Cover Page for Protocol

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
Document date*	31 May 2021

*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.

16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

Protocol

EXPECT
Trial ID: NN1250-4300

Updated protocol including:
Protocol, final version 1.0 dated 24 May 2017
Global Amendment no. 1, version 1.0 dated 23 February 2018
Global Amendment no. 3, version 1.0 dated 03 May 2019
Global Amendment no. 4, version 1.0 dated 17 December 2020

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

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AP	alkaline phosphatase
APGAR	appearance, pulse, grimace, activity, respiration
AST	aspartate aminotransferase
BG	blood glucose
BID	*bis in die* (twice daily)
BP	blood pressure
CCDS	company core data sheet
CGM	continuous glucose monitoring (including flash glucose monitoring)
CI	confidence interval
CLAE	clinical laboratory adverse event
CTR	clinical trial report
DFU	direction for use
DMC	data monitoring committee
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
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
FDA	U.S. Food and Drug Administration
FPG	fasting plasma glucose
FSFV	first subject first visit
GCP	Good Clinical Practice
GW	gestational week
HbA_{1c}	glycosylated haemoglobin
hCG	human chorionic gonadotropin
HDL	high-density lipoprotein
HELLP	haemolysis, elevated liver enzymes, low platelet count
IAsp	insulin aspart

IB	investigator's brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IDeg	insulin degludec
IDet	insulin detemir
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
LSFV	last subject first visit
LSLV	last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
OD	once daily
PCD	primary completion date
PE	pre-eclampsia
PG	plasma glucose
PP	per protocol
PPG	post-prandial glucose
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
SD	standard deviation
SIF	safety information form
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
TMM	trial materials manual
TTT	treat-to-target
US	ultrasound
UTN	Universal Trial Number

Glossary

Congenital anomaly	A morphological, functional and/or biochemical developmental disturbance in the embryo or foetus whether detected at birth or not. The term congenital anomaly is broad and includes congenital abnormalities, foetopathies, genetic diseases with early onset, developmental delay, etc.
Date of conception	Formation of a viable zygote by the union of the male sperm and female ovum; fertilization. Typically occurs about 11-21 days after the first day of the last period.
Delivery	The visit in which the end of the pregnancy takes place, including live birth, foetal death or termination of pregnancy.
Early foetal death	The death of a foetus < 20 completed gestational weeks.
Ectopic pregnancy	Extrauterine pregnancy, early foetal death, most often in the fallopian tube.
Foetus	Unborn offspring from the embryo stage (> 8 completed gestational weeks) until delivery.
HELLP syndrome	Obstetric complication usually considered a variant or complication of pre-eclampsia (abbreviation for: **H**aemolysis, **E**levated **L**iver enzymes, **L**ow **P**latelet count).
Infant	Infant from delivery until the end of the first year of life.
Macrosomia	Birth weight above a defined limit at any gestational age.
Major abnormalities	A life threatening structural anomaly or one likely to cause significant impairment of health or functional capacity and which needs medical or surgical treatment.
Minor anomalies	Relatively frequent structural anomaly not likely to cause any medical or cosmetic problems.
Neonatal mortality	Death of an infant between 7 days and 28 completed days after delivery.
Perinatal mortality	Death of a foetus/infant between ≥ 20 completed gestational weeks and < 7 completed days after delivery.
Planned caesarean section	A caesarean section which has been planned > 8 hours prior to delivery.
Postpartum	The period beginning immediately after delivery and extending for about six weeks.
Pregnancy outcome	The outcome of the pregnancy which includes three main categories: foetal death, termination of pregnancy, and live birth.
Pre-term delivery	Delivery < 37 completed gestational weeks.
Termination of pregnancy (induced/elective abortion)	Artificial interruption of pregnancy.
Unplanned caesarean section	A caesarean section which has not been planned or planned ≤ 8 hours prior to delivery.

1 Summary

Objective(s) and endpoint(s)

Primary objective

To compare the effect on glycaemic control of insulin degludec once daily plus insulin aspart 2-4 times daily with meals and insulin detemir once daily or twice daily plus insulin aspart 2-4 times daily with meals in a population of pregnant women with type 1 diabetes mellitus.

Secondary objectives

To compare the effect on maternal safety of insulin degludec once daily plus insulin aspart 2-4 times daily with meals and insulin detemir once daily or twice daily plus insulin aspart 2-4 times daily with meals in a population of pregnant women with type 1 diabetes mellitus.

To compare the effect on pregnancy outcome of insulin degludec once daily plus insulin aspart 2-4 times daily with meals and insulin detemir once daily or twice daily plus insulin aspart 2-4 times daily with meals in a population of pregnant women with type 1 diabetes mellitus.

Primary endpoint

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

Key secondary endpoints

Supportive maternal efficacy endpoints

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

Supportive maternal safety endpoints

- 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 gestational week 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).

Supportive pregnancy outcome endpoints

- Birth weight (kg).
- Pre-term delivery (delivery < 37 completed gestational weeks) (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 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).

Trial design

This is a randomised (1:1), open-label, parallel, multi-centre, multi-national, treat-to-target, active controlled trial comparing the effect and safety of insulin degludec once daily with insulin detemir once daily or twice daily both in combination with insulin aspart 2-4 times daily with meals in pregnant women with type 1 diabetes mellitus.

Eligible subjects will be randomised either non-pregnant with the intention to become pregnant or pregnant from gestational week 8-13 (+ 6 days). The total trial duration for subjects will depend on whether subject is randomised non-pregnant or pregnant and be maximum 25 months.

Trial population

It is planned to randomise a total of 214 subjects.

Key inclusion criteria

- Female, age ≥ 18 years at the time of signing informed consent.
- Diagnosed with type 1 diabetes mellitus ≥ 1 year prior to the day of screening.
- Treated with multiple daily subcutaneous insulin injections or continuous subcutaneous insulin infusion (CSII) or inhaled insulin ≥ 90 days prior to the day of screening.
- The subject is planning to become pregnant within 12 months from randomisation and willing to undertake pre-pregnancy counselling *or* the subject is pregnant with an intrauterine singleton living foetus (gestational week 8 to 13 (+6 days)) without any observed anomalies at randomisation, confirmed by an ultrasound scan.
- HbA_{1c} at screening ≤ 8.0% (64 mmol/mol) by central laboratory.

Key exclusion criteria

- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening.
- Pregnant and having proteinuria as evaluated by urine protein-to-creatinine ratio ≥ 300 mg/g in urine sample measured at screening.
- Subject being treated or became pregnant with assistance of *in vitro* fertilisation or other medical infertility treatment.

- Receipt of any concomitant medication contraindicated in pregnancy according to local label within 28 days before screening and between screening and randomisation for non-pregnant subjects and 28 days before conception and between conception and randomisation for pregnant subjects.
- Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or pharmacologically dilated fundoscopy performed within the past 90 days prior to randomisation for non-pregnant subjects or within 28 days prior to randomisation for pregnant subjects.
- History of severe hyperemesis gravidarum (requiring hospitalisation).

Key assessments

- HbA_{1c} (central laboratory)
- Hypoglycaemic episodes
- Adverse events during the pregnancy period
- Adverse events in the foetus and infant

Trial products

Investigational medicinal products:

- Test product: insulin degludec 100 U/mL (Tresiba® [Tregludec® in Israel]), 3 mL PDS290 pen injector (FlexTouch®) for subcutaneous injection.
- Reference therapy: insulin detemir 100 U/mL (Levemir®), 3 mL pre-filled pen (FlexPen®) for subcutaneous injection.
- Other medicinal products: insulin aspart 100 U/mL (NovoRapid®), 3 mL pre-filled pen (FlexPen®) for subcutaneous injection.

2 Flowchart

2.1 Trial flowchart for site visits in the conception period of the trial

	Screening	Randomisation	Non-pregnant/conception period of the trial													End of treatment and follow-up			Premature discontinuation			Additional visit
Site visits (V)	V1	V2	V6	V10	V14	V18	V22	V26	V30	V34	V38	V42	V46	V50	V54	V90 EOT	FU1[a]	V92 FU2	V90A EOT-A	FU1-A[a]	V92A FU2-A	V54D[b]
Weekly phone contact number (P). For details see Section 2.2		P3 P4 P5	P7 P8 P9	P11 P12 P13	P15 P16 P17	P19 P20 P21	P23 P24 P25	P27 P28 P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48 P49	P51 P52 P53			P91			P91A		P54A – P54G
Timing of visit (weeks), d (days)	-21d	0	4	8	12	16	20	24	28	32	36	40	44	48	52	53	EOT +7d	EOT +30d	--	EOT-A +7d	EOT-A +30d	--
Visit window (days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±3	+5	+5		+5	+5	±7
SUBJECT RELATED INFORMATION AND ASSESSMENTS																						
Informed consent	X																					
Inclusion/exclusion criteria	X	X																				
Randomisation		X																				
Premature discontinuation criteria[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X							X
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography	X																					
Medical history/concomitant illness	X																					
Obstetric history	X																					
Diabetes history	X																					
Hypoglycaemia Unawareness	X																					
Baseline hypoglycaemia questionnaire	X																					
Concomitant medication (diabetes)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication (other)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X

	Screening	Randomisation	Non-pregnant/conception period of the trial													End of treatment and follow-up			Premature discontinuation			Additional visit
Site visits (V)	V1	V2	V6	V10	V14	V18	V22	V26	V30	V34	V38	V42	V46	V50	V54	V90 EOT	FU1[a]	V92 FU2	V90A EOT-A	FU1-A[a]	V92A FU2-A	V54D[b]
Weekly phone contact number (P). For details see Section 2.2		P3 P4 P5	P7 P8 P9	P11 P12 P13	P15 P16 P17	P19 P20 P21	P23 P24 P25	P27 P28 P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48 P49	P51 P52 P53			P91			P91A		P54A – P54G
Timing of visit (weeks), d (days)	-21d	0	4	8	12	16	20	24	28	32	36	40	44	48	52	53	EOT +7d	EOT +30d	--	EOT-A +7d	EOT-A +30d	--
Visit window (days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±3	+5	+5		+5	+5	±7
Height	X																					
Alcohol use/tobacco use		X																				
Pregnancy test (Serum hCG)[d]	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X							
Home pregnancy test (Urine stick)[d]		X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)					X[e]			
EFFICACY																						
2-point profile			X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]			X			X
9-point profile		X																				
HbA_{1c}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X
Fasting plasma glucose		X																				
SAFETY																						
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaints	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology and biochemistry	X															X			X			
Urinalysis	X																					
Body Weight	X																					
Eye examination	X															X			X			
Vital signs	X	X														X			X			X
Physical examination	X															X			X			

	Screening	Randomisation	Non-pregnant/conception period of the trial													End of treatment and follow-up			Premature discontinuation			Additional visit
Site visits (V)	V1	V2	V6	V10	V14	V18	V22	V26	V30	V34	V38	V42	V46	V50	V54	V90 EOT	FU1[a]	V92 FU2	V90A EOT-A	FU1-A[a]	V92A FU2-A	V54D[b]
Weekly phone contact number (P). For details see Section 2.2		P3 P4 P5	P7 P8 P9	P11 P12 P13	P15 P16 P17	P19 P20 P21	P23 P24 P25	P27 P28 P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48 P49	P51 P52 P53			P91			P91A		P54A – P54G
Timing of visit (weeks), d (days)	-21d	0	4	8	12	16	20	24	28	32	36	40	44	48	52	53	EOT +7d	EOT +30d	--	EOT-A +7d	EOT-A +30d	--
Visit window (days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±3	+5	+5		+5	+5	±7
ECG	X																					
OTHER ASSESSMENTS																						
BG-meter start date[g]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
TRIAL MATERIAL																						
IWRS session	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X
Dispensing visit		X	X	X	X	X	X	X	X	X	X	X	X	X	X							X
First date on trial product		X																				
New dose of trial insulin		X	X	X	X	X	X	X	X	X	X	X	X	X	X							X
Dose of trial insulin		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X
Last dose of trial product																X			X			
Drug accountability		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X
REMINDERS																						
End of treatment																X			X			
End of trial																		X				
Sign-off case-book																		X				
Attend visit fasting		X																				
Hand out and instruct in BG-meter	X																					
Hand out and instruct in diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X
Collect diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X

	Screening	Randomisation	Non-pregnant/conception period of the trial													End of treatment and follow-up			Premature discontinuation			Additional visit
Site visits (V)	V1	V2	V6	V10	V14	V18	V22	V26	V30	V34	V38	V42	V46	V50	V54	V90 EOT	FU1[a]	V92 FU2	V90A EOT-A	FU1-A[a]	V92A FU2-A	V54D[b]
Weekly phone contact number (P). For details see Section 2.2		P3 P4 P5	P7 P8 P9	P11 P12 P13	P15 P16 P17	P19 P20 P21	P23 P24 P25	P27 P28 P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48 P49	P51 P52 P53			P91			P91A		P54A – P54G
Timing of visit (weeks), d (days)	-21d	0	4	8	12	16	20	24	28	32	36	40	44	48	52	53	EOT +7d	EOT +30d	--	EOT-A +7d	EOT-A +30d	--
Visit window (days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±3	+5	+5		+5	+5	±7
Hand out directions for use[f]		X																				
Training in trial product, pen-handling		X																				
Make appointment for eye examination[d]		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)							X
Check if pregnancy test has been done[d]		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)								
Dispensing of pregnancy tests[d]	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)								

[a] The first follow-up contacts P91 and P91A are phone contacts.

[b] The additional site visit (V54D) is applicable for subjects with a positive pregnancy test and if there are more than 4 weeks between the last site visit and the scheduled ultrasound visit (V55).

[c] Subjects discontinuing treatment prematurely must complete the additional premature discontinuation visits (V90A, P91A and V92A). Hereafter, all remaining planned visits in the conception period of the trial should be completed, except for the V90 2-point profile. Efforts should be made to ensure attendance at V54 for collection of a serum pregnancy test.

[d] Dispensing of home pregnancy test kits (urine stick) is applicable for subjects in the conception period of the trial. As soon as the subject has a positive urine pregnancy test, a confirmatory serum pregnancy test, an appointment for the V55 eye examination, and an ultrasound scan must be made.

[e] Before the subject prematurely discontinues trial product the investigator should ensure that a pregnancy test (urine stick) is performed before switching the subject to a suitable marketed insulin regimen.

[f] The investigator must ensure that the direction for use for the individual trial products (IDeg and IAsp or IDet and IAsp) are handed out to the subject.

[g] See Section 8.5.25 for details.

2.2 Trial flowchart for phone contacts in the conception period of the trial

	Non-pregnant, conception period of the trial	Additional Phone Contacts in case of pregnancy[a]		Follow-up	Premature discontinuation
Weekly phone contacts (P) in-between monthly site visits	P3-P53	P54 ABC	P54 EFG	P91 (FU1)	P91A (FU1-A)
Timing of contacts, W (weekly), d (days)	1-51W	--	--	EOT +7d	EOT-A +7d
Contact window (days)	±3	±3	±3	+5	+5
Premature discontinuation criteria	X	X	X		
Withdrawal criteria	X	X	X	X	X
Concomitant medication (diabetes)	X	X	X	X	X
Concomitant medication (other)	X	X	X		
Home pregnancy test (Urine stick)	(X)				
2-point profile	X	X	X		
Adverse events	X	X	X	X	X
Hypoglycaemic episodes	X	X	X	X	X
Technical complaints	X	X	X	X	X
New dose of trial insulin	X	X	X		
Dose of trial insulin	X	X	X		
Make appointment for eye examination	(X)	(X)	(X)		
Check if pregnancy test has been done	(X)				

[a] The additional phone contacts P54A-P54G are applicable for subjects becoming pregnant in the conception period of the trial to ensure weekly contacts between the last site visit and the scheduled ultrasound scan visit (V55).

