Protocol

Including amendment no 1 dated 05 June 2014
and amendment no 2 dated 25 July 2014
and amendment no 3 dated 16 November 2015
to Protocol, final version 5.0 dated 22 October 2013,

SWITCH 1
Trial ID: NN1250-3995

A randomised, double blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, both with insulin aspart as mealtime insulin in subjects with type 1 diabetes

Redacted protocol
Includes redaction of personal identifiable information only.

Trial phase: 3b

Protocol originator
[redacted], Clinical Operations
[redacted], Clinical Operations

Table of Contents

Table of Figures

Page

Table of Tables

Page

List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
BG	blood glucose
BID	"bis in die" twice daily
BMI	body mass index
CCDS	company core data sheet
CKD-Epi	chronic kidney disease epidemiology collaboration
CLAE	clinical laboratory adverse event
CRF	case report form
CSII	continuous subcutaneous insulin infusion
DUN	dispensing unit number
EAC	event adjudication committee
EASD	European Association for the study of Diabetes
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDAAA	Food and Drug Administration Amendment Act
FPFV	first patient first visit
FPG	fasting plasma glucose
GCP	Good Clinical Practice

HbA_{1c}	glycosylated haemoglobin
hCG	human chorionic gonadotropin
IAsp	insulin aspart
IB	investigator's brochure
I:carb	Insulin:carbohydrate
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDeg	insulin degludec
IDet	insulin detemir
IEC	independent ethics committee
IGlar	insulin glargine
IRB	institutional review board
IV/WRS	interactive voice/web response system
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
MESI	medical event of special interest
MI	myocardial infarction
NPH	Neutral Protamine Hagedorn
NYHA	New York Heart Association
OD	once daily
PCI	percutaneous coronary intervention
PG	plasma glucose
PRO	patient reported outcome
PYE	patient years of exposure

SAE	serious adverse event
s.c.	subcutaneous
SF-36®v2	Short-Form 36 Health Survey® version 2
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
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TMM	trial materials manual
TRIM-HYPO	Treatment Related Impact Measure for minor Hypoglycaemic events
T-T-T	treat-to-target
UTN	Universal Trial Number

1 Summary

Objective(s) and endpoint(s):

Primary objective

To compare the rates of severe or BG (blood glucose) confirmed symptomatic hypoglycaemia of IDeg once daily (OD) + IAsp to IGlar OD + IAsp, by demonstrating that the upper limit of the 95% confidence interval of the rate ratio is below or equal to a non-inferiority margin of 1.10, and if confirmed, to a superiority limit of 1.0

Secondary objective

To compare the rates of severe or BG confirmed symptomatic nocturnal hypoglycaemia with IDeg OD + IAsp to IGlar OD + IAsp, by demonstrating that the upper limit of the 95% confidence interval of the rate ratio is below or equal to a non-inferiority margin of 1.10, and if confirmed, to a superiority limit of 1.0.

To confirm superiority of IDeg OD + IAsp compared to IGlar OD + IAsp in terms of proportion of subjects with severe hypoglycaemic episodes.

To compare efficacy of IDeg OD + IAsp in controlling glycaemia with respect to change from baseline in HbA_{1c} after 32 weeks of treatment. This is done by comparing the difference in change from baseline in HbA_{1c} after 32 weeks of treatment between IDeg OD + IAsp and IGlar OD + IAsp to a non-inferiority limit of 0.4%.To compare IDeg OD + IAsp and IGlar OD + IAsp in terms of safety, other parameters of glycaemic control and patient reported outcome (PRO).

Primary endpoint

Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64).

Key secondary endpoints

- Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64).
- Proportion of subjects with one or more severe hypoglycaemic episodes during the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64).

Safety endpoint

The following safety endpoint will be assessed for each treatment period:

- Incidence of treatment emergent adverse events during 32 weeks of treatment

Efficacy endpoints

The following efficacy endpoints will be assessed for each treatment period:

- Change from baseline in HbA_{1c} after 32 weeks of treatment
- FPG after 32 weeks of treatment

Trial design:

This trial is a 64-week, randomised, controlled, double blind, two-period, cross-over, multi-centre, treat-to-target trial comparing the safety and efficacy of IDeg and IGlar both administered once daily, in a basal-bolus regimen with IAsp as mealtime insulin in subjects with type 1 diabetes mellitus.

