and standard errors from the 1000 datasets are pooled to one estimate and associated standard errors using Rubin's rule to draw inference. From these pooled estimates the 95% CI for the treatment difference is calculated.

Table 5-3 Factors and Covariate for imputation model for secondary estimand

Factors and covariates	Type	Categories	Order
Region at baseline	Categorical fixed effect	Europe (Austria, Denmark, Greece, Ireland, Italy, United Kingdom and Serbia), North America (Canada), South America (Argentina and Brazil) and Asia/Oceania (Australia, Israel and Russia).	1
Stratification factor at baseline	Categorical fixed effect	Asia, Europe, North America, Oceania	2
Pregnancy status at randomisation, baseline HbA_{1c}	Interaction factor	Not applicable	3

*This imputation will be done within two groups of randomised treatment arms.

**Baseline refers to treatment baseline.

Table 5-4 Factors and covariates for the main analysis for secondary estimand

Factors and covariates at baseline	Type	Categories
Randomised treatment	Categorical fixed effect	IDeg, IDet
Region	Categorical fixed effect	Europe (Austria, Denmark, Greece, Ireland, Italy, United Kingdom and Serbia), North America (Canada), South America (Argentina and Brazil) and Asia/Oceania (Australia, Israel and Russia).

Stratification factor	Categorical fixed effect	Randomised as pregnant and planned continuous use of CGM, randomised as pregnant and no planned continuous use of CGM, randomised as non-pregnant and planned continuous use of CGM, randomised as non-pregnant and no planned continuous use of CGM
Pregnancy status at randomisation and treatment baseline HbA_{1c}	Interaction factor	Treatment baseline for HbA1c for randomised pregnant , Treatment baseline for HbA1c for randomised non-pregnant

.

*Baseline refers to treatment baseline

5.3.3 Sensitivity analysis

To investigate the sensitivity of the primary analysis results, complementary and separate analyses will be performed for the primary and secondary estimand in line with guidelines from EMA47 and the U.S. National Research Council. The evaluation of the robustness of the primary analysis results will be based on approaches using multiple imputations. Similar sensitivity analyses are made for the primary and secondary estimand:

1. A multiple imputation analysis based on the PPpregnant : The analysis is similar to the primary analysis for the primary and secondary estimand, but based on PPpregnant. The analysis investigates the impact of protocol deviations on the primary analysis.

2. A multiple imputation tipping point analysis based on the FASpregnant : In this sensitivity analysis, missing data will first be imputed according to the primary analysis for the primary and secondary estimand. Second, for the IDeg arm a penalty will be added to the imputed values of last planned HbA1c prior to delivery after GW 16. The approach is to gradually increase this penalty by 0.5 until the confirmed HbA1c conclusion from the primary analysis is reversed. The analysis investigates how sensitive the results of the primary analyses for the primary/secondary estimands are towards the assumption that missing data have the same mean level as available data within the groups specified for the imputation.

Table 5-5 Statistical analysis to address primary and secondary objectives

SI No.	Endpoints	Landmark visit	Endpoint type	Imputation approach and Statistical model	Analysis set	Sensitivity analyses
	Primary Endpoint					
1	Last planned HbA_{1c} prior to delivery after GW 16	Last planned visit prior to delivery after GW 16	Continuous	MI ANCOVA	$FAS_{pregnant}$	• MI based on the $PP_{pregnant}$ • MI tipping point analysis based on the $FAS_{pregnant}$
	Secondary Endpoint					
1	$HbA_{1c} \leq$ 6.0% (42 mmol/mol) from last planned HbA_{1c} prior to delivery after GW 16 (yes/no)	Last planned visit prior to delivery after GW 16	Categorical	MI Logistic regression	$FAS_{pregnant}$	NA
2	$HbA_{1c} \leq$ 6.5% (48 mmol/mol) from last planned HbA_{1c} prior to delivery after GW 16 (yes/no)	Last planned visit prior to delivery after GW 16	Categorical	MI Logistic regression	$FAS_{pregnant}$	NA
3	Last planned average PPG prior to delivery after GW 16	Last planned visit prior to delivery after GW 16	Continuous	MI ANCOVA	$FAS_{pregnant}$	NA
4	Last planned FPG prior to delivery after GW 16	Last planned visit prior to delivery after GW 16	Continuous	MI ANCOVA	$FAS_{pregnant}$	NA

5.4 Secondary endpoints analysis

5.4.1 Efficacy endpoints

5.4.1.1 Supportive secondary endpoints

The supportive secondary endpoints will be evaluated for:

- The primary estimand based on $FAS_{pregnant}$ using the in-trial data
- The secondary estimand based on $FAS_{pregnant}$ using the on-treatment data

No sensitivity analyses are planned for these.