2.3 Trial flowchart for site visits in the pregnancy period of the trial

	Screening	Randomisation	Additional visits		Pregnancy period						Delivery	End of treatment and follow-up			Premature discontinuation		
Site visit (V)	V1	V2[a]	V55[a]	V55D[b]	V59	V63	V67	V71	V75	V79	V86[c]	V90 EOT	FU1[d]	V92 FU2	V90A EOT-A	FU1-A[d]	V92A FU2-A
Weekly phone contact number (P). For details see Section 2.4			P55A P55B P55C	P56 P57 P58	P60 P61 P62	P64 P65 P66	P68 P69 P70	P72 P73 P74	P76 P77 P78	P80 – P85	P87 P88 P89		P91			P91A	
Timing of visits. GW (gestational weeks). d (days)	-21d	GW8-13 +6d	GW8-13 +6d	GW12	GW16	GW20	GW24	GW28	GW32	GW36	--	V86 +28d	EOT +7d	EOT +30d	--	EOT-A +7d	EOT-A +30d
Visit window (days)				±7	±7	±7	±7	±7	±7	±7		±3	+5	+5	±3	+5	+5
SUBJECT RELATED INFORMATION AND ASSESSMENTS																	
Informed consent[e]	X																
Inclusion/exclusion criteria	X	X															
Randomisation		X															
Premature discontinuation criteria[f]		X	X	X	X	X	X	X	X	X	X						
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography	X																
Medical history/concomitant illness	X																
Obstetric history	X																
Diabetes history	X																
Hypoglycaemia Unawareness	X																
Baseline hypoglycaemia questionnaire	X																
Concomitant medication (diabetes)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication (other)	X	X	X	X	X	X	X	X	X	X	X	X			X		
Height	X																
Alcohol use/tobacco use		X	X														
Pregnancy test (Serum hCG)	X																

	Screening	Randomisation	Additional visits		Pregnancy period						Delivery	End of treatment and follow-up			Premature discontinuation		
Site visit (V)	V1	V2[a]	V55[a]	V55D[b]	V59	V63	V67	V71	V75	V79	V86[c]	V90 EOT	FU1[d]	V92 FU2	V90A EOT-A	FU1-A[d]	V92A FU2-A
Weekly phone contact number (P). For details see Section 2.4			P55A P55B P55C	P56 P57 P58	P60 P61 P62	P64 P65 P66	P68 P69 P70	P72 P73 P74	P76 P77 P78	P80 – P85	P87 P88 P89		P91			P91A	
Timing of visits, GW (gestational weeks), d (days)	-21d	GW8-13 +6d	GW8-13 +6d	GW12	GW16	GW20	GW24	GW28	GW32	GW36	--	V86 +28d	EOT +7d	EOT +30d	--	EOT-A +7d	EOT-A +30d
Visit window (days)				±7	±7	±7	±7	±7	±7	±7		±3	+5	+5	±3	+5	+5
Estimated date of conception	X																
Pregnancy ultrasound scan		X	X														
EFFICACY																	
2-point profile			X	X	X	X	X	X	X	X	X	X[f]			X		
9-point profile		X	X		X		X		X	X							
HbA_{1c}	X	X	X	X	X	X	X	X	X	X		X			X		
Fasting plasma glucose		X	X		X		X		X	X							
SAFETY																	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pre-eclampsia					X	X	X	X	X	X	X				X	X	X
Hypoglycaemic episodes		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaints	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology and biochemistry	X		X				X			X		X			X		
Urinalysis	X	X	X	X	X	X	X	X	X	X							
Body Weight	X	X	X	X	X	X	X	X	X	X							
Eye examination	X		X					X				X			X		
Vital signs	X	X	X	X	X	X	X	X	X	X		X			X		
Physical examination	X		X									X			X		
ECG	X																

	Screening	Randomisation	Additional visits		Pregnancy period						Delivery	End of treatment and follow-up			Premature discontinuation		
Site visit (V)	V1	V2[a]	V55[a]	V55D[b]	V59	V63	V67	V71	V75	V79	V86[c]	V90 EOT	FU1[d]	V92 FU2	V90A EOT-A	FU1-A[d]	V92A FU2-A
Weekly phone contact number (P). For details see Section 2.4			P55A P55B P55C	P56 P57 P58	P60 P61 P62	P64 P65 P66	P68 P69 P70	P72 P73 P74	P76 P77 P78	P80 – P85	P87 P88 P89		P91			P91A	
Timing of visits, GW (gestational weeks), d (days)	-21d	GW8-13 +6d	GW8-13 +6d	GW12	GW16	GW20	GW24	GW28	GW32	GW36	--	V86 +28d	EOT +7d	EOT +30d	--	EOT-A +7d	EOT-A +30d
Visit window (days)				±7	±7	±7	±7	±7	±7	±7		±3	+5	+5	±3	+5	+5
OTHER ASSESSMENTS / PREGNANCY AND DELIVERY																	
BG-meter start date[h]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Insulin degludec cord blood											X						
Pregnancy outcome											X						
Delivery information											X						
Infant health status											X	X	X	X			
TRIAL MATERIAL																	
IWRS session	X	X	X	X	X	X	X	X	X	X		X			X		
Dispensing visit		X	X	X	X	X	X	X	X	X							
First date on trial product		X															
New dose of trial insulin		X	X	X	X	X	X	X	X	X	X						
Dose of trial insulin		X	X	X	X	X	X	X	X	X	X	X			X		
Last dose of trial product												X			X		
Drug accountability		X	X	X	X	X	X	X	X	X		X			X		
REMINDERS																	
End of treatment												X			X		
End of trial														X			
Sign-off case-book														X			
Attend visit fasting		X	X		X		X		X	X							

	Screening	Randomisation	Additional visits		Pregnancy period						Delivery	End of treatment and follow-up			Premature discontinuation		
Site visit (V)	V1	V2[a]	V55[a]	V55D[b]	V59	V63	V67	V71	V75	V79	V86[c]	V90 EOT	FU1[d]	V92 FU2	V90A EOT-A	FU1-A[d]	V92A FU2-A
Weekly phone contact number (P). For details see Section 2.4			P55A P55B P55C	P56 P57 P58	P60 P61 P62	P64 P65 P66	P68 P69 P70	P72 P73 P74	P76 P77 P78	P80 – P85	P87 P88 P89		P91			P91A	
Timing of visits, GW (gestational weeks), d (days)	-21d	GW8-13 +6d	GW8-13 +6d	GW12	GW16	GW20	GW24	GW28	GW32	GW36	--	V86 +28d	EOT +7d	EOT +30d	--	EOT-A +7d	EOT-A +30d
Visit window (days)				±7	±7	±7	±7	±7	±7	±7		±3	+5	+5	±3	+5	+5
Hand out and instruct in BG-meter	X																
Hand out and instruct in diary	X	X	X	X	X	X	X	X	X	X		X			X		
Collect diary		X	X	X	X	X	X	X	X	X		X		X	X		X
Hand out directions for use[g]		X															
Training in trial product, pen-handling		X	X				X										
Make appointment for eye examination							X			X							

[a] The V1 and V2 site visits are only applicable for subjects randomised pregnant. The V55 site visit is only applicable for subjects randomised non-pregnant and becoming pregnant in the conception period of the trial.

[b] The additional site visit V55D is only applicable for subjects randomised pregnant before GW 12 or for subjects that were randomised non-pregnant and become pregnant in the conception period of the trial and have an ultrasound scan completed before GW 12.

[c] The delivery visit (V86) is not considered a site visit, but relevant information from the delivery will be collected.

[d] The first follow-up contacts P91 and P91A are phone contacts.

[e] If required by local legislation, the father of the foetus (if known) must be asked to sign an agreement form for collection of blood samples and health information at and after delivery.

[f] Subjects discontinuing treatment prematurely must complete the additional premature discontinuation visits (V90A, P91A and V92A). Hereafter, all remaining planned visits in the pregnancy period of the trial should be completed, except for the V90 2-point profile. Efforts should be made to ensure attendance at V79 (GW 36) for collection of an HbA_{1c} sample before delivery.

[g] The investigator must ensure that the direction for use for the individual trial products (IDeg and IAsp or IDet and IAsp) are handed out to the subject.

[h] See Section 8.5.25 for details.

2.4 Trial flowchart for phone contacts in the pregnancy period of the trial

	Additional phone contacts[a]		Pregnancy period		Postpartum period			Follow-up	Premature discontinuation
Weekly phone contacts (P) in-between monthly site visits	P55ABC	P56-P58	P60-P82	P83-P85[b]	P87	P88	P89	P91 (FU1)	P91A (FU1-A)
Timing of contacts, GW (gestational weeks), d (days)	--	--	GW13-GW39	GW40-GW42	7d after delivery	14d after delivery	21d after delivery	EOT +7d	EOT-A +7d
Visit Window (days)	±3	±3	±3	±3	±3	±3	±3	+5	+5
Premature discontinuation criteria	X	X	X	X	X	X	X		
Withdrawal criteria	X	X	X	X	X	X	X	X	X
Concomitant medication (diabetes)	X	X	X	X	X	X	X	X	X
Concomitant medication (other)	X	X	X	X	X	X	X		
2-point profile	X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	X	X	X	X	X	X	X	X	X
Technical complaints	X	X	X	X	X	X	X	X	X
Pregnancy outcome					X	X	X		
Infant health status					X	X	X	X	
New dose of trial insulin	X	X	X	X	X	X	X		
Dose of trial insulin	X	X	X	X	X	X	X		

[a] The additional phone contacts P55A-P55C are applicable for subjects randomised pregnant before GW 12 or for subjects that were randomised non-pregnant and become pregnant in the conception period of the trial and have an ultrasound scan completed before GW 12. The additional phone contacts P56-P58 are to be completed as needed until visit 59 can be completed in GW 16.

[b] The phone contacts P83-P85 are only applicable for subjects with delivery after GW 40.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

3.1 Background information

The use of insulin analogues has increased significantly in the treatment of type 1 diabetes mellitus (T1DM). Insulin analogues are used in pregnant women with diabetes, as this group has a particular requirement for the safe and efficacious treatment that insulin analogues can deliver. Pregnancy in women with T1DM is associated with an increased risk of complications for both the mother and the foetus/infant. It is considered a medical challenge to ensure that these women receive the most optimal glycaemic control without inducing hypoglycaemia especially if glycaemic control is outside the target and as the treatment needs to be adjusted during pregnancy. If pregnant women receive optimal treatment, it will both increase their own well-being and reduce the overall risk of diabetes complications and pregnancy complications both for the mother and the infant. During recent decades, pregnancy outcomes in women with T1DM have improved considerably.

Hypoglycaemia and hyperglycaemia remain major challenges in the treatment of pregnant women with T1DM. In a prospective observational study of pregnant women with T1DM 45% of the women experienced severe hypoglycaemia during pregnancy. A history of severe hypoglycaemia the year preceding pregnancy was shown to be a significant risk factor for severe hypoglycaemia during pregnancy.[3]

Information on the safety profile of insulin products is considered an important part of the foundation of information for health care professionals in considering individualised treatment for pregnant women with T1DM. Thus it is important to compare different insulin analogues in terms of efficacy and safety to be able to offer pregnant women with T1DM the best possible option for insulin treatment.

Insulin degludec

Insulin degludec (IDeg) is an insulin analogue with unique pharmacological properties and a long duration of action.[4] Insulin degludec has been approved in more than 70 countries as Tresiba® (Tregludec® in Israel) and is indicated for treatment of diabetes mellitus in adults and children from the age of 1 year.

Insulin degludec has not been tested in a clinical trial with pregnant subjects, but has been investigated in animal studies covering fertility, embryo-foetal development and pre-and post-natal development in rats and during the period of embryo-foetal development in rabbits. Human insulin (Neutral Protamine Hagedorn insulin) was included as comparator and overall, the effects of IDeg were similar to those observed with human insulin.[5] In these studies both human insulin and IDeg caused pre-and post-implantation losses and visceral/skeletal abnormalities when given subcutaneously at a dose of 21 U/kg/day in rats and 3.3 U/kg/day in rabbits, resulting in 5 times (rat) and 10 times (rabbit) the human exposure (AUC, area under the curve) at a human subcutaneous dose of 0.75 U/kg/day. There is no clinical experience with IDeg during lactation. In rats, IDeg was secreted in the milk; however the concentration in the milk was lower than in plasma. It is unknown whether IDeg is secreted in human milk. No metabolic effects are anticipated in the breastfed newborn/infant.[6]

For further details, refer to the current version of the IDeg Investigator's Brochure (IB)[5], the Tresiba® Summary of Product Characteristics (SmPC)[6], and/or the local approved product information and any updates thereof.

Insulin detemir

Insulin detemir (IDet) is a long-acting insulin analogue approved as Levemir® and indicated for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above (in Russia children aged 2 years and above). Insulin detemir is furthermore approved for treatment of pregnant women with T1DM based on a completed randomised clinical trial (NN304-1687).[7]

For further details, refer to the current version of the Levemir® SmPC[8] and/or the local approved product information and any updates thereof.

Insulin aspart

Insulin aspart (IAsp) is marketed as NovoRapid® and is a fast-acting insulin analogue indicated for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above (in Russia children aged 2 years and above). Insulin aspart is furthermore approved for treatment of pregnant women with T1DM based on a completed randomised clinical trial (ANA-1474).[9]

For further details, refer to the current version of the NovoRapid® SmPC[10] and/or the local approved product information and any updates thereof.

For an overall assessment of benefits and risks of the trial, see Section 18.1

3.2 Rationale for the trial

Large prospective trials in women with T1DM have consistently shown that poor glycaemic control leads to poor pregnancy outcomes with increased risk of spontaneous abortion (rates of 17-24%)

with 3-4 (and up to 10) times higher risk of malformation and 2-3 times higher risk of foetal mortality compared to risks in healthy women.[11-15]

Macrosomia is reported to occur in approximately 25-40% of infants in mothers with diabetes.[16, 17] Accordingly, keeping blood glucose in the target range both immediately before conception and during pregnancy is essential to reduce the above risks for the mother and the infant.[18-22] Furthermore, hypoglycaemia is known to have a deleterious effect on outcome of pregnancies in women with diabetes both for the mother and the infant.[23] Accordingly, treatment of pregnant women affected by diabetes mellitus is a delicate balance between the need for intensive glucose control and reducing the risk of hypoglycaemia.

The current trial aims to evaluate effect and safety outcomes for IDeg in pregnant women with T1DM.

4 Objectives and endpoints

4.1 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.

4.2 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.

4.3 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.

4.4 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)[24]
- $HbA_{1c} \leq 6.5\%$ (48 mmol/mol) from last planned HbA_{1c} prior to delivery after GW 16 (yes/no)[25]
- 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 (kg)
- 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)[26] (yes/no)
- Live born infants (yes/no)
- Number of adverse events in the infant from 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)

4.5 Exploratory endpoints

Cord blood IDeg levels in live born infants.

4.6 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

5 Trial design

5.1 Type of trial

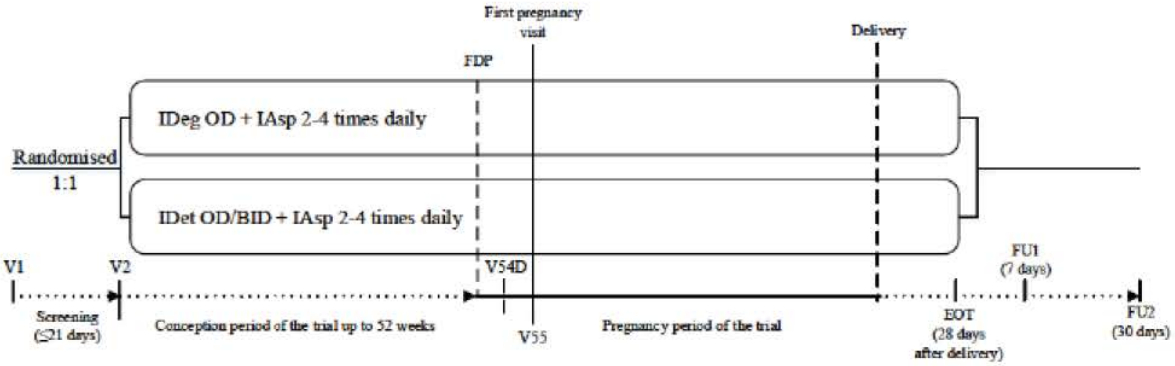
This is a randomised (1:1), open-label, parallel, multi-centre, multi-national, treat-to-target (TTT), active controlled trial comparing the effect and safety of IDeg OD plus IAsp 2-4 times daily with meals with IDet OD/BID plus IAsp 2-4 times daily with meals in pregnant women with T1DM.

Subjects will be randomised either non-pregnant with the intention to become pregnant or pregnant from GW 8-13 + 6 days. The gestational age of the foetus will be based on the ultrasound scan performed in the screening period before or at the randomisation visit (visit 2) for subjects randomised pregnant and before or at visit 55 for subjects randomised non-pregnant. 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.

The duration of the trial depends on the time of conception relative to the time of enrolment and delivery as summarised schematically in Figure 5–1 and Figure 5–2. 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 5–1.

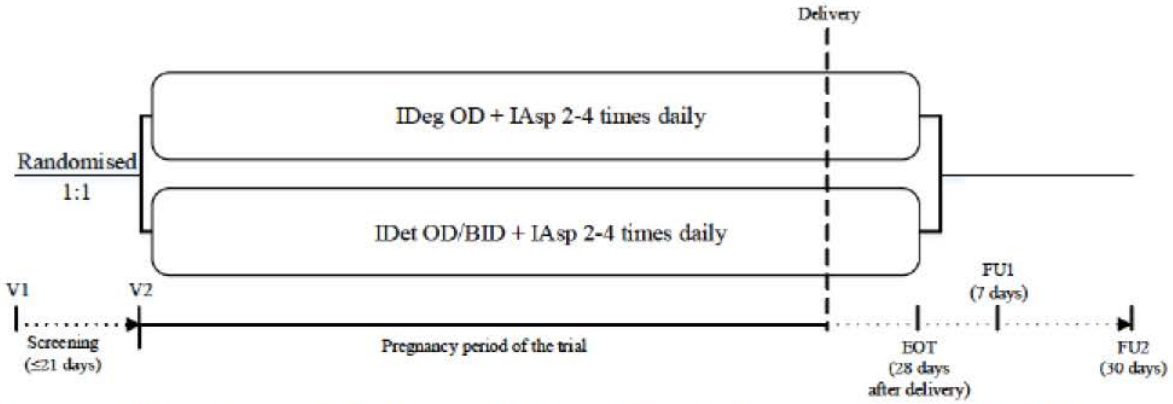
Table 5–1 Trial duration for subjects

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 5–1 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 5–2 Trial design for subjects who are pregnant at randomisation.

5.2 Rationale for trial design

The open-label trial design has been chosen as the timing of dosing might not be the same between both treatment groups, since IDeg is administered OD and IDet is administered either OD or BID.

A blinded trial would require a double dummy approach which is considered not ethically feasible and unnecessary burdensome for the subject.

Stratification with respect to the subject's pregnancy status at time of randomisation (pregnant/non-pregnant) as well as planned continued use of the subject's own CGM (yes/no) is applied in order to avoid any potential confounding introduced by these factors.

The TTT principle is applied to adjust the insulin dose for each individual subject with the aim of achieving similar glycaemic targets for IDeg and IDet. This allows for a valid comparison of the safety endpoints.

5.3 Treatment of subjects

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

Following randomisation, pre-trial insulin treatment must be discontinued and the subject will be switched to randomised treatment. Initiation and doses of trial basal insulin is based on plasma glucose values and are adjusted according to the Insulin Titration Guideline in Appendix A. There is no minimum or maximum daily insulin dose specified. Surveillance of insulin titration will be performed by Novo Nordisk.

End of treatment will be 28 days after delivery for pregnant subjects. For subjects who do not become pregnant in the conception period of the trial, the end of treatment visit (visit 90) will be 7 days after visit 54.

After end of treatment each subject will have a 30 days safety follow-up period consisting of two follow-up contacts (P91 and V92), see Section 8.5.3.

The maximum duration of treatment of a single subject will depend on whether the subject is randomised non-pregnant or pregnant as summarised in Table 5–1.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products, either at the scheduled end of treatment visit or if trial product is discontinued prematurely, the subject should be switched to a suitable marketed product at the discretion of the investigator or it will be made available according to local regulations.

5.5 Rationale for treatment

Subjects becoming pregnant in the conception period of the trial will be exposed to IDeg or IDet, both in combination with IAsp during organogenesis. The TTT design and consequent visit schedule is used in order to ensure optimal insulin titration based on self-measured plasma glucose (SMPG) values and to ensure improvement in glycaemic control.

The basal-bolus treatment regimen has been chosen for this trial since this is considered the standard of care for pregnant women with T1DM.