Subjects will be switched from pre-trial insulin treatment and randomly allocated into one of two treatment sequences in a blinded manner:

- IDeg OD + IAsp 2−4 times daily followed by IGlar OD + IAsp 2−4 times daily
- IGlar OD + IAsp 2−4 times daily followed by IDeg OD + IAsp 2−4 times daily

Within each treatment arm subjects will be randomised 1:1 to morning or evening dosing. The dosing time will be kept throughout both treatment periods.

The trial includes two 32-week treatment periods in a cross-over design. Total trial duration for the individual subjects will be up to 67 weeks.

Trial population:

An expected number of 446 randomised subjects with type 1 diabetes previously treated with a basal-bolus regimen or continuous subcutaneous insulin infusion (CSII).

Key inclusion criteria:

- Male or female, age ≥ 18 years at the time of signing informed consent
- Subjects fulfilling at least one of the below criteria:
  a) Experienced at least one severe hypo episode within the last year (according to the ADA definition, April 2013)
  b) Moderate chronic renal failure, defined as glomerular filtration rate 30 - 59 mL/min/1.73 m^2 per CKD-Epi
  c) Hypoglycaemic symptom unawareness
  d) Diabetes mellitus duration for more than 15 years
  e) Recent episode of hypoglycaemia (defined by symptoms of hypoglycaemia and/or episode with low glucose measurement (≤ 70 mg/dL [≤ 3.9 mmol/L])) within the last 12 weeks prior to Visit 1 (screening)
- Type 1 diabetes mellitus (diagnosed clinically) ≥ 52 weeks prior to Visit 1
- Current treatment with a basal−bolus regimen (consisting of neutral protamine Hagedorn (NPH) insulin OD / BID or insulin detemir (IDet) OD / BID plus 2−4 daily injections of any rapid acting or fast acting meal time insulin) or CSII (with rapid acting insulin) for ≥ 26 weeks prior to Visit 1
- HbA_{1c} ≤ 10% by central laboratory analysis
- BMI ≤ 45 kg/m^2

Key exclusion criteria:

- Treatment with IGlar or IDeg within the last 26 weeks prior to Visit 1 (short term use [≤ 2 weeks] is allowed, but not within 4 weeks prior to screening)
- Use of any other anti-diabetic agent than those stated in the inclusion criteria within the last 26 weeks prior to Visit 1

Assessments:

- Hypoglycaemic episodes
- HbA_{1c}
- FPG
- SMPG values (4-point and 9-point profiles)
- Adverse events

Trial products:

- Insulin degludec (IDeg) 100U/ml, 10 ml vial
- Insulin glargine (Lantus®) (IGlar) 100U/ml 10 ml vial
- Insulin aspart (NovoLog®) (IAsp) 100U/ml Pre-filled pen (FlexPen®)

Trial products are for subcutaneous injection.

2 Flow chart

Table 2–1 Flow chart – site visits

		Treatment period A (32 weeks)								Treatment period B (32 weeks)									
Trial NN1250-3995	**Screening**	**Randomisation**	**Wash-out 16 weeks**			**Maintenance 16 weeks**				**Cross-over**	**Wash-out 16 weeks**			**Maintenance 16 weeks**				**End of Treatment**	**Follow up**
Visit Number (V)	**V1**	**V2**	**V6**	**V10**	**V14**	**V18**	**V22**	**V26**	**V30**	**V34**	**V38**	**V42**	**V46**	**V50**	**V54**	**V58**	**V62**	**V66**	**V67**
☎ Weekly Phone Contact number (P) (For details see separate flow chart below)		**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**	**P55 P56 P57**	**P59 P60 P61**	**P63 P64 P65**		
Time of visit (weeks)	**-2[1]**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**65[2]**
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
SUBJECT RELATED INFO/ ASSESSMENT																			
Informed consent	X																		
Inclusion/Exclusion criteria	X	X																	
Randomisation		X																	
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Demography[3]	X																		
Date of diagnosis of diabetes	X																		
Diabetes treatment history	X																		
Concomitant illness / medical history / smoking habits	X																		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X																		
Body weight	X	X								X								X	
Adverse events and technical complaints	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
Fundoscopy or fundus photography	X[4]									X[5]								X[5]	
Vital signs	X									X								X	
Physical examination	X									X								X	