Supportive maternal binary efficacy endpoints

- $HbA_{1c} \leq 6.0\%$ (42 mmol/mol) from last planned HbA_{1c} prior to delivery after GW 16 (yes/no)
- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) from last planned HbA_{1c} prior to delivery after GW 16 (yes/no)

For both estimands missing data for the responses of the above binary endpoints will be obtained from dichotomizing imputed values of HbA1c. Hence, 1000 imputed datasets simulated as for the primary analyses of the primary and secondary estimand for HbA1c, respectively, will be applied in the corresponding analyses of the dichotomized endpoints. The imputed complete data sets will be analysed using a logistic regression model with treatment, stratification factor and region as categorical fixed effects and a pregnancy status at randomisation-by-baseline HbA1c interaction. Inference comparing treatments will be drawn using Rubin's rule. The odds ratio between IDeg and IDet will be estimated together with the corresponding two-sided 95% CI. The p-value corresponding to a two-sided test of no difference (odds ratio equal to 1) will be reported.

Supportive maternal continuous efficacy endpoints

- Last planned average PPG prior to delivery after GW 16
  - Average of three main meals
- Last planned FPG prior to delivery after GW 16

Average PPG is defined as the average of the available BG measurements 90 minutes after breakfast, lunch and main evening meal respectively. If all 3 measurements are missing the average PPG is missing. Subjects with missing average PPG at baseline are excluded from the PPG analysis and subjects with missing FPG at baseline are excluded from the FPG analysis. The above continuous endpoints will be analysed using similar modelling approaches as for the primary endpoint with the associated baseline response as a covariate.

5.4.2 Safety endpoints

5.4.2.1 Maternal safety endpoints

Maternal safety endpoints assessed during and after the pregnancy period

Summaries will be based on $SAS_{pregnant}$ unless otherwise specified.

Table 5-6 Analysis of supportive maternal safety endpoint

Endpoint	Endpoint type	Analysis method	Analysis set	Further information
Number of hypoglycaemic episodes by classification	Discrete	Summary by treatment arm separately for randomised pregnant and randomised non-pregnant *	$SAS_{pregnant}$	Refer to protocol section 17.4.2.1 For completeness we have also presented a summary based on full analysis set (in-trial data)
Development of sight-threatening retinopathy from treatment baseline as well as from pregnancy baseline to the end of treatment visit	Categorical	Summary by treatment arm separately for randomised pregnant and randomised non-pregnant (Shift table)	SASpregnant	Refer to protocol section 17.4.2.2
Pre-eclampsia	Discrete	Summary by treatment arm separately for randomised pregnant and randomised non-pregnant *	$SAS_{pregnant}$	Refer to protocol section 17.4.2.2
Mode of delivery	Discrete	Summary by treatment arm separately for randomised pregnant and randomised non-pregnant	$SAS_{pregnant}$	Refer to protocol section 17.4.2.2
Change in body weight from pregnancy baseline to last	Continuous	Summary by treatment arm and visits separately for randomised pregnant	$SAS_{pregnant}$	Refer to protocol section 17.4.2.2

planned visit before delivery		and randomised non-pregnant		For completeness we have also presented a summary of change from treatment baseline for randomised non-pregnant subjects.
Number of adverse events during pregnancy period.	Discrete	Summary by treatment arm*	$SAS_{pregnant}$	

*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) will be presented.

Endpoint	**Analysis method**	**Analysis set**	**Further information**

Number of adverse events during pregnancy period.	Summary by treatment arm*	$SAS_{pregnant}$	• Summaries of TEAEs and of serious TEAEs will be presented as an overview including all TEAEs, serious TEAEs, TEAEs by severity, TEAEs by relation to treatment and TEAEs leading to treatment discontinuation or withdrawal.
			• Summary tables based on system organ class and preferred terms are made for:
			  • All TEAEs
			  • Serious TEAEs
			  • TEAEs possibly or probably related to trial product
			  • Severe, moderate and mild TEAEs
			  • TEAEs with preferred term that are experienced by at least 5% of

			the subjects in any treatment or by at least 5% of all subjects • Summary tables of all SAEs including non-treatment emergent SAEs will be presented including summary tables based on system organ class and preferred terms.