Insulin detemir has been chosen as comparator, since IDet is approved for use during pregnancy. Since IDet is used both OD and BID in clinical practice, this is also allowed in this trial.

Insulin aspart has been chosen as the bolus treatment since IAsp is approved for use during pregnancy.

All trial products are administered subcutaneously and should be injected in the thigh, upper arm or abdomen. The injection area should be consistent throughout the trial, however rotation of injection sites within the area is recommended to prevent lipohypertrophy.

Detailed information about trial products is available in the current edition and any updates of the IDeg IB[5] and/or SmPC[6], the SmPC for IDet[8] and IAsp[10] and/or local approved product information, if applicable.

6 Trial population

6.1 Number of subjects

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.

6.2 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered "yes".

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Female, age ≥ 18 years at the time of signing informed consent.
3. Diagnosed with type 1 diabetes mellitus ≥ 1 year prior to the day of screening.
4. Treated with multiple daily subcutaneous insulin injections or continuous subcutaneous insulin infusion (CSII) or inhaled insulin ≥ 90 days prior to the day of screening.
5. The subject is planning to become pregnant within 12 months from randomisation and willing to undertake pre-pregnancy counselling *or* the subject is pregnant with an intrauterine singleton living foetus (gestational week 8 to 13 (+6 days)) without any observed anomalies at randomisation, confirmed by an ultrasound scan.
6. HbA_{1c} at screening ≤ 8.0% (64 mmol/mol) by central laboratory.
7. Willingness and ability to take folic acid according to local guidelines.

6.3 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered "no".

1. Known or suspected hypersensitivity to trial products or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Receipt of any investigational medicinal product within 28 days before screening and between screening and randomisation for non-pregnant subjects and 28 days before conception and between conception and randomisation for pregnant subjects.
   For Brazil: Participation in other trials within 1 year prior to the day of screening unless there is a direct benefit to the research subject at the investigator's discretion.
4. Receipt of any concomitant medication contraindicated in pregnancy according to local label within 28 days before screening and between screening and randomisation for non-pregnant subjects and 28 days before conception and between conception and randomisation for pregnant subjects.
5. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening.
6. Untreated hyperthyroidism or hypothyroidism.
7. Any disorder, except for conditions associated with Type 1 Diabetes Mellitus which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
8. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma *in situ* are allowed.
9. Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening and between screening and randomisation.
10. Subjects presently classified as being in New York Heart Association (NYHA) Class III and IV.
11. Planned coronary, carotid or peripheral revascularisation known on the day of screening.
12. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR < 60 mL/min/1.73 m^2 as defined by KDIGO 2012 classification using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening.[27]
13. Pregnant and having proteinuria as evaluated by urine protein-to-creatinine ratio ≥ 300 mg/g in urine sample measured at screening.
14. Impaired liver function, defined as alanine aminotransferase ≥ 2.5 times upper normal limit or bilirubin > 1.5 times upper normal limit at screening.
15. Inadequately treated blood pressure (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) at screening.
16. Known to be HIV positive.
17. Known to be Hepatitis B or Hepatitis C positive.
18. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or pharmacologically dilated fundoscopy performed within the past 90 days prior to randomisation for non-pregnant subjects or within 28 days prior to randomisation for pregnant subjects.

19. History of severe hyperemesis gravidarum (requiring hospitalisation).
20. Subject being treated or became pregnant with assistance of *in vitro* fertilisation or other medical infertility treatment.

6.4 Criteria for premature discontinuation of trial product

Efforts must be made so that subjects attend and complete all scheduled visit procedures. Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule or missing assessments. Only subjects who decline any further contact with the site in relation to the trial or do not become pregnant within the conception period of the trial will be considered as withdrawn from the trial (see Section 6.5).

The subject may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

The subject must be prematurely discontinued from trial product if the following applies:
1. Included in the trial in violation of the inclusion and/or exclusion criteria.
2. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.

See Section 8.3.3 (non-pregnant subjects) and Section 8.4.4 (pregnant subjects) for procedures to be performed for subjects discontinuing trial product prematurely.

6.5 Withdrawal criteria

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected.

After randomisation the subject must be withdrawn from the trial if one of the following applies:
1. If subject *before* having become pregnant initiates any medication that is contraindicated during pregnancy according to local labelling. (If subject *has already* become pregnant when initiating medication that is contraindicated during pregnancy according to local labelling, the subject should not be withdrawn, but should stop the contraindicated medicine if judged safe for the subject by the investigator and stay in the trial on trial medication).
2. Commencement of medical infertility treatment during the course of the trial since medical infertility treatment can increase the risk of malformations.
3. Randomised non-pregnant and still non-pregnant 12 months after randomisation.

See Sections 8.3.4 or 8.4.5 for procedures to be performed for subjects withdrawing consent.

6.6 Subject replacement

Subjects who discontinue trial product prematurely or are withdrawn will not be replaced.

6.7 Rationale for trial population

Subjects with T1DM have been chosen for this trial due to previous experience from NN304-1687[7] and ANA-1474[9]. Furthermore, women with T1DM are preferred over women with type 2 diabetes mellitus, since the latter may have been treated with oral antidiabetic drugs from before they became pregnant and until randomisation and the safety of currently available oral antidiabetic drugs is not assured during early pregnancy.

Gestational diabetes mellitus has been excluded because the women may only develop the disease late in pregnancy. Furthermore, at least a fraction of these may become well-controlled on diet alone.

Both from an obstetric and a methodological viewpoint it would have been optimal to recruit the subjects prior to pregnancy to facilitate the best glycaemic control before conception. This would reduce the risk of maternal and foetal complications and provide a common baseline. However, even though diabetic patients are carefully instructed to plan their pregnancy, a high proportion of the women come to the clinic with an unplanned pregnancy.[28] In addition, most women who wish to become pregnant are not referred to obstetric clinics with specialised diabetes knowledge before they actually become pregnant. Therefore both pregnant and non-pregnant subjects can enter the trial.

Organogenesis is the period of time where the important organs are developing in the foetus and is completed by GW 8. It is during this period that the foetus is most at risk of complications. If pregnant subjects change insulin therapy during organogenesis it is likely that the glycaemic control will deteriorate transiently. Due to this potential deterioration a change in insulin therapy during organogenesis may risk harming the foetus. Therefore, subjects enrolled being pregnant will be randomised after completion of GW 8 and before completion of GW 13 (+ 6 days).

7 Milestones

Planned duration of recruitment period (i.e. first subject first visit (FSFV) to last subject first visit (LSFV)): 102 weeks.

End of trial is defined as LSLV.

Recruitment

The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects screened during the recruitment period

and found eligible for randomisation can be randomised within the timelines specified in the flowchart (see Section 2).

Trial registration

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[29] it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[30], the Food and Drug Administration Amendment Act (FDAAA)[31], European Commission Requirements[32, 33] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk email contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The Primary Completion Date (PCD) is the last planned assessment of the primary endpoint.

For subjects randomised as pregnant, the latest the primary endpoint may be assessed is 28 weeks after the last pregnant subject is randomised.

For subjects randomised as non-pregnant, the latest the primary endpoint may be assessed is 86 (52+34) weeks after the last non-pregnant subject is randomised. This would correspond to a situation where the last non-pregnant subject randomised conceives (is in gestational week 2) 52 weeks after randomisation and then has delivery after the gestational week 36 visit, at which the primary endpoint is assessed. Hence, for this group the last assessment of the primary endpoint is defined to be 86 weeks after the last non-pregnant subject is randomised.

Based on the above, the estimated PCD is in this trial defined as the latest of the two dates:

- 28 weeks after the last pregnant subject is randomised
- 86 weeks after the last non-pregnant subject is randomised

However, the estimated PCD will not be later than planned LSLV. For registration purposes the estimated PCD will be registered to be equal to the planned LSLV on clinicaltrials.gov.

The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

8 Methods and assessments

The following sections describe the assessments and procedures conducted during the trial in relation to subject related information/assessments as well as efficacy, safety and laboratory assessments. Timing of these is specified in the flowcharts in Sections 2.1 and 2.2 for subjects randomised non-pregnant as well as Sections 2.3 and 2.4 for subjects randomised pregnant.

The timing of visits for the conception period of the trial is based on the randomisation date whereas the timing of visits for the pregnancy period of the trial is based on gestational weeks.

The trial-related assessments and procedures are considered to be an addition to the local standard pregnancy care.

8.1 Screening

Informed consent must be obtained before any trial related activity, see Section 18.2. The date of informed consent must be entered in the electronic case report form (eCRF).

At screening, subjects will be provided with a card stating that they are participating in a trial and given contact address(-es) and telephone number(s) of relevant trial site staff. Subjects should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

A screening session must be performed in the IWRS. Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. Only subjects who have signed the informed consent form should be included on the logs. The subject screening log and subject enrolment log may be combined in one log.

A blood glucose (BG) meter and a diary will be provided to the subject. The subject will be instructed that entries must be made in the diary according to Section 8.5.14 and the instructions provided.

Eligibility assessments with regards to the inclusion and exclusion criteria must be performed. If any inclusion criterion is answered "no" or any exclusion criterion answered "yes" the subject is a screening failure and no further assessments should be done.

Answers to inclusion or exclusion criteria cannot be ticked "yes" or "no" in the eCRF before source data is available. In this case "result pending" should be ticked. This is particularly relevant for exclusion criterion 3, the central laboratory results and in some cases the ECG and eye examination evaluations. Answers to these criteria must be changed to "Yes" or "No" when information, results and/or evaluations become available. The subject cannot be randomised until all results are available.

8.1.1 Screening failures

For screening failures the screening failure form in the eCRF must be completed with the reason for not continuing in the trial. Serious adverse events (SAEs) from screening failures must be transcribed by the investigator into the eCRF. Follow-up on SAEs must be carried out according to Section 12. A screening failure session must be made in the IWRS and the casebook must be signed.

Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria. This includes re-sampling if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters.

8.2 Randomisation

Randomisation should take place no later than 21 days after the screening visit, but must not take place before all screening assessment results are available and reviewed and the subject confirmed eligible. For an eligible subject a randomisation session must be performed in the IWRS where subject will be randomised into one of the two treatment regimens and trial product will be dispensed.

The subject must attend the randomisation visit fasting as defined in Section 8.5.2.

Non-pregnant subjects

Subjects with a negative screening serum pregnancy test will be randomised in the non-pregnant/conception period of the trial and must follow procedures in Section 8.3 until a positive result of the home pregnancy test. Before randomisation a urine pregnancy test should be taken in order to confirm the subject is still non-pregnant. In case of a positive urine pregnancy test a confirmatory serum pregnancy must be taken and if pregnant, the subject may not be randomised until GW 8-13 (+6 days).

The subject and their partner, if appropriate, will undergo pre-pregnancy counselling and education on diabetes control according to standard practice at site. The subject should be recommended to use contraception during a short period of time after randomisation until reasonable glycaemic control is achieved as judged by the investigator.

The subject will receive the following home testing kit:

- **Home pregnancy testing kit (urine stick)**
  - The subject should be instructed to take a pregnancy test as soon as a period is missed. In case of a negative test, but symptoms of pregnancy remain, the subject should contact site. In case of a positive test the subject will follow procedures in Section 8.3.1.
  - For Argentina and Austria: As per local requirements a home pregnancy test must be taken monthly and as soon as a period is missed. This should be documented in the subject's medical records.

In addition, the site can provide a home ovulation kit to the subject. This can be used to perform tests in the middle of the menstrual cycle to detect the time for increase in luteinising hormone (LH) indicating ovulation and optimal timing for conception.

Pregnant subjects

Subjects with a positive screening serum pregnancy test will be randomised in the pregnancy period of the trial and must follow procedures in Section 8.4. For subjects randomised pregnant visit 2 will be considered the pregnancy baseline visit. The randomisation visit must take place when the subject is in GW 8-13 (+6 days).

8.3 Visit procedures for non-pregnant subjects

8.3.1 Pregnancy in the non-pregnant/conception period

In case of a positive home pregnancy test (urine stick) the subject should contact the site immediately and an unscheduled confirmatory serum pregnancy test must be collected as soon as possible for analysis by the central laboratory.

If the confirmatory serum pregnancy test is positive the site must schedule an ultrasound (US) scan as per Section 8.4.1 and an eye examination as per Section 8.5.19. In case there are more than 4 weeks between the last site visit and the scheduled US scan the subject must attend the additional site visit 54D to ensure sufficient supplies of trial products and optimal glycaemic control in the first period of the pregnancy. The additional site visit must be scheduled midway between the last site visit and the scheduled US visit 55. In-between the subject must attend the additional weekly phone contacts 54A to 54G, as needed.

The subject will follow remaining visit procedures for pregnant subjects in Section 8.4.

8.3.2 End of non-pregnant/conception period

At the end of non-pregnant/conception period of the trial (visit 54) a serum pregnancy test must be taken.

In case of a positive serum pregnancy test the subject will follow remaining visit procedures for pregnant subjects (Section 8.4) starting with the additional weekly phone contacts 54A to 54G, as needed. In case there are more than 4 weeks between the last site visit and the scheduled US scan the subject must attend the additional site visit 54D to ensure sufficient supplies of trial products and optimal glycaemic control in the first period of the pregnancy. The additional site visit must be scheduled midway between the last site visit and the scheduled ultrasound visit 55.

In case of a negative serum pregnancy test the subject is withdrawn from the trial. The investigator must perform a treatment discontinuation session in the IWRS and treatment with trial product must

be stopped. The end of treatment visit must be completed and the subject should be switched to a suitable marketed insulin regimen at the discretion of the investigator. The P91 and V92 follow-up contacts must be performed 7 and 30 days after the end of treatment visit V90 respectively.

If the subject has already prematurely discontinued treatment and the additional end of treatment visit V90A and additional follow-up contacts P91A and V92A have been performed, assessments corresponding to the V92 follow-up visit (except infant health) must be performed and is considered the end of trial visit.

8.3.3 Premature discontinuation of trial product

If a non-pregnant subject prematurely discontinues trial product, the investigator must perform the additional end of treatment visit V90A as soon as possible, Section 8.3.2. The additional follow-up contacts P91A and V92A must be performed 7 and 30 days after discontinuation of trial product respectively, Section 8.5.3.

Before the subject prematurely discontinues trial product the investigator should ensure that a pregnancy test (urine stick) is performed. In case of a positive pregnancy test, the investigator should discuss the potential risks to the foetus by changing insulin treatment during early pregnancy before the subject is switched to a suitable marketed insulin regimen.

The primary reason for premature discontinuation of trial product must be specified in the additional end of treatment form in the eCRF and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS.

Hereafter the subject should attend all remaining planned visits in the non-pregnant/conception period of the trial. If applicable, the phone contacts should preferably be completed weekly in the eCRF and documented in the subject's medical records in order to optimise glycaemic control. In case the subject becomes pregnant in this period, follow instructions in Section 8.4.4.

For subjects not able or willing to attend all planned site visits, these can be converted to phone contacts, except visit 54. Efforts should be made to ensure attendance at this visit for collection of a serum pregnancy sample.

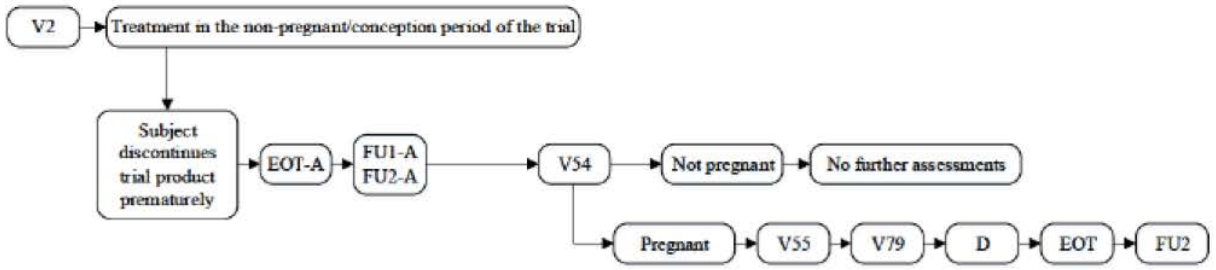
In case of a negative visit 54 pregnancy test, the subject is withdrawn from the trial, Section 8.3.4.

In case of a positive visit 54 serum pregnancy test the subject should attend all remaining planned visits during pregnancy according to Section 2.3. For subjects not able or willing to attend all planned site visits, these can be converted to phone contacts. Efforts should be made to ensure attendance at the most important key visits, i.e. visit 55, visit 79 and the delivery visit (visit 86).

In addition, information about infant health and safety should be collected:

- 28 days after delivery (end of treatment visit V90). This visit can be converted to a phone contact.
- 58 days after delivery (V92 follow-visit). This visit should be a site visit.

The key visits to be completed for subjects discontinuing treatment prematurely are summarised in Figure 8–1.



Abbreviations: V2 = randomisation visit, EOT = end of treatment (V90), FU2 = follow-up visit 2 (V92), EOT-A = additional end of treatment (V90A), FU1-A/FU2-A = additional follow-up contacts 1 (P91A) and 2 (V92A), V54 = last visit in the conception period of the trial. V55 = pregnancy baseline visit (ultrasound scan), V79 = gestational week 36, D = delivery (V86).

Figure 8–1 Overview of key visits for subjects discontinuing trial product prematurely in the non-pregnant/conception period of the trial.

8.3.4 Withdrawal from trial

If a subject withdraws consent, the investigator must aim to undertake procedures similar to those for the end of treatment visit as soon as possible. If the subject agrees, the P91 and V92 follow-up contacts must be performed 7 and 30 days after discontinuation of trial product respectively.

The end of trial form must be completed and final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be made in the IWRS (if applicable) and the casebook must be signed.

If the subject has already discontinued treatment prematurely and attended the additional end of treatment visit 90A as well as the additional follow-up contacts P91A and V92A prior to withdrawal, the end of treatment visit V90 and follow-up contacts P91 and V92 should not be completed.

Before the subject discontinues trial product and is switched to a suitable marketed insulin regimen, the investigator should ensure the subject has a negative pregnancy test (urine stick). If the subject is confirmed non-pregnant no further assessments should be done. If the subject is confirmed pregnant the investigator should collect information about the pregnancy, pregnancy outcome and infant health on the paper pregnancy forms as per Section 12.5.