		Treatment period A (32 weeks)								Treatment period B (32 weeks)									
Trial NN1250-3995	**Screening**	**Randomisation**	**Wash-out 16 weeks**			**Maintenance 16 weeks**				**Cross-over**	**Wash-out 16 weeks**			**Maintenance 16 weeks**				**End of Treatment**	**Follow up**
Visit Number (V)	**V1**	**V2**	**V6**	**V10**	**V14**	**V18**	**V22**	**V26**	**V30**	**V34**	**V38**	**V42**	**V46**	**V50**	**V54**	**V58**	**V62**	**V66**	**V67**
☎ Weekly Phone Contact number (P) (For details see separate flow chart below)		**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**	**P55 P56 P57**	**P59 P60 P61**	**P63 P64 P65**		
Time of visit (weeks)	**-2[1]**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**65[2]**
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
ECG	X[4]									X								X	
4-point profile[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
9-point profile[7]		X				X				X				X				X	
PRO questionnaire (SF-36®v2)[8]		X								X								X	
PRO questionnaire (TRIM-HYPO)[8]		X								X								X	
Hypoglycaemic episode – Interview questionnaire[9]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
End of trial																			X
BLOOD SAMPLING																			
Attend visit fasting[10]		X				X				X				X				X	
Fasting plasma glucose		X				X				X				X				X	
HbA_{1c}	X	X		X	X	X	X	X	X	X			X	X	X	X	X	X	
Biochemistry	X									X								X	
Haematology	X									X								X	
Pregnancy test[11]	X																	X	
TRIAL MATERIAL																			
IV/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	X		
Drug accountability (IV/WRS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
REMINDERS																			
Dose and frequency of pre-trial insulin	X																		
Initial I:Carb ratio and PG correction factor[12]		X								X									

		Treatment period A (32 weeks)								Treatment period B (32 weeks)									
Trial NN1250-3995	**Screening**	**Randomisation**	**Wash-out 16 weeks**			**Maintenance 16 weeks**				**Cross-over**	**Wash-out 16 weeks**			**Maintenance 16 weeks**				**End of Treatment**	**Follow up**
Visit Number (V)	**V1**	**V2**	**V6**	**V10**	**V14**	**V18**	**V22**	**V26**	**V30**	**V34**	**V38**	**V42**	**V46**	**V50**	**V54**	**V58**	**V62**	**V66**	**V67**
☎ Weekly Phone Contact number (P) (For details see separate flow chart below)		**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**	**P55 P56 P57**	**P59 P60 P61**	**P63 P64 P65**		
Time of visit (weeks)	**-2[1]**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**65[2]**
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
Actual time point for injection of IDeg/IGlar captured once weekly			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Dates and doses of trial products (every day)			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
New prescribed dose of trial products			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Last date and dose on IDeg/IGlar										x								x	
Training in carbohydrate counting		x								x									
Instructions in Use for vials[13]		x																	
Dispense Directions for Use for IAsp		x																	
Instruction/hand out of glucose meter	x																		
Instruction/hand out of/collect eDiary		x																x	
Hand-out/Instruction/collect paper diary	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Make appointment for eye examination								x								x			
Sign off case book																			x

[1] Randomisation should take place as soon as trial products are available on site and all screening (including laboratory) results are available, reviewed and the subject is confirmed eligible and no later than 14 days after Visit 1

[2] Follow-up visit (Visit 67) will take place no earlier than 7 days and no later than 12 days after Visit 66

[3] Demography data encompass date of birth, sex, race and ethnicity

[4] The procedures may be done between Visit 1 and Visit 2, as long as the results are available before Visit 2. ECG and fundoscopy/fundus photography performed within 12 weeks before Visit 1 are acceptable if results are available at Visit 2

[5] Fundoscopy/fundus photography performed within a period of three weeks before Visit 34 and 66 is acceptable if results are available before the respective visit

[6] Measurements are to be taken every day, before breakfast, lunch, main evening meal and bedtime