For further reference on adverse events endpoint related analysis refer to protocol section 17.4.2.2

5.4.3 Pregnancy outcome endpoints

As the following pregnancy outcome endpoints have to be summarised for all infants or foetuses, these will be summarised for the full analysis set for all pregnant women.

Supportive continuous and binary pregnancy outcome endpoints :

- Birth weight (g)
- Birth weight SD-score
- Live born infants with birth weight < 10^{th} percentile for gestational age and sex (local references) (yes/no)
- Live born infants with birth weight > 90^{th} percentile for gestational age and sex (local references) (yes/no)
- Pre-term delivery (delivery < 37 completed GWs) (yes/no)
- Early foetal death (delivery < 20 completed GWs) (yes/no)
- Perinatal mortality (death of foetus/infant between ≥ 20 completed GWs before delivery and < 1 completed week after delivery) (yes/no)
- Neonatal mortality (death of infant between ≥ 7 completed days after delivery and < 28 completed days after delivery) (yes/no)
- Presence of major abnormalities (classified according to EUROCAT) (yes/no) : This endpoint refers to the categorisation determined by the adjudication committee.
- Neonatal hypoglycaemic episodes defined as plasma glucose ≤ 1.7 mmol/L (31 mg/dL) during the first 24 hours after birth or ≤ 2.5 mmol/L (45 mg/dL) between 24 hours and 48 hours after birth (yes/no)

The endpoints will be summarised by treatment arm for all infants and further sub-divided in the following groups:

- Mother randomised as pregnant
- Mother randomised as pregnant and exposed to trial drug at some point during the pregnancy period
- Mother randomised as pregnant and not exposed to trial drug at any point during the pregnancy period
- Mother randomised as non-pregnant
- Mother randomised as non-pregnant and exposed to trial drug at some point during the pregnancy period
- Mother randomised as non-pregnant and not exposed to trial drug at any point during the pregnancy period

For the above mentioned endpoints summary statistics will be provided. Instead of summarising only as (yes/no) categories some endpoints will be categorised into (yes/no/Unaddressed) categories where 'Unaddressed' refer to cases where the parents did not consent to share information after delivery or did not complete the pregnancy outcome form and to withdrawn subjects who did not give any further information.

Adverse events in the infants from delivery to final follow-up

This endpoint will be summarised for infants related to safety analysis set for pregnant women.

It is unknown whether adverse events on the day of delivery occurred before or after the actual delivery, as exact times were not collected. Adverse events and deliveries on either side of midnight could also be coherent. Therefore, adverse events from 1 calendar day before delivery to final follow-up are included.

Adverse events will be coded using the most recent version of the MedDRA database.

Adverse events will be summarised descriptively for all infants and additionally sub-divided in the following groups:

- Mother randomised as pregnant
- Mother randomised as pregnant and exposed to trial drug at some point during the pregnancy period

- Mother randomised as pregnant and not exposed to trial drug at some point during the pregnancy period
- Mother randomised as non-pregnant
- Mother randomised as non-pregnant and exposed to trial drug at some point during the pregnancy period
- Mother randomised as non-pregnant and not exposed to trial drug at any point during the pregnancy period

The summaries will display the number of infants with at least one event (N), the percentage of infants with at least one event (%) and the number of events (E). Summaries will be presented as an overview including all AEs, serious AEs, AEs by severity and AEs by relation to treatment.

Furthermore, summary tables based on system organ class and preferred terms are made for:

- All AEs
- SAEs
- AEs possibly or probably related to trial product
- Severe, moderate and mild AEs
- AEs with preferred term that are experienced by at least 5% of the infants in any treatment or by at least 5% of all infants

5.5 Safety endpoints analysis

Not applicable

5.6 Exploratory endpoint and other assessments analysis

The exploratory endpoint listed in Section 1.1.2.3 and other assessments listed in Section 1.1.2.4 will be presented as per summary statistics.

For other assessments the summary statistics will be presented for safety analysis set pregnant.