Although a subject is not obliged to give her reason(s) for withdrawing consent, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for withdrawing consent must be specified in the end of trial form in the eCRF.

8.4 Visit procedures for pregnant subjects

8.4.1 Ultrasound scan

Using standard equipment at the site an ultrasound (US) scan must be performed either at the screening visit or before randomisation occurs at visit 2. For subjects randomised pregnant the randomisation visit must take place when the subject is in GW 8-13 (+6 days).

Subjects randomised non-pregnant and becoming pregnant in the conception period of the trial must have an US scan performed in connection with visit 55 when the subject is in GW 8-13 (+6 days).

The US scan will be used to determine the following information and must be entered in the eCRF:

- If the pregnancy is in alignment with inclusion criterion 5
    - For subjects randomised non-pregnant multiple pregnancies are accepted
- Gestational age (completed gestational weeks and days), estimated conception date and estimated delivery date
- Foetal Crown-Rump Length (CRL)

For subjects where the ultrasound scan is completed before GW 12 the additional site visit 55D must be completed. The additional phone contacts P55A-P55C and P56-P58 should be completed as needed to ensure weekly contacts until visit 59.

8.4.2 Delivery visit

The delivery visit (visit 86) is not considered a site visit, but relevant information concerning labour, delivery and neonatal assessment/infant health must be entered in the specific forms in the eCRF, if available. If required by local legislation, the father of the foetus (if known) must be asked to sign an agreement form before delivery, see Section 18.2.

Information collected for the mother

The following information will be collected for the mother:

- Type and dose of insulin (if not trial products) as well as relevant concomitant medication including administration of glucose during management of labour and delivery. The use of insulin and glucose should be according to local practice.
- Mode of delivery, e.g. vaginal, operative vaginal, planned or unplanned caesarean section, induced or spontaneous delivery.

Infant health information collected

The following information will be collected for the infant:

- Details on the pregnancy outcome including:
  - Birth date
  - Gender
  - Gestational age (completed gestational weeks and days)
  - Head circumference of the newborn[a]
  - Length of the newborn[a]
  - APGAR scores assessed at 1 minute and 5 minutes after birth

  [a] Measured in centimetres (cm) to one decimal place
- Standard Deviation (SD) score for birth weight (measured in grams (g) according to local normal curves for gestational age and sex) including the birth weight percentile.
- Details on the infant health status, including if the infant has any congenital anomaly or birth injury observed at gross examination or events such as induced abortion, resuscitation, respiratory distress syndrome (RDS), moderate or severe neonatal asphyxia, early foetal death or neonatal or perinatal death must be reported in the eCRF and as an SAE as per Section 12.5.2.
- To measure umbilical cord IDeg levels a cord blood sample should be drawn from the umbilical cord (applicable for subjects randomised to IDeg only). The sample should be collected at birth immediately after the umbilical cord has been cut.
- Umbilical cord pH (as part of standard of care).
- Postpartum neonatal plasma glucose and neonatal hypoglycaemia as defined in Section 8.5.16.4.
- Treatment given to the infant, e.g. with surfactant, ventilator or continuous positive airway pressure (CPAP).

8.4.3 End of treatment

The end of treatment visit should take place 28 days after delivery. A treatment completion session must be performed in the IWRS, treatment with trial product must be stopped, and the subject should be switched to a suitable marketed insulin regimen at the discretion of the investigator.

Both the mother and the infant will undergo a physical examination and infant health will be assessed (not applicable in case of fatal outcome) as outlined in Section 12.

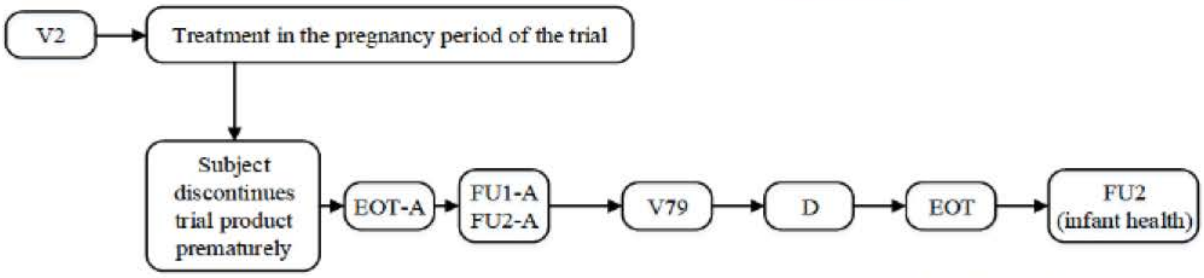
8.4.4 Premature discontinuation of trial product

If a pregnant subject prematurely discontinues trial product, the investigator must perform the additional end of treatment visit 90A as soon as possible, Section 8.4.3. The additional follow-up contacts P91A and V92A must be performed 7 and 30 days after discontinuation of trial product respectively, Section 8.5.3.

The primary reason for premature discontinuation of trial product must be specified in the end of treatment form in the eCRF, and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS.

Pregnant subjects discontinuing treatment prematurely should hereafter attend all remaining planned visits of the trial. If applicable, the phone contacts should preferably be completed weekly in order to maintain glycaemic control.

For subjects not able or willing to attend all planned site visits, these can be converted to phone contacts. Efforts should be made to ensure collection of the scheduled 9-point profiles as per flowchart Section 2.3 and attendance at the most important key visits, i.e. visit 79 for collection of an HbA_{1c} sample prior to delivery, the delivery visit, the end of treatment visit V90 (except 2-point profile), and the originally scheduled V92 follow-up visit. The key visits to be completed for subjects discontinuing treatment prematurely are summarised in Figure 8–2.



Abbreviations: V2 = pregnancy baseline visit (ultrasound scan), EOT = end of treatment (V90), FU2 = follow-up visit 2 (V92), EOT-A = additional end of treatment (V90A), FU1-A/FU2-A = additional follow-up contacts 1 (P91A) and 2 (V92A), V79 = gestational week 36, D = delivery (V86).

Figure 8–2 Overview of key visits for subjects discontinuing treatment prematurely in the pregnancy period of the trial.

8.4.5 Withdrawal from trial

If a subject withdraws consent, the investigator must aim to undertake procedures similar to those for the end of treatment visit as soon as possible. If the subject agrees, the P91 and V92 follow-up contacts must be performed 7 and 30 days after discontinuation of trial product respectively.

The end of trial form must be completed and final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be made in the IWRS and the casebook must be signed.

If the subject has already discontinued treatment prematurely and attended the additional end of treatment visit 90A as well as the additional follow-up contacts P91A and V92A prior to withdrawal, the end of treatment visit V90 and follow-up contacts P91 and V92 should not be completed.

The investigator should collect information about the pregnancy, pregnancy outcome and infant health on the paper pregnancy forms as per Section 12.5.

Although a subject is not obliged to give her reason(s) for withdrawing consent, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for withdrawing consent must be specified in the end of trial form in the eCRF.

8.5 Visit procedures and assessments for both non-pregnant and pregnant subjects

8.5.1 Phone contacts

Throughout the trial (both in the conception and the pregnancy periods of the trial) weekly phone contacts are scheduled according to Sections 2.2 and 2.4. Phone contacts must be completed in the eCRF and documented in the subject's medical records. A phone contact may be converted to a site visit if preferred.

It must be clearly agreed how each contact is conducted. Even if it is agreed that the subject calls the investigator, it is the responsibility of the investigator that the contact takes place.

Additional phone contacts in the conception period of the trial

The additional phone contacts P54A-P54G are flexible phone contacts applicable for non-pregnant subjects becoming pregnant in the conception period of the trial only. These phone contacts should be completed as needed to ensure weekly contacts between the last site visit and the scheduled ultrasound scan at visit 55.

Additional phone contacts in the pregnancy period of the trial

The additional phone contacts P55A-P55C and P56-P58 are flexible phone contacts that should be completed as needed to ensure weekly contacts until visit 59.

The additional phone contacts P83-P85 are flexible phone contacts applicable for pregnant subjects with delivery after GW 40.

8.5.2 Fasting visits

Subject must attend specific visits in a fasting condition as outlined in the flowchart Sections 2.1 and 2.3 for collection of an FPG blood sample. Fasting is defined as having consumed only water and taken no insulin at least eight hours prior to the visit. Non-antidiabetic medication(s) are to be taken.

If a subject attends a fasting visit in a non-fasting condition, blood sampling should be re-scheduled preferably within the visit window. If blood sampling has already been done before realising the subject was not fasting, only the FPG sample needs to be re-drawn.

8.5.3 Follow-up period

There are two follow-up contacts after end of treatment, P91 and V92.

The first follow-up contact (P91) is a phone contact and must take place 7 days after end of treatment. At this visit information about antidiabetic medication and all AEs including hypoglycaemic episodes in the period from end of treatment visit V90 to P91 is collected.

The second follow-up contact (V92) is a site visit and is considered the end of trial visit. This site visit must take place 30 days after end of treatment visit V90. Information about antidiabetic medication and all AEs including hypoglycaemic episodes in the period between the two follow-up contacts is collected. Status on infant health (if applicable) will be collected for the period from end of treatment visit V90 until V92.

8.5.4 Unscheduled site visits

If the subject attends the site outside the visit schedule, the unscheduled visit form in the eCRF must be completed. The unscheduled visit form must not be completed if the subject attends the site only to obtain trial products or for re-scheduled visits. Unscheduled visits can be performed at any time at the discretion of the investigator e.g. in relation to follow-up on an AE.

If additional trial product is needed an additional dispensing session must be performed in the IWRS. If blood sampling is needed the requisition form should refer to the visit number to which the sample belongs.

8.5.5 Demography

Demography will be recorded at screening and consists of:

- Date of birth (according to local regulation)
- Sex (pre-defined based on inclusion criteria, Section 6.2)
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.5.6 Concomitant illness, medical history and obstetric history

A **concomitant illness** is any illness including diabetes complications that is present at the start of the trial (i.e. at the screening visit) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Medical history is a relevant medical event including diabetes complications (as judged by the investigator) that the subject has experienced in the past.

Obstetric history is information about previous pregnancies. The information collected includes the number of previous pregnancies, the number of live births as well as previous maternal/foetal

pregnancy complications and congenital anomaly(-ies). Obstetric history should also include relevant pregnancy related medical events.

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

It must be possible to verify the subject's medical history in source documents such as subject's medical record. If a subject is not from the investigator's own practice, the investigator must make reasonable effort to obtain a copy of subject's medical record from relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

8.5.7 Diabetes history

Diabetes history consisting of date of diagnosis of T1DM will be recorded in the eCRF at screening.

8.5.8 Hypoglycaemia unawareness

Information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8.[34]

The investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" The subject can answer never, rarely, sometimes, often or always.

Subjects answering 'never, rarely or sometimes' are considered as having impaired awareness of hypoglycaemia.

8.5.9 Baseline hypoglycaemic episode interview questionnaire

The baseline hypoglycaemic episode interview questionnaire in Appendix B must be performed at the screening visit and can be recorded directly in the eCRF. The questionnaire will be performed in an interview by the investigator or delegated site staff and will be used to investigate the subject's experience with hypoglycaemic episodes.

8.5.10 Concomitant medication (diabetes)

A **concomitant antidiabetic medication** is any diabetes medication other than the trial product(s). At the randomisation visit any pre-trial insulin(s) must be discontinued and stop date(s) recorded in the eCRF.

For subjects randomised non-pregnant this includes diabetes medication taken up to 28 days before screening as well as during the trial, including the screening, conception and/or pregnancy period(s) of the trial and until the end of trial. The information must be recorded in the concomitant antidiabetic medication form in the eCRF.

For subjects randomised pregnant this includes diabetes medication taken at least 28 days before conception as well as during the trial, including the screening and pregnancy periods of the trial and until the end of trial. The information must be recorded in the concomitant antidiabetic medication form in the eCRF.

The information collected for each antidiabetic medication must be recorded in the concomitant antidiabetic medication form in the eCRF. Details include trade name or generic name, indication, route of administration, total daily dose, start date and stop date.

8.5.11 Concomitant medication (other)

A **concomitant medication** is any medication, including folic acid, other than the trial product(s).

For subjects randomised non-pregnant this includes medication taken up to 28 days before screening as well as during the trial, including the screening, conception and/or pregnancy period(s) of the trial and until end of treatment.

For subjects randomised pregnant this includes medication taken up to 28 days before conception, as well as during the trial, including the screening and pregnancy periods of the trial and until end of treatment.

For the infant this includes medication administered in the period after birth until end of the follow-up periods.

Details of any concomitant medication for the subject must be recorded at the screening visit in the eCRF. Changes in concomitant medication must be recorded at each visit as they occur. Details of any concomitant medication for the infant must be recorded in the eCRF after delivery.

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation.

If a change is due to an AE, then this must be reported according to Section 12. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.5.12 Alcohol use

For subjects randomised non-pregnant, information about the average consumption of alcohol within the last 8 weeks before randomisation must be recorded in the eCRF at the randomisation visit 2. For non-pregnant subjects becoming pregnant in the conception period of the trial,

information about the average consumption of alcohol within the first 8 weeks of pregnancy must be recorded in the eCRF at visit 55.

For subjects randomised pregnant, information about the average consumption alcohol within the first 8 weeks of pregnancy must be recorded in the eCRF at the randomisation visit 2.

8.5.13 Tobacco use

For subjects randomised non-pregnant, information about tobacco use within the last 8 weeks before randomisation must be recorded in the eCRF at the randomisation visit 2. For non-pregnant subjects becoming pregnant in the conception period of the trial, information about tobacco use within the first 8 weeks of pregnancy must be recorded in the eCRF at visit 55.

For subjects randomised pregnant, information about tobacco use within the first 8 weeks of pregnancy must be recorded in the eCRF at the randomisation visit 2.

Smoking is defined as smoking at least one cigarette or equivalent daily in average. Details of smoking status to be recorded cover if the subject never smoked, is a previous smoker (including smoking stop date) or is a current smoker.

8.5.14 Self-measured plasma glucose and diaries

The subject will be provided with a BG-meter including auxiliaries as well as instructions for use. The subject will be instructed in how to use the device including regular calibration according to the manufacturer's instruction. The instruction should be repeated if deemed required by the site staff.

At each site visit the subject will be provided with a new diary. The diary must be collected at the next site visit and retained at the site as source data in accordance with Section 14.

The subject must be instructed how to record the results of the SMPG values including a 9-point profile in the diary. The record should include date, time and value. All data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected.

Occasional review by the investigator of the values stored in the memory of the BG-meter and correct reporting of these in the diary is advised in order to ensure adequacy of the data reported in the trial database.

If clarification of entries or discrepancies in the diary is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

The BG-meter uses test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values which will be shown on the display.

Only the BG-meter provided by Novo Nordisk should be used for the measurements required in the protocol. Measurements done by the subject's own CGM must not be used for trial-related assessments.

2-point and 9-point SMPG profiles

The subject will be asked to perform daily SMPG measurements for a 2-point profile throughout the trial until end of treatment at the following time points:

- Before breakfast
- Before main evening meal

For details refer to the Insulin Titration Guideline in Appendix A.

In addition, SMPG measurements for a 9-point profile must be completed in the period between screening and randomisation and at specific visits in the pregnancy period of the trial as per flowchart in Section 2.3. The SMPG measurements should be measured and recorded in the diary at the time points listed in Table 8–1.

The SMPG measurements before breakfast should preferably be performed after having consumed only water since midnight and before insulin injection. The SMPG measurements before lunch, main evening meal and bedtime should be performed before insulin injection. All measurements will be recorded in the diary by the subject.

Table 8–1 Time points for the 9-point profile collected 2 days before selected visits

Time point	Two days before visit	One day before visit
Before breakfast	✓[a]	✓[a]
90 minutes after the start of breakfast	✓	
Before lunch	✓	
90 minutes after the start of lunch	✓	
Before main evening meal	✓[a]	
90 minutes after the start of main evening meal	✓	
Before bedtime	✓	
At 4 am	✓	

[a] Measurements included in the 2-point profile

8.5.15 Basal insulin dose

Starting after randomisation the subject should be instructed to report date, dose and time point of administration of basal insulin (IDeg/IDet) in the diary throughout the trial on three days prior to a visit and/or phone contact.

The recommended basal insulin doses will be calculated in the eCRF based on recommendation from the Insulin Titration Guideline in Appendix A. At each site visit or phone contact the investigator must review and adjust the basal insulin doses based on the recommendation in the eCRF and inform subject about the adjusted doses.

In the eCRF investigator must record the first date and the last date of trial product (IDeg/IDet).

8.5.16 Adverse events

Adverse events (AEs) must be reported at each visit in accordance with the procedures outlined in Section 12.

8.5.16.1 Medication error

If a medication error is observed during the trial, the following information is required and a specific event form must be completed in the eCRF in addition to the AE form:

- Trial product(s) involved
- Classification of medication error
- Whether the subject experienced any hypoglycaemic episode and/or adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see Section 12.1.4.

8.5.16.2 Adverse events requiring additional data collection

For the following AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form.

In case any of these events fulfil the criteria for an SAE, these must be reported accordingly, see Section 12.2. For events requiring adjudication, see Section 12.7.3.

Neoplasm

All events of benign, pre-malignant/carcinoma *in situ* and malignant neoplasms must be reported during the trial and the following additional information should be obtained as part of standard of care and be reported in the neoplasm eCRF, if available:

- Type of neoplasm
- Diagnostic imaging
- Participation in screening programs
- Symptoms and laboratory results leading to identification of event
- Treatment given for the event
- Pathological examination (outcome and staging)
- Relevant risk factors associated with the event

Pre-eclampsia

If pre-eclampsia (PE) is observed during the trial, the following additional information must be reported in the PE eCRF, if relevant and available:

- New-onset hypertension
- Proteinuria
- Presence of eclampsia
- Treatment given for the event
- HELLP syndrome
- Other severe organ involvement
- Relevant risk factors associated with the event

New-onset hypertension is defined as BP ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic, based on at least 2 measurements taken at least 4 hours apart) occurring after GW 20.

Proteinuria is defined as ≥ 300 mg protein in a 24 hours urine sample, a protein-to-creatinine ratio of ≥ 300 mg/g in a urine sample or a urine dipstick protein of 1+.

Congenital anomaly(-ies)

All events of congenital anomaly(-ies) observed for the infant will be collected in the specific eCRFs for pregnancy outcome after delivery. Cases of abnormal pregnancy outcome must be reported as an AE and will be subject for event adjudication.

8.5.16.3 Hypoglycaemic episodes

Plasma glucose should always be measured and recorded when a hypoglycaemic episode is suspected.

All plasma glucose values:

- ≤ 3.9 mmol/L (70 mg/dL) or
- > 3.9 mmol/L (70 mg/dL) occurring in conjunction with hypoglycaemic symptoms

should be reported in the diary according to the instructions below throughout the trial from randomisation to the end of trial.

Upon onset of a hypoglycaemic episode the subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines[35].

An SMPG value ≤ 3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms must trigger a hypoglycaemic episode form to be completed by the subject. Repeated SMPG measurements and/or symptoms, occurring within a period of 60 min after onset on a hypoglycaemic episode, will by default be considered as one hypoglycaemic episode until a succeeding SMPG value is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved and should be reported on one hypoglycaemic episode form. SMPG measurements ≤ 3.9 mmol/L (70 mg/dL) or hypoglycaemic symptoms after the 60 min period shall trigger the reporting of a new hypoglycaemia episode and prompt the subject to fill out a new hypoglycaemic episode form until a succeeding measurement is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved.

In case of several low SMPG values within the 60 minutes interval, the lowest value is the one that will be reported as the SMPG value for the hypoglycaemic episode but the start time of the episode will remain as the time for the first SMPG value and/or symptom.

The record should include the following information:

- Start date and time of the hypoglycaemic episode
- The plasma glucose level before treating the episode (if available) and any follow up measurements.
  The lowest value measured during the hypoglycaemic episode will be reported as the plasma glucose value for the episode, the remaining values will be kept as source data in the diary.
- Whether the episode was symptomatic (Yes/No)
- A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode.
- Whether the subject was able to treat herself
- If the severity of a hypoglycaemic episode aggravates, only one hypoglycaemic episode should be reported reflecting the most severe degree of hypoglycaemia.
- Date, time and dose of last trial product administration prior to the episode
- Date and time of last main meal (not including snacks) prior to the episode
- Whether the episode occurred in relation to physical activity
- Whether the episode related to a change in any concomitant illness
- Any sign of fever and/or other acute disease
- Whether the subject was asleep when the episode occurred
    - If yes, whether the symptoms of the episode woke up the subject

The answer to the question: "Was the subject able to treat herself?" must be answered "No" for 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[35].

Oral carbohydrates must not be given if the subject is unconscious.

If the question "Was the subject able to treat herself?" is answered "No", the following information should be recorded by the subject:

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)?
- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by another person (i.e. oral carbohydrates, glucagon, i.v. glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet change, medication error (i.e. overdose, mix-up between products, incorrect use of device), miscalculation of insulin dose, other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[36] (layman term used in the diary is specified in brackets if different from the protocol term)?
    - Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
    - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
    - General malaise: headache or malaise (feeling discomfort/unease)
- Other symptoms

The investigator must review the diary for low SMPG values not reported as hypoglycaemic episodes. The subject must be questioned whether any of the low values were severe, i.e. whether the subject was able to self-treat or not. If the subject was not able to self-treat, it has to be reported as a severe hypoglycaemic episode.

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data.[37, 38]

The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies low SMPG values not reported as hypoglycaemic episodes.

If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form, a safety information form (SIF) and an event adjudication form must also be filled in, see Section 12.

8.5.16.4 Neonatal hypoglycaemic episodes

A neonatal plasma glucose assessment should be taken preferably within the first 1-2 hours postpartum and documented in the subject's medical record as per local procedure. If deemed necessary the neonatal plasma glucose assessment should be repeated.

The definition of neonatal hypoglycaemia is plasma glucose values:

- ≤ 1.7 mmol/L (31 mg/dL) within the first 24 hours after birth or
- ≤ 2.5 mmol/L (45 mg/dL) between 24 hours and 48 hours after birth

In case a neonatal hypoglycaemic episode is measured, the episode must be recorded in the eCRF at the delivery visit. If the neonatal hypoglycaemic episode fulfils the criteria for an SAE, this must be reported according to Section 12.2.

8.5.17 Laboratory assessments

Laboratory analyses will be performed by both a central and special laboratory. The central laboratory will provide all laboratory supplies for the sampling of all blood and urine samples collected during the trial (Table 8–2) as well as a manual with detailed description of procedures and further information regarding e.g. tubes and labels to the sites.

Fasting plasma glucose (FPG) is measured in order to evaluate metabolic control. The subject must attend these visits fasting as outlined in Section 8.5.2.

An FPG result ≤3.9 mmol/L (70 mg/dL) should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator according to Section 12.1.1).

Table 8–2 Laboratory parameters included in the trial

Haematology	**Glucose metabolism**
• Haemoglobin • Haematocrit • Erythrocytes • Thrombocytes • Leucocytes	• Glycosylated haemoglobin (HbA_{1c}) • Fasting Plasma Glucose (FPG)
	Urinalysis
	• Protein-to-creatinine ratio[b,c]
Pregnancy[a]	**Insulin degludec cord blood[d]**
• Human chorionic gonadotropin (hCG)	• Umbilical cord blood IDeg derivate levels
Biochemistry	
• Creatinine • Albumin • Bilirubin (total) • Sodium • Potassium	• Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Alkaline phosphatase (AP) • Estimated Glomerular filtration rate (eGFR)[b]

[a] Serum pregnancy analyses performed by central laboratory at screening, in case of a positive home pregnancy test during the conception period of the trial and at visit 54.

[b] Calculated by the central laboratory at screening to determine eligibility according to exclusion criteria.

[c] Calculated by the central laboratory during the pregnancy period to screen for proteinuria without collecting 24-hours urine.

[d] Analysis performed by the special laboratory and results provided to the central laboratory. Collection of umbilical cord blood sample is only applicable for subjects randomised to IDeg.

The central laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units. Results from the exploratory IDeg cord blood analyses will not be provided to the trial sites (unless required by the country's Health Authority or IEC/IRB) as these results will not be used for any clinical evaluation by the investigator during the trial, Section 24.2 . The exploratory levels of IDeg cord blood will be analysed using the analytical method used for pharmacokinetic measurements by the special laboratory.

Review of laboratory reports must be documented either on the laboratory report or in the subject's medical record. All laboratory reports must be retained at the site as source data.

Only laboratory samples specified in the protocol must be sent to the central laboratory for analysis. If additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for

concomitant illnesses and AEs and report these according to Section 8.5.6 and Section 12 respectively.

Laboratory samples will be destroyed no later than at finalisation of the clinical trial report (CTR).

8.5.18 Body weight and height

Body weight should be assessed in light clothes without shoes. Body weight should be measured in pounds (lb) or kilograms (kg) and recorded in the eCRF to one decimal place.

Height should be assessed without shoes. Height should be measured in inches (in) or meter (m) and recorded in the eCRF to two decimal places.

Body weight and height will be used for calculation of the BMI in the eCRF.

8.5.19 Eye examination

A fundus photography or pharmacologically dilated fundoscopy must be performed as a subject must not be randomised without results confirming absence of proliferative retinopathy or maculopathy requiring acute treatment. The procedure may be performed by the investigator or local ophthalmologist/optometrist according to local practice.

For **subjects screened non-pregnant** the pharmacologically dilated fundoscopy/fundus photography can be performed within 90 days before randomisation if the results are available before randomisation. In case the subject becomes pregnant in the conception period of the trial, an additional eye examination must be completed as soon as possible, but no later than 7 days after visit 55.

For **subjects screened pregnant** the pharmacologically dilated fundoscopy/fundus photography can be performed within 28 days before randomisation if the results are available before randomisation.

The eye examination at visit 71 can be performed within 28 days before or after the visit.

The eye examination at end of treatment can be performed within 28 days before end of treatment as long as the result is available at the end of treatment visit.

The evaluation of the eye examination results by the investigator must be documented in the subject's medical records and recorded in the eCRF in accordance with the following categories: Normal, abnormal and if the abnormal result was clinically significant (Yes/No) and if considered as sight-threatening retinopathy.

In case of "abnormal, clinically significant" the investigator must record the finding on the medical history/concomitant illness form if present at screening. Any new abnormal, clinically significant finding during the trial and any clinically significant worsening from baseline must be recorded as an AE.

8.5.20 Vital signs

Diastolic BP, systolic BP and pulse will be measured following standard clinical practice preferably in the sitting position during the trial, and must be recorded in the eCRF. The evaluation by the investigator must be in accordance with the following categories: Normal, abnormal and if the abnormal result was clinically significant (Yes/No).

In case of "abnormal, clinically significant" the investigator must record the finding on the medical history/concomitant illness form if present at screening. Any new abnormal, clinically significant finding during the trial and any clinically significant worsening from baseline must be recorded as an AE.

8.5.21 Physical examination

A general physical examination will be done at the screening visit and selected visits during the pregnancy period of the trial. The examination must be recorded in the eCRF and includes:

- Head, ears, eyes, nose, throat, neck
- Respiratory system
- Cardiovascular system
- Skin
- Gastrointestinal system including mouth
- Musculoskeletal system
- Central and peripheral nervous system

The evaluation by the investigator must be in accordance with the following categories: Normal, abnormal and if the abnormal result was clinically significant (Yes/No).

In case of "abnormal, clinically significant" the investigator must record the finding on the medical history/concomitant illness form if present at screening. Any new abnormal, clinically significant finding during the trial and any clinically significant worsening from baseline must be recorded as an AE.

8.5.22 Electrocardiogram

A 12-lead ECG will be performed according to local practice at screening or in the period between screening and randomisation if the result is available before randomisation.

The evaluation of the ECG must be documented either on the printout or in the subject's medical record. The evaluation by the investigator must be recorded in the eCRF in accordance with the following categories: Normal, abnormal and if the abnormal result was clinically significant (Yes/No).

In case of "abnormal, clinically significant" the investigator must record the finding on the medical history/concomitant illness form if present at screening. Any new abnormal, clinically significant finding during the trial and any clinically significant worsening from baseline must be recorded as an AE.

8.5.23 Training in pen handling

The subject must be trained in how to handle the pen devices when handed out the first time. Training must be repeated during the trial as specified in the flowcharts in Section 2.1 and Section 2.3 in order to ensure correct use of the device. The following should be emphasised:

- Always use a new needle for each injection as this will prevent contamination and blocked needles
- Priming the pen to ensure product flow
- Injection technique as per Direction for Use (DFU) for the individual trial products (IDeg and IAsp or IDet and IAsp)
- Always check that the correct insulin pen is used (basal or bolus), e.g. by colour coding and label. Use the pen differentiation guide as a reference.

8.5.24 Subject compliance

Throughout the trial, the investigator will remind the subject to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

It is important to ensure subject treatment compliance. During treatment with trial products, the investigator should evaluate adherence to trial treatment at each weekly contact (site visit or phone contact).

8.5.25 Discontinuation of MyGlucoHealth BG-meter and eDiary

This section applies to subjects enrolled prior to implementation of Protocol Amendment no. 1.

Subjects who have used the glycaemic data collection system (the combination of the MyGlucoHealth Wireless BG-meter and an electronic diary) have been instructed to discontinue this system and use an alternative BG-meter until a new trial BG-meter and paper diary is provided by Novo Nordisk.

The following must be recorded by the investigator in the eCRF:

- Start date of new trial BG-meter

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the Trial Materials Manual (TMM).

Trial products must not be dispensed to any person not included in the trial. Trial products must not be used, if they do not appear clear and colourless.

9.1 Trial products

The trial products summarised in Table 9–1 will be provided by Novo Nordisk A/S, Denmark.

Folic acid will not be supplied by Novo Nordisk. However, folic acid will be reimbursed if required by the country's regulatory authority or IRB/IEC.

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Delivery device
Insulin degludec (Tresiba®/Tregludec® [Israel]) (IMP, test product)	100 U/mL	Solution for injection	Subcutaneous	3 mL PDS290 pen injector (FlexTouch®)
Insulin detemir (Levemir®) (IMP, reference therapy)	100 U/mL	Solution for injection	Subcutaneous	3 mL pre-filled pen (FlexPen®)
Insulin aspart (NovoRapid®) (IMP, bolus insulin)	100 U/mL	Solution for injection	Subcutaneous	3 mL pre-filled pen (FlexPen®)

IMP: investigational medicinal product

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[39], local regulations and trial requirements.

Each trial site will be supplied with sufficient amounts of trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to enrolment and randomisation.

The investigator must document that the direction for use (DFU) for the individual trial products (IDeg and IAsp or IDet and IAsp) is given to the subject orally and in writing at the first dispensing visit (visit 2). Also, the pen differentiation guide must be provided to the subject at the first dispensing visit (visit 2). Additional DFUs and pen differentiation guides can be provided as needed at the following dispensing visits.

9.3 Storage

The investigator must ensure that trial product is kept under proper storage conditions (Table 9–2) and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range). Additional details regarding handling of temperature deviations can be found in the TMM.

Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

Table 9–2 Storage conditions

Trial product	Storage conditions (not in-use)	In-use conditions	In-use time[a]
Insulin degludec	• Store in refrigerator (2°C to 8°C) • Protect from light • Do not freeze	• Do not store above 30°C • Protect from light • Can be stored in refrigerator (2°C to 8°C) • Do not freeze	• Use within 8 weeks
Insulin detemir	• Store in refrigerator (2°C to 8°C) • Protect from light • Do not freeze	• Store below 30°C • Protect from light • Can be stored in refrigerator (2°C to 8°C) • Do not freeze	• Use within 6 weeks
Insulin aspart	• Store in refrigerator (2°C to 8°C) • Protect from light • Do not freeze	• Store below 30°C • Protect from light • Do not refrigerate • Do not freeze	• Use within 4 weeks

[a] In-use time starts when first dose is taken.

9.4 Drug accountability and destruction

Drug accountability of all trial products received at site is the responsibility of the investigator. Drug accountability must be documented in the IWRS by confirming dispensing of allocated trial products and confirming trial products returned by the subject or lost.

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.

Non-allocated trial products including expired or damaged products must be accounted as unused at the latest at closure of the trial site.

Destruction of trial products can be performed on an on-going basis and will be done according to local procedures after accountability is finalised and reconciled by the monitor. Destruction of products must be documented in the IWRS.

9.5 Auxiliary supplies

The following will be provided by Novo Nordisk:

- DFU for the pen devices
- Novo Nordisk needles for the pen devices (Only needles provided by Novo Nordisk must be used for administration of trial product.)
- BG-meter including strips, lancets and control solution for BG-meter

For further auxiliary supplies information, refer to the TMM.

10 Interactive web response system

A trial-specific IWRS will be set up which can be accessed at any time via the internet. Access to the IWRS must be restricted to and controlled by authorised persons.

The IWRS is used for:

- Screening
- Randomisation
- Medication arrival
- Dispensing
- Dispensing verification (when barcode scanner is used)
- Screening failure
- Treatment discontinuation
- Completion of treatment
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure

The IWRS is used for randomisation. Subjects complying with the inclusion and exclusion criteria will be randomised 1:1 into one of the two treatment regimens in an open-label manner. Randomisation will be stratified according to the subject's pregnancy status at time of randomisation (pregnant/non-pregnant) as well as planned continued use of the subject's own CGM (Yes/No).

In IWRS this means there will be two different treatment regimens:

- IDeg OD + IAsp 2-4 times daily
- IDet OD/BID + IAsp 2-4 times daily

Recruitment will be closed as soon as the total number of planned subjects to be randomised is achievable, taking the number of screened, the screening failure ratio and non-pregnant randomised subjects into account. All investigators will be notified immediately when the recruitment period ends after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation can be randomised.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

For both the pregnant subject and foetus/infant there are specific AEs that should not be reported as AEs unless they fulfil the seriousness criteria. These are outlined in Sections 12.5.1 and 12.5.2.

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should not be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form in the diary instead of on an AE form in the eCRF, see Section 8.5.16.3

The following three definitions are used when assessing an AE for both the subject and the foetus/infant:

- Severity
    - **Mild** – no or transient symptoms, no interference with the subject's daily activities.
    - **Moderate** – marked symptoms, moderate interference with the subject's daily activities.
    - **Severe** – considerable interference with the subject's daily activities; unacceptable.

- Causality
  Relationship between an AE and the relevant trial product(s):
  - **Probable** – Good reason and sufficient documentation to assume a causal relationship.
  - **Possible** – A causal relationship is conceivable and cannot be dismissed.
  - **Unlikely** – The event is most likely related to aetiology other than the trial product.

- Final outcome
  - **Recovered/resolved** – The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
  - **Recovering/resolving** – The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
  - **Recovered/resolved with sequelae** – The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
  - **Not recovered/not resolved** – The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
  - **Fatal** – This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.
  - **Unknown** – This term is only applicable if the subject is lost to follow-up.

12.1.2 Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

- Death, including death of the foetus/infant as a result of spontaneous abortion, perinatal or neonatal death.
- A life-threatening[a] experience.
- In-patient hospitalisation[b] or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity[c] of the subject.
- A congenital anomaly or birth defect of the foetus/infant.
- Important medical events that may not result in death, be life threatening[a] or require hospitalisation[b] may be considered an SAE when – based on appropriate medical judgement – they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE[d].

a. The term "life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

b. The term "hospitalisation" is used when a subject:
   - Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
   - Stays at the hospital for treatment or observation for more than 24 hours. The hospitalisation for delivery/caesarean section is not considered as an SAE in this trial. However, prolonged hospitalisation due to complications in relation to delivery/caesarean section should be reported as an SAE.

   Medical judgement must always be exercised and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

c. A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in her body function or structure, physical activity and/or quality of life).

d. For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

The following AEs must always be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:

- Suspicion of transmission of infectious agents via the trial product.
- Risk of liver injury defined as ALT or AST > 3 x upper normal limit (UNL) and total bilirubin > 2 x UNL, where no alternative aetiology exists (Hy's law).

12.1.3 Non-serious adverse event

A non-serious AE is any AE which does not fulfil the definition of an SAE.

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug.
  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product.
- Accidental administration of a lower or higher dose than intended. That is a dose lower or higher than 20 % of the prescribed/intended dose. However, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

Medication errors must be reported on an AE form and a specific event form, see Section 8.5.16.1.