5.7 Interim analyses

No interim analysis is planned for the efficacy data in this trial.

5.7.1 Data monitoring committee

Refer to protocol section 12.7.2.

6 Supporting documentation

6.1 Appendix 1 List of abbreviations

AE	*adverse event*
ALT	*alanine aminotransferase*
AP	*alkaline phosphatase*
AST	*aspartate aminotransferase*
BG	*blood glucose*
BID	*bis in die (twice daily)*
CGM	*continuous glucose monitoring (including flash glucose monitoring)*
CI	*confidence interval*
EAC	*event adjudication committee*
eCRF	*electronic case report form*
EMA	*European Medicines Agency*
EudraCT	*European Clinical Trials Database*
EUROCAT	*European Concerted Action on Congenital Anomalies and Twins*
FAS	*full analysis set*
FPG	*fasting plasma glucose*
GW	*gestational week*
HbA_{1c}	*glycosylated haemoglobin*
hCG	*human chorionic gonadotropin*
HELLP	*haemolysis, elevated liver enzymes, low platelet count*
IAsp	*insulin aspart*
ICH	*International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*
IDeg	*insulin degludec*
IDet	*insulin detemir*
IMP	*investigational medicinal product*
MedDRA	*Medical Dictionary for Regulatory Activities*
OD	*once daily*

PE	*pre-eclampsia*
PG	*plasma glucose*
PP	*per protocol*
PPG	*post-prandial glucose*
SAE	*serious adverse event*
SAP	*statistical analysis plan*
SD	*standard deviation*
SmPC	*summary of product characteristics*
T1DM	*type 1 diabetes mellitus*
TTT	*treat-to-target*
US	*ultrasound*
UTN	*Universal Trial Number*

6.2 Appendix 2: Changes to protocol-planned analyses

In this SAP the following changes are being made to the statistical consideration in the protocol are as elaborated below for :

6.2.1 Maternal safety endpoints

Pre-eclampsia

For Pre-eclampsia summary, the number and percentage of subjects experiencing PE as well as the event rate per 100 years of observation will be displayed.

6.2.2 Pregnancy outcome endpoints

- Birth weight of infants will be summarised in 'g' (grams) instead of kg
- It is unknown whether adverse events on the day of delivery occurred before or after the actual delivery, as exact times were not collected. Adverse events and deliveries on either side of midnight could also be coherent. Therefore, adverse events from 1 calendar day before delivery to final follow-up are included.
- Instead of summarising only as (yes/no) categories some endpoints will be categorised into (yes/no/Unaddressed) categories where 'Unaddressed' refer to the cases where either the parents of the infant have not given consent to share information after delivery or the subjects who were withdrawn from trial and they did not give any further information or if the subjects did not fill the pregnancy outcome form.

6.3 Appendix 3: Definition and calculation of endpoints, assessments and derivations

6.3.1 Endpoint derivations and assessments

6.3.1.1 Steps involved in defining last planned visit prior to delivery after GW 16 (LPVISPDL) :

The 188 subjects who were in full analysis set for pregnant women only qualify for the statistical analysis , hence LPVISPDL will be defined for only these subjects.

Step 1: Subjects delivering before GW16 is excluded from the analysis and LPVISPDL is not defined

Step 2: For subjects with visit 79 as the last site visit, LPVISPDL is set to 79.

Step 3: For subjects with visit 59, 63, 67, 71, or 75 as the last site visit prior to delivery the following is done:

- If the difference of the visit date and the delivery date was ≤ 35 days (28 days between scheduled site visits + 7 days visit window = 35 days), LPVISPDL is set to the last visit.

- If the difference of the visit date and the delivery date was > 35 days, LPVISPDL is set to the following planned site visit 4 weeks later.

Step 4: For subjects registered to miss site visit 79 due to the Covid-19 pandemic, LPVISPDL is set to 79.

Step 5: For subjects withdrawing from trial before GW16 without further information, delivery is assumed to be after GW16 and LPVISPDL is set to 79.

Hence, data assessed at the planned visit prior to delivery will be used in the analysis, provided the visit corresponds to the visit on or after GW 16.

7 References

1. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6 (R1), Step 4. 10 June 1996.

2. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Guideline for Statistical principle for clinical trials Step 4. 5 February 1998.