12.1.5 Adverse events requiring additional data collection

Adverse events requiring additional data collection are AEs where the additional data will benefit the evaluation of the product safety. Some events in this trial will be adjudicated by an independent external committee as described in Section 12.7.3.

Table 12–1 lists AEs that require completion of specific event forms in the eCRFs and/or are subject to event adjudication.

For details about specific event forms, see Section 8.5.16.2.

Table 12–1 Adverse events requiring completion of specific event forms and/or are subject to event adjudication

Event	Specific event form	Event adjudication
Pre-eclampsia (PE)	Yes	No
Neoplasm	Yes	No
Medication error	Yes	No
Congenital anomaly	No[a]	Yes
Severe hypoglycaemia or hypoglycaemic episodes reported as an SAE	No[b]	Yes
Fatal event[c]	No	Yes

[a] Information about congenital anomaly(-ies) will be collected in the pregnancy outcome eCRF.

[b] Hypoglycaemic episodes will be registered in the diary by the subject and transferred to eCRF by the investigator.

[c] All fatal events in subjects will be adjudicated to determine if the cause of death was related to a severe hypoglycaemic episode. All fatal events for infants including *in utero* deaths will be adjudicated for cause of death.

12.1.6 Technical complaints

A technical complaint is any written, electronic, or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

- The physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- All packaging material including labelling
- Problems related to devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen and the needle)

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (V92). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the subject must be asked about AEs and technical complaints, for example by asking: "Have you experienced any problems since the last contact?".

All AEs, observed either by the investigator or subject, must be reported by the investigator and evaluated.

All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a SIF must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one SIF can be used to describe all the SAEs.

For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the trial at the latest.

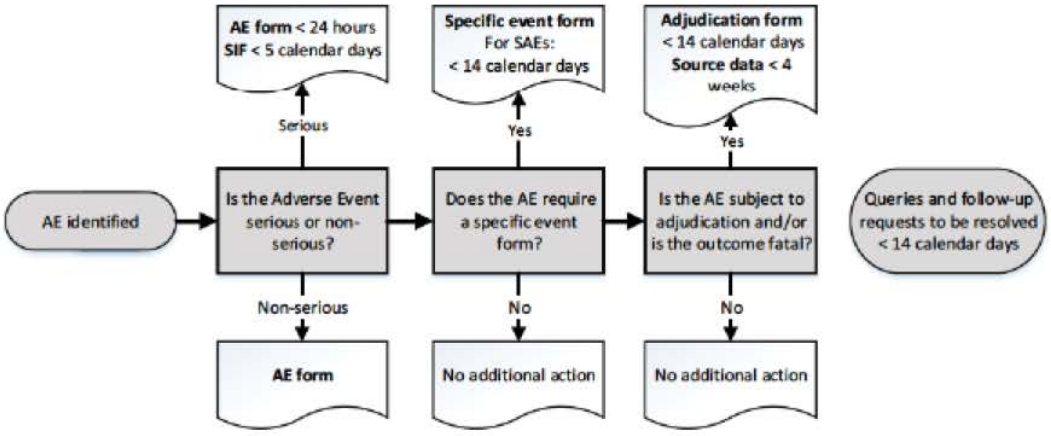
Timelines for initial reporting of AEs

The investigator must complete the following forms in the eCRF within the specified timelines:

- **SAEs:** The AE form **within 24 hours** and the SIF **within 5 calendar** days of the investigator's first knowledge of the SAE. Both forms must be signed **within 7 calendar** days from the date the information was entered in the eCRF.
- **For SAEs requiring reporting on a specific event form:** In addition to the above the specific event form **within 14 calendar days** from the investigator's first knowledge of the AE.

- **Events for Adjudication:** The adjudication form should be completed **within 14 calendar days** of the investigator's first knowledge of the AE, see Section 12.3. The investigator should provide copies of the source documentation preferably within 4 weeks of event identification.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk by fax, email or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the form into the eCRF. Contact details (fax, telephone, email and address) are provided in the investigator trial master file.



Timelines are for the completion of forms from the time of investigator's awareness AEs requiring specific event forms are descibed in Section 12.1.5 AEs for adjudication are described in Section 12.7.3

AE: Adverse event **SIF:** Safety information form

Figure 12–1 Reporting of AEs.

Novo Nordisk assessment of AE expectedness

Novo Nordisk assessment of expectedness is performed according to the current versions and any update of the IBs for IDeg[5], IDet[40] and IAsp[41].

Reporting of trial product-related SUSARs by Novo Nordisk

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP[1]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including the European Medicines Agency (EMA), of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP[1], unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication

If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.

Follow-up information must be reported to Novo Nordisk according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.
  The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

The investigator must ensure that the recording of the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

SAEs after end of trial: If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product occurring to a subject after the subject has

ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Insulin degludec (IDeg), 100 U/mL, 3 mL PDS290 pen injector (FlexTouch®)
- Insulin detemir (IDet), 100U/mL, 3 mL pre-filled pen (FlexPen®)
- Insulin aspart (IAsp), 100 U/mL, 3 mL pre-filled pen (FlexPen®)
- Novo Nordisk needles for pen devices

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk.

Contact details (fax, email and address) are provided in Attachment I to the protocol.

The investigator must assess whether the technical complaint is related to any AEs and/or SAEs.

Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each batch or lot number must be completed

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints **within 5 calendar days**

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, email or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included

in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the batch or lot number and, if available, the DUN. All parts of the DUN should be returned.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions described for the product.

12.5 Adverse events related to pregnancies

The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy and AEs in the foetus and newborn infant(s) until 2 months of age in the eCRF.

Standard local practice for treatment/procedures during pregnancy

Treatment or procedures of mother and/or foetus/infant(s) that are standard local practice and/or done for prophylactic purposes do not constitute AEs. Examples could be prophylactic i.v. glucose given to a newborn infant of a diabetic mother or prophylactic antibiotic treatment of a newborn infant due to an infection in the mother. The infection should, however, be reported as AE in the mother.

Terms not to be used for reporting

The diagnosis and symptoms used for reporting should always describe the condition as specific as possible. Unspecific diagnoses such as "diabetic foetopathy" should not be used. Instead the specific diagnose and/or symptom(s) under this term should be reported as individual AEs.

Preterm delivery

Preterm delivery where the outcome of the delivery is without complications should not be reported as an AE in itself, neither on mother or infant.

Pregnant subjects who withdraw consent

For pregnant subjects who withdraw consent, efforts should be made to obtain information related to the pregnancy and pregnancy outcome. Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) must be reported on the **paper pregnancy forms** Maternal Form 1A and 1B, respectively. In case of an abnormal pregnancy outcome, further information must be reported on the Maternal Form 2. In addition, information from the biological father (if

known) must be reported on the Paternal Form, after an informed consent has been obtained, Section 18.2.1.

Initial reporting and follow-up information must be reported **within 14 calendar days** of the investigator's first knowledge of initial or follow-up information. Reporting timelines for AEs in connection with the pregnancy as well as in the foetus and newborn infant(s) are defined in Section 12.2.

The paper forms must be forwarded to Novo Nordisk either by fax, email or courier. Contact details are provided in Attachment II to the protocol.

12.5.1 Reporting adverse events in connection with the pregnancy

The investigator has to report relevant AEs in connection with the pregnancy. The forms and timelines for reporting AEs are defined in Section 12.2.

Pregnancy-related symptoms considered "normal" for a pregnant subject should only be reported as SAEs if they fulfil the seriousness criteria. Examples could be:

- Nausea
- Vomiting
- Skin itching
- Vaginitis
- Back pain
- Breast tenderness
- Hot flushes
- Swollen ankles or fingers

12.5.2 Reporting adverse events on foetus and/or infant(s)

The investigator has to report relevant AEs in the foetus and newborn infant(s). The SAEs that must be reported include abnormal outcome, such as foetal death (including spontaneous or induced abortion), and congenital anomaly(-ies) (including those observed at gross examination or during autopsy of the foetus), as well as other pregnancy complications fulfilling the criteria of an SAE.

Adverse events pertaining to the foetus/infant must be reported with the foetus/infant as the subject of the AE. The forms and timelines for reporting AEs are defined in Sections 12.2 and 12.7.3.

Reporting of an abnormal pregnancy outcome

In case of an abnormal pregnancy outcome, e.g. congenital anomaly(-ies), foetal death including spontaneous abortion and/or any abnormalities of the infant relevant information will be collected in the specific eCRF for pregnancy outcome after delivery. Cases of abnormal pregnancy outcome must be reported as an SAE and will be subject to event adjudication, Section 12.7.3. Before information for the paternal eCRF is collected a paternal informed consent must be obtained, Section 18.2.1.

Some symptoms in the foetus and/or infant(s) are considered "normal" for a foetus/infant and should only be reported as SAEs if they fulfil the seriousness criteria. Examples could be:

- Irritability
- Breastfeeding problems
- Normal crying
- Common neonatal skin reactions (diaper or hormone rash)
- Neonatal hypoglycaemia (section 8.5.16.4)
- Macrosomia
- Hyperbilirubinaemia (not requiring medical treatment)

Reporting of foetal or neonatal death

Foetal or neonatal death as a result of induced abortion should not be reported as an AE, except in situations where the foetus/neonate was deceased prior to the induced abortion.

In case of foetal or neonatal death the following applies:

- In case of foetal or neonatal death e.g. due to spontaneous abortion, ectopic pregnancy or stillbirth, an SAE must be reported with the mother as the subject of the AE.
- In case the foetus/neonate also has a diagnosis e.g. an anomaly, an additional SAE must be reported with the foetus/neonate as the subject of the AE.

Induced abortions

Induced abortion should not be reported as an AE as it is considered a procedure. Causes of induced abortions should always be reported as SAEs on either mother or foetus, as applicable.

Reporting of caesarean section

A caesarean section itself should not be reported as an AE as it is considered a procedure. Instead, the following details for the caesarean section will be recorded in the specific eCRF for the delivery visit:

- Planned caesarean section (decision taken > 8 hours prior to delivery). The reason for the planned caesarean section will be stated as e.g.:
  - Medically indicated e.g. previous caesarean section, narrow pelvis etc.
  - Non-medical reason(s)
  - AE or SAE e.g. breech presentation, failed induction, suspicion of macrosomia, deterioration of pre-eclampsia etc.
- Unplanned caesarean section (decision taken ≤ 8 hours prior to delivery). The reason for the unplanned caesarean section will be stated as e.g.:
  - AE or SAE e.g. maternal bleeding
  - Foetal distress (always reported as an SAE)
  - Lack of progression

12.5.3 Congenital anomaly

Details about the congenital anomaly(-ies) will be collected in the specific eCRF for pregnancy outcome after delivery. All congenital anomalies must be reported as an SAE, Section 12.5.2.

As events of congenital anomalies are crucial for the ongoing safety monitoring, all congenital anomalies will be monitored closely by the Data Monitoring Committee (DMC, Section 12.7.2) and will be adjudicated by an independent adjudication committee (EAC, Section 12.7.3).

If a congenital anomaly is observed at ultrasound during pregnancy and reported as an SAE, but not confirmed after birth, the AE description should be updated with "No adverse effect" or "No adverse drug effect" in the eCRF.

The EMA Guideline on the exposure to medicinal products during pregnancy classifies anomalies as congenital anomalies, major abnormalities or minor anomalies.[42] Specific definitions for each major abnormality are included in the European network of population-based registries for the epidemiologic surveillance of congenital anomalies (EUROCAT).[26]

Rates of congenital anomalies and malformations have in some studies been shown to be 4-5% in pregnant subjects with T1DM.[13,14] The most common anomalies affect the central nervous system, heart, skeleton, kidneys, gastrointestinal tract or lungs.

12.6 Precautions and/or overdose

The administration of insulin, including an overdose of insulin, may result in hypoglycaemia. Symptoms may occur suddenly, see Section 8.5.16.3.

Asymptomatic hypoglycaemia and mild to moderate symptoms of hypoglycaemia should be treated with carbohydrates. Severe hypoglycaemia resulting in loss of consciousness should be treated with parenteral glucose, glucagon or dextrose at the discretion of the investigator.

Detailed information is available in the current edition and any updates of the IBs for IDeg[5], IDet[40] and IAsp[41] and/or local approved product information, if applicable.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk has an internal IDeg safety committee to perform ongoing safety surveillance on blinded trial data. The IDeg safety committee may recommend unblinding of any data for further analysis, and in this case an independent *ad hoc* group will be established in order to maintain the blinding of the internal Novo Nordisk trial personnel.

12.7.2 Data monitoring committee

The data monitoring committee (DMC) is an independent, external committee composed of members whose expertise covers relevant specialties including statistics. The DMC is established to review and evaluate accumulated data from the trial at predefined time points as well as *ad hoc*. This is in order to protect the safety of the subjects and to evaluate the benefit-risk balance. The DMC will have access to unblinded data, and will provide recommendations on trial continuation, modification or termination.

Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

12.7.3 Event adjudication committee

An independent external event adjudication committee (EAC) is established to perform validation of selected AEs listed in Table 12–2 according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical data related to the specific AE.

The events are reviewed by the EAC in a blinded manner. The EAC will have no authorisations to impact on trial conduct, trial protocol or amendments. The EAC is composed of permanent members covering required medical specialities. The EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk.

Event adjudication will be performed for pre-defined AEs in randomised subjects including AEs with an onset date during the screening period and selected AEs in the infant(s). Event adjudication will not be performed for AEs in screening failures.

For all events for adjudication, the source documentation should be anonymised by investigator according to the Event Adjudication Site Manual. Prior to submitting the source documentation to the EAC, the Event Adjudication supplier will ensure translation into English, if applicable.

For each source document the investigator should specify/indicate on the adjudication form when/if the required documents will be available. If a document is unobtainable this needs to be specified. If no source data are available, a clinical narrative should be provided.

Table 12–2Events for adjudication

Event	Description of event in scope for adjudication	Adjudication outcome
Fatal event (subject)	All cause death	Severe hypoglycaemia
Severe hypoglycaemia or hypoglycaemic episodes reported as an SAE (subject)	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 episode, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the episode was induced by a low plasma glucose concentration.	Severe hypoglycaemia
Congenital anomaly(-ies)	A morphological, functional and/or biochemical developmental disturbance in the embryo or foetus whether detected at birth or not. The term congenital anomaly is broad and includes congenital abnormalities, foetopathies, genetic diseases with early onset, developmental delay, etc.	Major abnormality or minor anomaly
Foetal or infant death (including spontaneous abortion)	All cause death	Cause of death

The assessment made by the EAC will be included in the clinical trial report (CTR) as well as the assessments made by the investigator. However, the adjudication made by the EAC, given its independent analysis of each event, will be attributed with greater importance of the two.

Direct reporting by the investigator

Adverse events for adjudication must be reported according to Section 12.2 and Table 12–1. In addition, the specific adjudication form should be completed within 14 calendar days of the investigator's first knowledge of the AE, and all relevant predefined documents provided within 4 weeks according to instructions in the event adjudication site manual.

Hypoglycaemic episodes will be reported by the subject in the diary. For severe hypoglycaemic episodes and hypoglycaemic episodes reported as an SAE the adjudication form must be completed in the eCRF.

Screening of AEs

All AEs will be screened to detect potential missed events for adjudication. If needed, the investigator will be requested to provide additional information such as an alternative aetiology, underlying cause(s) and/or clinical details.

Based on the information provided, the Event Adjudication supplier or the EAC can decide to have an AE adjudicated even if not initially reported as an event for adjudication by the investigator. If so, the investigator must complete the adjudication form in the eCRF and upload source data when the request is received from Novo Nordisk or the Event Adjudication supplier.

Events identified by the EAC

During the review of source data the EAC may identify additional events relevant for adjudication which have not been reported by the investigator as such. In case an additional event is identified, the site will be informed and asked to consider reporting the event. If the site does not report the event, it may still be adjudicated.

For further details regarding event adjudication refer to the Event Adjudication Site Manual.

13 Case report forms

Novo Nordisk will provide a system for the eCRFs. This system and support services to the system will be provided by an external supplier.

The investigator must ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the casebook in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

The following will be provided as paper CRFs to be used when access to the eCRF is revoked or if the eCRF is unavailable:

- AE forms
- SIF forms
- Pregnancy forms (for pregnant subjects who withdraw consent)
- Technical complaint forms (also to be used to report complaints that are not subject related (e.g. discovered at trial site before allocation)

On the paper CRFs write legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing "ND" (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing "NA" (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

13.1 Corrections to case report forms

Corrections to the eCRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date the investigator has signed the casebook, the casebook must be signed and dated again by the investigator.

Corrections to the data in the paper CRFs may only be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that was crossed out. Each correction must be initialled, dated and explained (if necessary) by the investigator or the investigator's delegated staff. If corrections are made by the investigator's delegated staff after the date of the investigator's signature on the affirmation statement, the affirmation statement must be signed and dated again by the investigator.

Corrections necessary after the CRFs have been removed from the trial site must be documented on a data clarification form (DCF) or a monitor-initiated discrepancy form (MIDF). If the affirmation statement for the subject has not yet been signed, any corrections must be approved by the investigator or her/his delegated staff. If the affirmation statement for the subject has already been signed, the investigator must approve any correction.

13.2 Case report form flow

The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within 5 days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes. Queries will be generated on an on-going basis and investigator must ensure that queries are resolved as soon as possible, preferably within 5 days.

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

14 Monitoring procedures

Monitoring will be conducted using a risk based approach including risk assessment, monitoring plans, centralised monitoring and visits to trial sites.

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the centralised monitoring of the eCRFs (remote assessment of data by Novo Nordisk), the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LSLV at the trial site.

The monitor must be given direct access to all source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

All data must be verifiable in source documentation other than the eCRF, except for age and BMI which are calculated in the eCRF and information from the Baseline Hypoglycaemic Episode Interview Questionnaire in Appendix B which is entered directly into the eCRF and will be considered source data.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The original of the completed diaries must not be removed from the trial site.

The monitor will ensure that the eCRFs are completed and that paper CRFs are collected. The following data will be source data verified for screening failures:

- Date for obtaining informed consent
- Screen failure reason

Monitors will review the subject's medical records and other source data e.g. the paper diaries to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

15 Data management

Data management is the responsibility of Novo Nordisk.

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The subject and any biological material obtained from the subject will be identified by subject number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

Data collected prior to the discontinuation of the glycaemic data collection system (the combined use of the MyGlucoHealth BG-meter and an electronic diary):

The eDiary software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11[43] and the EU directive for personal data protection[44]. After trial finalisation, Novo Nordisk and each site will be supplied with long-life DVDs. These DVDs will contain site-specific subject records including the subject's eDiary data and audit trail as well as any data additions and corrections made on each form. The eDiary vendor will furthermore retain and securely store copies of all archived documents and data for 50 years or as required by local data retention laws for trial data.

17 Statistical considerations

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock.

The internal Novo Nordisk blinding plan will describe how blinding of the randomised treatments for internal Novo Nordisk personnel will be maintained until the database has been released for statistical analysis. No interim analyses or other analyses of unblinded data will be performed before the database is locked.

Data from all sites will be analysed and reported together.

In statistical analyses where stratification is included, pregnancy status (Pregnant/Non-pregnant) and planned continuous use of CGM (Yes/No) will be based on the actual information. Hence, if subjects by mistake are allocated to a wrong randomisation list, the correct stratification factor will be applied.

In the statistical models explanatory factors will be parameterized as follows:

- Treatment: IDeg, IDet
- Stratification factor: 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.
- Region: 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).

Two different baselines will be applied; a treatment baseline and a pregnancy baseline. 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. For subjects randomised non-pregnant and becoming pregnant in the conception period of the trial, the pregnancy baseline corresponds to data from visit 55.

When summarising change from baseline for effect and safety variables assessed during or after the pregnancy period, both 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.

Laboratory values below the lower limit of quantification (LLoQ) will be set to ½LLoQ. The number of values below LLoQ by treatment and visit will be summarised if deemed relevant.

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.

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.

Missing data considerations

Data assessed prior to the GW 16 visit will not be used in the analysis nor will it be considered missing and imputed. To predict how data would have been prior to delivery after GW 16 is considered hypothetical for subjects with a delivery prior to GW 16. Based on data from NN304-1687 it is assumed that at most 10% of the women may have delivery prior to GW 16.[7]

Missing data considerations – primary estimand

When estimating the primary estimand, missing data will mainly be due to withdrawal from the trial. In the trials NN1250-3770, NN1250-3583 and NN1250-3585 (all with IDeg as IMP and parallel trial design) with a duration of 26-52 weeks in subjects with T1DM, the proportion of withdrawn subjects varied between 8% and 16%. In these trials subjects were withdrawn if they discontinued trial drug and did not attend any scheduled visits after discontinuation.

For subjects randomised as non-pregnant, the trial may potentially be of close to 2 years duration, suggesting higher drop-out rates than observed in the above mentioned trials. However, pregnant women and women with the intention to become pregnant are likely more adherent than subjects with diabetes in general. It is assumed that at most 15% of the women randomised as non-pregnant and 10% of the women randomised as pregnant will discontinue treatment. It is expected that approximately 80% of the pregnant women will be randomised as pregnant, and that in total, the percentage of subjects discontinuing treatment is smaller than 12%. Provided it is possible to retrieve data from half of these subjects, 6% of the subjects may have missing data due to withdrawal from the trial.

Within each treatment arm, missing data at the last planned visit prior to delivery after GW 16 from subjects who have discontinued treatment will be imputed from the distribution of retrieved data at the last planned visit prior to delivery after GW 16 among subjects who have discontinued treatment. Missing data at the last planned visit prior to delivery after GW 16 from subjects who have not discontinued treatment will be imputed based on the distribution among subjects who have not discontinued treatment at the last planned visit prior to delivery after GW 16. If a simple intercept model is infeasible to estimate among discontinued subjects, an on-treatment factor will be included in the model instead of doing the imputation separately by on-treatment and off-treatment. A detailed description of the imputation procedure is described in Section 17.3.1.

Missing data considerations – secondary estimand

When estimating the secondary estimand, missing data will mainly be due to discontinuation of treatment. As argued above it is expected that at most 12% of subjects will have missing data due to discontinuation of treatment.

Within each treatment arm, missing data at the last planned visit prior to delivery after GW 16 will be imputed from subjects who have not discontinued treatment at the last planned visit prior to delivery after GW 16. A detailed description of the imputation procedure is described in Section 17.3.2.

To document the extent and reason for missing data, descriptive summaries and graphical representation of extent, reason(s) for and pattern of missing data will be presented by treatment arm.

17.1 Sample size calculation

The sample size is based on the primary objective, the primary endpoint and the primary estimand. The difference in last planned HbA_{1c} prior to delivery after GW 16 will be compared to a non-inferiority (NI) margin of 0.4% for IDeg versus IDet.

No placebo controlled trials with IDet neither in pregnant women with T1DM or in subjects with T1DM have been conducted. Hence, it is unknown what the difference in HbA_{1c} between IDet and placebo would be in pregnant women with T1DM. The NI margin of 0.4% was applied in the phase 3a program for IDeg as well as the IDet pregnancy trial NN304-1687[2], but is larger than the NI of 0.3% currently being recommended by EMA.[45] Investigations of feasibility have shown that it would not be possible to recruit the number of subjects needed for applying 0.3% as a NI margin. As the objective of the primary analysis mainly is to demonstrate that the difference in glycaemic control between the two treatment regimens is small enough for a reasonable comparison of safety, a NI margin of 0.4% is considered appropriate.

Formally, let D be the mean treatment difference (IDeg-IDet) in 'Last planned HbA_{1c} 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:

$$H0: D \geq 0.4\% \text{ against } HA: D < 0.4\%$$

Non-inferiority will be considered confirmed if the upper bound of the two-sided 95% CI for D (mean treatment difference in HbA_{1c}) is strictly below 0.4%. This is equivalent to using a one-sided test of size 2.5%.

The sample size is calculated using a t-statistic under the assumptions of a one-sided test of size 2.5%, NI margin of 0.4% and a mean treatment difference of 0.0%. The standard deviation (SD) of the observed HbA_{1c} values prior to delivery was 0.7% in the NN304-1687 trial.[7] To apply retrieved data and impute missing data may potentially increase the SD. Therefore, the sample size has been calculated for values of SD equal to 0.85 and 0.90.

The primary analysis is based on the full analysis set for pregnant women ($FAS_{pregnant}$, Section 17.2) and missing data will be imputed. Hence, the sample size for the primary analysis is not adjusted for drop-outs. The numbers are however based on the assumption that 10% of the women will have delivery prior to GW 16, and hence not contribute with data in the analysis, Table 17–1.

Table 17–1 Sample size for evaluation of non-inferiority based on $FAS_{pregnant}$ with 80% power – number of pregnant women

Non-inferiority limit	Standard Deviation (SD)	Total number of women with delivery after GW 16	Total number of randomised and pregnant women
0.4%	0.85	144	160
	0.90	162	180

A sensitivity analysis will be made for the per protocol analysis set for pregnant women ($PP_{pregnant}$, Section 17.2), Based on data from NN304-1687 it is assumed that approximately 10% of subjects may be excluded from the per protocol analysis set.[7] The sample size needed for evaluation of NI based on the $PP_{pregnant}$ analysis set for pregnant women is summarised in Table 17–2.

Table 17–2 Sample size for evaluation of non-inferiority based on $PP_{pregnant}$ with 80% power – number of pregnant women

Non-inferiority limit	Standard Deviation (SD)	Total number of randomised and pregnant women (assuming 10% $FAS_{pregnant}$ excluded from $PP_{pregnant}$)
0.4%	0.85	**178**
	0.90	200

Based on this a sample size of **178** randomised and pregnant women has been chosen. At most ⅓ of the women are to be randomised as non-pregnant. The proportion of subjects randomised as non-pregnant and becoming pregnant during the trial is estimated to be approximately 50% based on experience from NN304-1687.This means that **214** women should be randomised, 142 should be randomised as pregnant and 72 should be randomised as non-pregnant. However, the percentage of women randomised as non-pregnant that actually become pregnant will be followed carefully. If this percentage is lower than 50% more women should be randomised to ensure 178 pregnant women.

If a NI margin of 0.3% was to be applied instead, 314 rather than 178 pregnant women would be needed to obtain a power of 80% for evaluating NI based on $PP_{pregnant}$. As described above, feasibility studies showed that it would not be possible to aim for this sample size.

17.2 Definition of analysis sets

The following analysis sets will be defined:

- **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".
- **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".

Exclusion of data from analyses will be used restrictively, and normally no data should be excluded from the $FAS_{pregnant}$ and the FAS_{all}. 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 CTR.

Definition of data selections and observation periods

The **in-trial** observation period 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.

A woman is defined to have **completed the trial period** if she is/becomes pregnant during the trial, is not withdrawn from the trial and attends the final follow-up visit V92.

The **on-treatment** observation period 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.

A woman is defined to have **completed the treatment period** if she is/becomes pregnant during the trial, receives the required treatment until the planned end of treatment visit and also attends this visit.

The **pregnancy period** 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.

The **pre-pregnancy period** 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.

The **post-pregnancy period** starts the day after the delivery and ends at the same time as the in-trial period.

These 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.

17.3 Primary endpoint

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

17.3.1 Primary analysis for the primary estimand

The primary estimand will be estimated based on the $FAS_{pregnant}$ using data from the last planned visit prior to delivery after GW 16. Hence, data assessed at the planned visit prior to delivery will be used in the analysis, provided the visit corresponds to the GW 16 visit or later. If delivery is in GW 40, data from GW 36 will be used. If data at this visit is missing, and data from an additional visit after GW 36 and prior to delivery is available, data from this visit will be used. Similarly, if delivery is in week GW 18, data from GW 16 will be applied. If data at this visit is missing, and data from an additional visit after GW 16 and prior to delivery is available, data from this visit will be applied. Available data from the in-trial period will be included regardless of whether trial product was discontinued or not.

The primary statistical analysis will be using multiple imputations to handle missing data assuming that the missing data mechanism is missing at random (MAR) within the groups used for imputation.

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 on-treatment 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 HbA_{1c} prior to delivery after GW 16
    - For subjects where HbA_{1c} 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 HbA_{1c} interaction.
    - For subjects where HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 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.

Analysis used for confirming non-inferiority of IDeg versus IDet

For each of the 1000 imputed datasets last planned HbA_{1c} prior to delivery after GW 16 will be analysed using an ANCOVA with treatment, region and the stratification factor as categorical fixed effects and a pregnancy status at randomisation-by-baseline HbA_{1c} interaction. In each analysis the treatment difference between IDeg and IDet and the associated standard error will be estimated. The estimates and standard errors from the 1000 datasets are pooled to one estimate and associated standard errors using Rubin's rule[46] to draw inference. From these pooled estimates the 95% CI for the treatment difference is calculated.

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.

Data from the in-trial pregnancy and post-pregnancy periods will be summarised and plotted by treatment arm and visits based on $FAS_{pregnant}$. Summaries and plots will also be presented separately for subjects randomised as pregnant and subjects randomised as non-pregnant.

17.3.2 Primary analysis for the secondary estimand

The secondary estimand will be estimated based on the $FAS_{pregnant}$ using data from the last planned visit prior to delivery after GW 16, similarly to the way in which the primary estimand was estimated. However, data retrieved outside of the on-treatment period will not be used in the analysis, but will be considered missing.

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 in the following steps:

- An ANCOVA will be fitted to the observed values of last HbA_{1c} prior to delivery after GW 16 for subjects where this assessment 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 HbA_{1c} interaction.
- 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 HbA_{1c} prior to delivery after GW 16 data for subjects missing these.

For each of the 1000 imputed datasets last planned HbA_{1c} prior to delivery after GW 16 will be analysed as described for the primary estimand.

Data from the on-treatment pregnancy and post-pregnancy periods will be summarised and plotted by treatment arm and visit based on $FAS_{pregnant}$. Summaries and plots will also be presented separately for subjects randomised as pregnant and subjects randomised as non-pregnant.

17.3.3 Sensitivity analyses

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 EMA[47] and the U.S. National Research Council[48]. 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:

- A multiple imputation analysis based on the $PP_{pregnant}$
  - The analysis is similar to the primary analysis for the primary/secondary estimand, but based on $PP_{pregnant}$. The analysis investigates the impact of protocol deviations on the primary analysis.
- A multiple imputation tipping point analysis based on the $FAS_{pregnant}$
  - In this sensitivity analysis, missing data will first be imputed according to the primary analysis for the primary/secondary estimand. Second, for the IDeg arm a penalty will be added to the imputed values of last planned HbA_{1c} prior to delivery after GW 16. The approach is to gradually increase this penalty until the confirmed HbA_{1c} 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.

17.4 Secondary endpoints

17.4.1 Efficacy endpoints

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.

Data from the in-trial pregnancy and post-pregnancy periods will be summarised and plotted by treatment arm and visit based on $FAS_{pregnant}$. Data from the on-treatment period will be presented

similarly. In addition, summaries and plots will be presented separately for subjects randomised as pregnant and subjects randomised as non-pregnant.

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 HbA_{1c}. Hence, 1000 imputed datasets simulated as for the primary analyses of the primary and secondary estimand for HbA_{1c}, 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 HbA_{1c} 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

The above continuous endpoints will be analysed using similar modelling approaches as for the primary endpoint with the associated baseline response as a covariate.

17.4.2 Safety endpoints

17.4.2.1 Classification of Hypoglycaemia in subjects

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of trial product administration, and no later than 7 days from the last day on trial product.

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

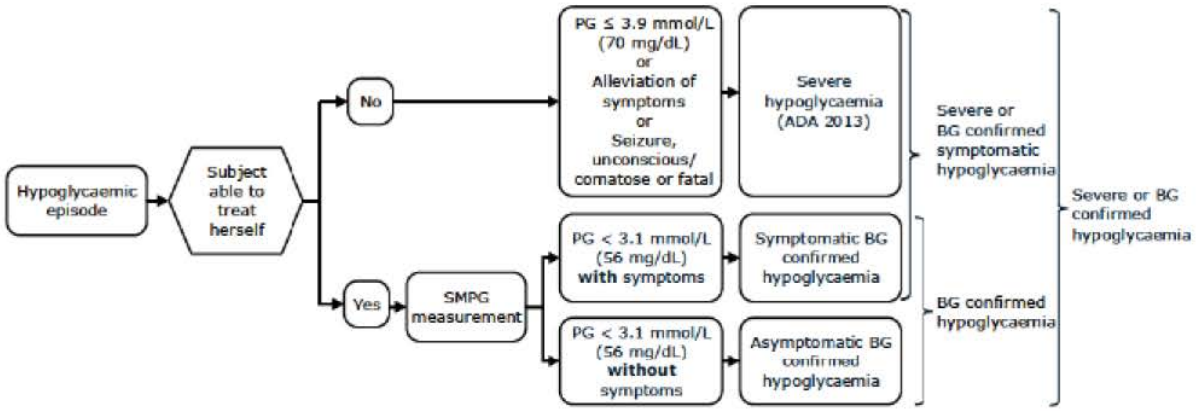
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–1) and the ADA classification of hypoglycaemia (see Figure 17–2).

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)[42]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

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

- Severe hypoglycaemia according to the ADA classification.[35]
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[35] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.
- BG confirmed hypoglycaemia: An episode that is BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[35] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.



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

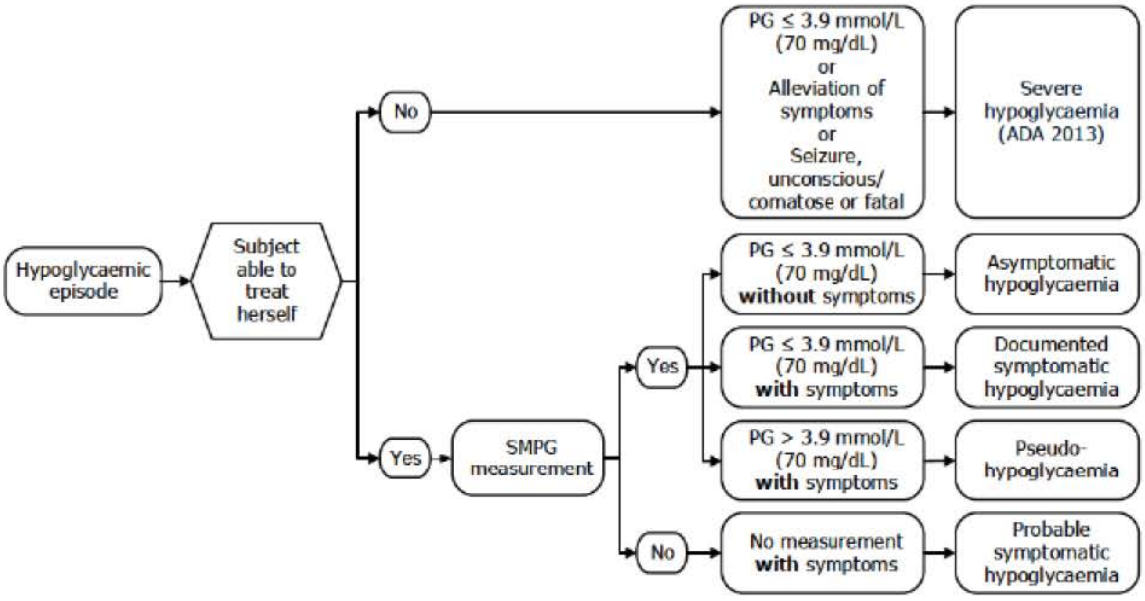
BG: blood glucose PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification[35] of hypoglycaemia

- Severe hypoglycaemia: 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.

- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).



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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–2 ADA classification of hypoglycaemia

Hypoglycaemia during the pregnancy period

Data on treatment-emergent hypoglycaemic episodes with onset during the pregnancy period 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).

Summaries will be based on $SAS_{pregnant}$ and will display:

- Number of severe or BG confirmed symptomatic hypoglycaemic episodes
- Number of nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes
- Number of severe hypoglycaemic episodes
- Number of hypoglycaemic episodes according to ADA definition

Data on all hypoglycaemic episodes with onset during the pregnancy period will be presented similarly.

Hypoglycaemia during the in-trial period, the pre-pregnancy period and the post-pregnancy period

Treatment emergent hypoglycaemic episodes with onset in the pre-pregnancy period, the post-pregnancy period as well as all treatment emergent hypoglycaemic episodes during the in-trial period will be summarised similarly as described for the hypoglycaemic events during the pregnancy period.

Data on all hypoglycaemic episodes within each of the three periods will be presented similarly.

17.4.2.2 Maternal safety endpoints

Maternal safety endpoints assessed during and after the pregnancy period

Summaries will be based on $SAS_{pregnant}$ unless otherwise specified. Data will be presented for all subjects in $SAS_{pregnant}$, as well as divided according to whether subjects were pregnant at randomisation or not.

Development of sight-threatening retinopathy from treatment baseline as well as from pregnancy baseline to the end of treatment visit

Sight-threatening retinopathy is defined as proliferative retinopathy or maculopathy. The proportion of subjects developing this between treatment baseline/pregnancy baseline to the end of treatment as well as to the additional end of treatment visit will be summarised by treatment arm.

Pre-eclampsia

Pre-eclampsia (PE) is defined as new-onset hypertension (blood pressure ≥140 mmHg systolic or ≥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 ≥ 300 mg protein in a 24 hours urine sample, a protein-to-creatinine ratio of ≥ 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.

The number and percentage of subjects experiencing PE as well as the event rate per 100 years of exposure (R) will be displayed.

Mode of delivery

The endpoint will be summarised by treatment arm based on the in trial data. The number and percentage of subjects in each category will be displayed. The endpoint will further be summarised according to the following sub-groups:

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

Change in body weight from pregnancy baseline to last planned visit before delivery
Change in body weight from pregnancy will be summarised by treatment arm and visit for all visits including last planned visit before delivery.

Adverse events during the pregnancy period
Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) database.

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. If the event onset date is before the first day of exposure on randomised treatment and increases in severity at some point during the on-treatment period, then this event should also be considered as a TEAE. Major adverse cardiovascular events (MACEs, defined as all cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes) are considered treatment-emergent until 30 days after the last day of randomised treatment.

Treatment emergent AEs are summarised descriptively. Data from TEAEs 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).

Adverse events with onset during the pregnancy period are defined as corresponding to the pregnancy period. Number of TEAEs during the pregnancy period will be summarised based on all subjects in $SAS_{pregnant}$.

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.

Furthermore, 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.

Adverse events during the in-trial period, the pre-pregnancy period and the post-pregnancy period

Adverse events with onset in the pre-pregnancy period, the post-pregnancy period as well as all AEs during the in-trial period will be summarised as described above for AEs with onset in the pregnancy period.

17.4.2.3 Pregnancy outcome endpoints

Supportive continuous and binary pregnancy outcome endpoints

- Birth weight
  - Birth weight (kg)
  - 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)
- 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 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 classification of congenital anomalies will be listed.

Adverse events in the infant from delivery to final follow-up
Adverse events will be coded using the most recent version of the MedDRA database.

Adverse events are 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

17.5 Exploratory endpoints and other assessments

The exploratory endpoints listed in Section 4.5 and other assessments listed in Section 4.6 will be presented using summary statistics.

18 Ethics

18.1 Benefit-risk assessment of the trial

The trial population consists of pregnant subjects with T1DM. For this population a good glycaemic control without experiencing hypoglycaemia is of great importance in order to minimise the risk for complications during pregnancy and for the pregnancy outcome. The same ethical principles apply to trials in pregnancy as in all other trials, however special attention must be given to the particular situation carrying and having a child. Consideration must be given to the emotional state of the mother in relation to the infant or the pregnancy with regard to the trial requirements. For all subjects participating in this trial, the anticipated benefits include a very close follow-up during their pregnancy potentially resulting in improved glycaemic control. Titration algorithms specifying recommended adjustments of the basal insulin dose at different plasma glucose levels are used in order to ensure subjects receive an optimal treatment. Subjects will receive intensive medical care by means of close contact to the clinical sites with at least weekly contacts.

Trial products will be provided by Novo Nordisk free of charge. Subjects will be provided with a BG-meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use. Subjects will receive IDeg and IAsp or IDet and IAsp in prefilled pens. For a description of risks and benefits please refer to current versions and any updates of the IDeg IB[5], the SmPC for IDeg[6], IDet[8] and IAsp[10] and/or local approved product information, if applicable.

Currently only IDet and IAsp are approved for use by pregnant subjects with T1DM. For many clinicians the use of IDeg during pregnancy seems a compelling choice as basal insulin due to its low variability and low risk of hypoglycaemia. There is no information available today indicating any other risks in connection with the use of IDeg, neither for the pregnant women nor for the foetus, than those found with IDet. The trial products may be associated with side effects, but relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participating in the trial. These precautions include thorough information regarding the correct administration of the trial product and handling of low BG measurements. Furthermore, subjects will be fully informed about possible AEs and inconveniences before initiation of any trial related activities.

Clinical benefits and risk considerations for the trial

For the individual subjects, the personal health-related benefits are related to the medical examination and the benefit from a treatment regimen anticipated being equal to or better than the treatment they receive at the time they enter the trial. However, subjects will have to spend some extra time monitoring and recording data and on additional visits to the clinic and phone contacts.

The high frequency of contacts between the subject and the investigator and the thorough evaluation of SMPG values will provide the opportunity for optimising the titration of basal and bolus insulin and thereby may contribute to obtaining improved HbA_{1c} results.

For the individual subjects, the anticipated side effects associated with the trial products are not different from what is seen with other insulins and include hypoglycaemia, hypersensitivity reactions, injection site reactions and lipodystrophy. The side effects will be mitigated by the close supervision of the subjects, the frequent measurements of BG levels and the review and monitoring of data by the DMC. Detailed information about trial products is available in the current edition and any updates of the IDeg IB[5], the SmPC for IDeg[6], IDet[8] and IAsp[10] and/or local approved product information, if applicable.

Subjects in this trial will benefit from a basal-bolus insulin treatment in a TTT setting under close supervision. It is concluded that the clinical benefits from the trial outweigh the potential risks of participating in this trial.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[1] and the requirements in the Declaration of Helsinki[2].

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand.

The subject must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

If required by local legislation, the father of the foetus (if known) must be asked to sign an agreement form before delivery in order to collect blood samples as well as health information about the infant after delivery. If the father of the foetus is not known this must be documented in the subject's medical records. If the father of the foetus refuses to give his consent, this information will not be collected.

The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local

requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the investigator must inform the subject in a timely manner, and a revised written subject information must be provided and a new informed consent must be obtained.

18.2.1 Paternal informed consent

In case of abnormal pregnancy outcome the biological father of the foetus/infant(s) (if known) must be asked to sign an informed consent in order to register relevant paternal information to evaluate the reason for the abnormality.

The procedure for obtaining and documenting the paternal informed consent follows the procedure in Section 18.2.

18.3 Data handling

If the subject withdraws from the trial or is lost to follow up, then the subject's data will be handled as follows:

- Data already collected and any data collected at the end of trial visit including follow-up visits will be retained by Novo Nordisk, entered into the database and used for the CTR.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements

If data is used, it will always be in accordance with local regulations and IRBs/IECs.

18.4 Information to subjects during trial

The site will be offered a communication package to the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subject at the discretion of the investigator. The subject may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Furthermore, the subject may receive letters during the trial.

All written information to subjects must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If the trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of subjects who have participated in the trial. If it has an impact, the actions needed to inform and protect the subjects should be described.

19 Protocol compliance

19.1 Protocol deviations

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the trial database.

Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

19.2 Prevention of missing data

The importance of subject retention will be addressed by Novo Nordisk in the training and communication with the trial sites.

The subjects will be carefully informed about the trial procedures before signing informed consent, so that they know the implications of participating in the trial.

Close surveillance of subject retention will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial product or withdrawal of consent to secure early mitigations in collaboration with the trial sites.

The investigator will make every effort to ensure that all assessments are performed and data is collected. If missing data does occur the reason will be collected via the protocol deviation process, see Section 19.1. Novo Nordisk will monitor protocol deviations on an on-going basis throughout the trial followed by appropriate actions (e.g. re-training of site staff).

20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received and the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- *Curricula vitae* of investigator and sub-investigator(s) (current, dated and signed – must include documented GCP training or a certificate)
- Signed receipt of IB, SmPC or similar labelling
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP[1], applicable regulatory requirements and the Declaration of Helsinki[2].

By signing the protocol agreement, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the trial site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-related medical decisions. The investigator will follow instructions from Novo Nordisk when processing data.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents including the subject identification code list must be kept in a secure locked facility, so no unauthorized persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of subjects to a specific qualified physician who will be readily available to subjects during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

23 Reports and publications

The information obtained during the conduct of this trial is considered confidential, and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted clinical trial report for this trial.

One investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the ICMJE for research publications[50].

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[29].

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

At the end of the trial, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

Where required by the journal, the investigator from each trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the ICMJE[50] (sometimes referred to as the Vancouver Criteria). The investigator(s) offered authorship will be asked to comment and approve the publication(s).

23.1.2 Site-specific publication(s) by investigator(s)

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database.

Individual investigators will have their own research subjects' data, and will be provided with the randomisation code after results are available.

24 Retention of clinical trial documentation and human biosamples

24.1 Retention of clinical trial documentation

Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

The files from the trial site/institution must be retained for 15 years after end of trial as defined in Section 7, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biosamples

The IDeg cord blood samples collected may be stored until after end of trial until they have been analysed. The IDeg cord blood samples will be destroyed no later than at finalisation of the CTR.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to the IB, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of

the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the subjects.

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

26 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence, or any other liability of the sites or investigators conducting the trial, or by persons for whom the said site or investigator are responsible.

Novo Nordisk accepts liability in accordance with:

For Australia: Medicines Australia Form of Indemnity for clinical trials version 160104B dated 16 January 2004.

For Russia: Federal Law of 12 April 2010 No. 61-FZ "On Circulation of Medicines".

For Austria: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBI II Nr. 105/2015.

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Appendix A: Insulin Titration Guideline

Trial ID: NN1250-4300

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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1 Introduction

The goal of insulin therapy is to achieve near normoglycaemia, i.e. to reach a pre-defined HbA_{1c} level with a low rate of hypoglycaemic episodes and as little weight gain as possible. Several trials have shown that this is difficult to achieve, unless plasma glucose (PG) values are intensively monitored and the insulin dose(s) frequently adjusted.[1-6]

To ensure treatment uniformity between the sites, as well as to ensure that subjects receive an optimal treatment, titration algorithms have been developed specifying recommended dose adjustments at different PG levels.

It is recognised that treatments differ between different regions and countries. Likewise, specific titration guidelines may not be applicable in certain clinical situations. It is important that other information, such as symptoms of hypoglycaemia and/or hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the subject's level of glycaemic control, is taken into consideration when decisions on dosing are made. The investigator should always use clinical judgement to avoid safety hazards. The investigator is responsible for the treatment of the subjects and can therefore overrule the guideline.

To optimise and maintain glycaemic control the investigator should throughout the trial be in weekly contact with the subjects to assist the subjects in adjusting insulin doses and to ensure the subject's welfare.

As this trial is performed in pregnant subjects with type 1 diabetes mellitus (T1DM), it is especially important that the investigator also considers that the insulin demand will vary during pregnancy, e.g. being lower during the first 20 gestational weeks than during the remainder of the pregnancy.

2 Treatment regimens

At randomisation, pre-trial insulin treatment must be discontinued. Eligible subjects are randomised 1:1 into one of the two treatment arms:

- Insulin degludec (IDeg) OD + insulin aspart (IAsp) 2-4 times daily with meals
- Insulin detemir (IDet) OD/BID + insulin aspart (IAsp) 2-4 times daily with meals

The treat-to-target (TTT) approach is applied in both treatment arms in order to optimise titration and glycaemic control throughout the trial.

There are no maximum or minimum doses.

2.1 Injection area

The trial products IDeg, IDet and IAsp should be injected subcutaneously into the thigh, upper arm (deltoid area) or the abdomen. The chosen region should be the same throughout the trial. Rotation of injection sites within a given region is recommended.

2.2 Time of injection

Insulin degludec should be administered OD any time of the day, preferably at the same time every day.

Subjects receiving IDet OD should administer the dose any time of the day, preferably at the same time each day. Subjects receiving IDet BID should administer one dose in the morning and the other dose in the evening or at bedtime.

Insulin aspart should be administered 2-4 times daily with the meals. Additional bolus dosing is allowed at the investigator's recommendation.

3 Initiation and titration

3.1 Initiation

Subjects randomised to IDeg should reduce their previous basal insulin dose by 20% and dose OD.

Subjects randomised to IDet should be transferred unit-to-unit. If the subjects switch from an OD regimen, they should continue on an OD regimen. If the subjects switch from a BID regimen they should continue on a BID regimen. Dose reduction should be considered.

The subjects should have their bolus insulin doses switched to IAsp unit-to-unit.

3.2 Basal titration

After randomisation the basal insulin doses should be adjusted once weekly by the investigator in connection with the scheduled visits/phone contacts.

The IDeg dose adjustment should be based on the mean of three pre-breakfast SMPG values measured on two days prior to titration and on the day of the visit. This also applies to subjects receiving IDet OD.

For subjects receiving IDet BID, the morning dose will be adjusted according to the mean pre-main evening meal SMPG values obtained on the three days prior to the day of the visit or contact. The evening dose will be adjusted according to the mean pre-breakfast SMPG values measured on the

two days prior to the day of the visit or contact and on the day of the visit or contact. Adjustments will be in accordance with Table 3–1 and Table 3–2.

If one or more SMPG values are missing, the dose adjustment should be performed on the remaining SMPG value(s). The insulin dose adjustment should aim to reach an SMPG of 4.0-5.0 mmol/L (71-90 mg/dL).

The dose calculation will be based on the most recent dose taken within the last three days before the contact.

Table 3–1 IDeg or IDet dose increase

Mean pre-breakfast or pre-main evening meal SMPG		Dose adjustment
mmol/L	mg/dL	U
4.0 – 5.0	71 – 90	No adjustment
5.1 – 10.0	91 – 180	+2
10.1 – 15.0	181 – 270	+4
> 15.0	> 270	+6

If one of the SMPG values is below target of 4.0 mmol/L (71 mg/dL) the insulin dose should be reduced according to Table 3–2.

Table 3–2 IDeg or IDet dose reduction

Lowest pre-breakfast or pre-main evening meal SMPG		Dose adjustment
mmol/L	mg/dL	U
<3.1	<56	-4
3.1 – 3.9	56 – 70	-2

3.3 Bolus titration

Insulin aspart adjustments should be at the investigator's discretion and in collaboration with the subject.

During pregnancy it is recommended to measure SMPG values 60 minutes after main meal start. These values can be used for further bolus dose optimisation. The American College of Obstetricians and Gynecologists and American Diabetes Association recommend a 60 minutes post-prandial SMPG ≤ 7.8 mmol/L (≤ 140 mg/dL).[7]

3.4 Deviations from the algorithm

It is recommended that the algorithm is followed. However, it is also important that the decision to adjust the IDeg or IDet doses is based on all relevant information as described in Section 1. A reason for deviating from the algorithm should be entered into the eCRF.

4 Data collection

The following data should be entered into the eCRF within 24 hours (on weekdays) after each site visit or phone contact:

- Per protocol SMPG values
- Doses of IDeg/IDet taken the last three days before the contact
- New prescribed dose of IDeg/IDet at the contact
- Reason(s) for deviation(s) from the titration algorithms, if any
- Hypoglycaemic episode(s)

5 Review procedure

Surveillance of titration data will be performed centrally by Novo Nordisk in an unbiased manner. It is important that data regarding dose titration is entered into the eCRF within 24 hours (on weekdays). If delays occur, action cannot be taken in due time before the subject's next site visit or phone contact. The aim is to reduce the time periods in which a subject may receive suboptimal treatment.

The data listed in Section 4 will be reviewed by Novo Nordisk within 24 hours (on weekdays). The reviewer may contact the investigator to get clarification regarding the reason for deviation or to request entry of missing data.

When the investigator receives an inquiry, a response should be received at Novo Nordisk within 24 hours (on weekdays).

During the trial, HbA_{1c} will be monitored by Novo Nordisk for additional surveillance of the glycaemic control. Novo Nordisk may be in contact with sites (visit or phone contact) to discuss progress in glycaemic control and titration of individual subjects based on SMPGs and HbA_{1c}. This will be done in an unbiased and whenever possible in a blinded manner.

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Appendix B: Baseline hypoglycaemic episode interview questionnaire

Trial ID: NN1250-4300

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

Interview questions for baseline hypoglycaemic episodes

Instructions to interviewer (do not read aloud to the subject):

- Please read the questions as written. However, you may rephrase if subject needs clarification.
- If the subject gives a range for a response (e.g. experienced 2 to 4 severe hypoglycaemic episodes), record the average of the response (3 times). If the average is a decimal number (3.5 times), then round down to the nearest integer (3 times) and record this number.
- If a subject changes her response, record the last response given.
- If the subject responds to a question by saying something like "I do not know, I never really think about it", ask the subject to take a minute and think about it.
- If the subject still does not remember or refuses to answer, please do not complete the question (leave the field blank).

Instructions to the subject (read aloud to the subject):

- The following questions are about your experience with hypoglycaemic episodes (low blood sugar levels).
- Please answer to the best of your recollection.
- Please try to think of the last 6 months for the first question and the last 4 weeks for the second question.
- Perhaps you experienced no symptoms, but noted the low blood sugar episode when measuring your blood sugar, possibly for another reason.

General questions

1. In the last **6 months** have you had a hypoglycaemic event from which you couldn't recover yourself and you needed help from someone else to recover, i.e. a 'severe hypoglycaemic event'?

   ☐ No (if no, go to question 2)

   ☐ Yes (ask the following questions)

   a) How many? _____

   b) How many of these events occurred at night (between midnight and 6 o'clock in the morning)?

   _____

2. In the last **4 weeks** have you had a hypoglycaemic event which you have been able to manage yourself, i.e. a 'non-severe hypoglycaemic event'?

   ☐ No

   ☐ Yes (ask the following questions)

   a) How many? _____

   b) How many of these events occurred at night (between midnight and 6 o'clock in the morning)?

   _____

Thank you, this ends the interview (stop here).

Global and country key Novo Nordisk staff

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff

Ethics Committee/IRB Approval Cover page

Trial ID:	NN1250-4300
Country code:	IT
Name of approving IEC/IRB:	Comitato EticoFondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
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