[7] Nine-point profiles (SMPG) must be started in the morning 2 days before Visits 2, 18, 34, 50 and 66. Measurements are to be performed before and after (90 min after the start of the meal) breakfast, lunch, main evening meal, before bedtime, at 4 am, and before breakfast on the following day. Please note that the 9-point profile is overlapping with the 4-point profile (SMPG)
[8] The PRO questionnaires should be completed by the subject preferably after conclusion of all fasting activities but before any other trial related procedures, including administration of any trial drug
[9] The hypoglycaemic episode – Interview questionnaire must be completed at every visit IF the subject reports one or more hypoglycaemic episodes. However, the questionnaire only asks questions about the LAST hypoglycaemic episode since LAST CONTACT (phone or visit)
[10] The subject must attend Visit, 2, 18, 34, 50 and 66 fasting, having consumed only water since midnight. Non-antidiabetic treatments are to be taken. If non-fasting, blood sampling should be re-scheduled preferably within the next two working days
[11] At Visit 1 and 66 a serum pregnancy test must be performed in women of child bearing potential. During the trial a urine pregnancy test must be performed if a menstrual period is missed or pregnancy is suspected. If a subject reports a missed menstrual period at a phone contact, the subject will have to attend the site for a urine pregnancy test.
[12] If the I:Carb ratio or PG correction factor changes during the trial, the new ratio should be recorded in the eCRF
[13] Instructions in Use for vials are given to each subject at the randomisation visit and repeated if deemed necessary by the investigator

Table 2–2 Flow chart – phone contacts

NN1250-3995 Phone contacts (P)[1] Time shown in site visit flow chart	All phone contacts
Visit window (days)	± 3
Withdrawal criteria	x
Concomitant medication	x
4-point profile[2]	x
Adverse events and technical complaints	x
Hypoglycaemic episodes	x
REMINDERS	
First date and dose on IDeg/IGlar	x (P3 and P35)
Actual time point for injection of IDeg/IGlar (captured once weekly)	x
Date and dose of trial product (every day)	x
New prescribed dose of trial products	x
Continue to update diary	x
When applicable: attend next visit fasting	(x)

[1]A phone contact may be converted to a site visit if needed. Phone contacts will occur on a weekly basis between the respective site visits
[2]4-point profiles (SMPG) should be taken every day. Measurements are to be taken before breakfast, lunch, main evening meal and bedtime

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

3.1.1 Therapeutic area – type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is a chronic disorder characterised by insulin deficiency and progressive complications due to hyperglycaemia. Subjects with T1DM are lacking insulin secretion entirely and therefore need complete exogenous insulin replacement to cover basal as well as meal-related (bolus) insulin requirements. A number of landmark studies have demonstrated the importance of maintaining tight glycaemic control to reduce the risk of long-term complications associated with T1DM.[3,4] The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend a glycosylated haemoglobin (HbA_{1c}) target of less than 7% (< 53 mmol/mol), without substantial hypoglycaemia.[5,6]

3.1.2 Insulin degludec

Insulin analogues have been developed that more closely mimic the action of endogenous insulin secretion as compared with human insulin preparations. Insulin analogues are now an established part of diabetes management.

The ability of insulin degludec (IDeg) to form soluble multi-hexamers upon subcutaneous injection creates a depot from which IDeg is continuously and slowly absorbed into the circulation reaching steady state after 2 to 3 days. The ultra-long and stable action profile is associated with important clinical benefits compared to currently marketed basal insulin analogues, including a duration of action beyond 42 hours at clinically relevant doses and a markedly lower day-to-day variability in glucose lowering effect[7]. The potential benefits associated with the distinct pharmacodynamic profile include optimisation of glycaemic control with less risk of hypoglycaemia and the possibility of adjusting the injection time from day to day to accommodate individual needs if required.

IDeg is developed to cover the basal insulin needs in patients with diabetes mellitus from early to late stages of the disease, either alone or in combination with prandial insulin and/or oral antidiabetic drugs.

It has been demonstrated that IDeg is a specific and full agonist at the human insulin receptor with the same mode of action as human insulin. The non-clinical programme revealed no safety concerns

for chronic subcutaneous administration of IDeg in humans, based on studies assessing single and repeated dose toxicity, reproductive and development toxicity, local tolerance and carcinogenic potential. The non-clinical development programme revealed findings attributed to the well-known pharmacological effects of insulin and no adverse effects other than those related to exaggerated pharmacology (hypoglycaemia) of insulin were observed. The non-clinical studies have thus demonstrated that the modifications introduced in IDeg have not changed its metabolic efficacy profile nor its safety profile compared to human insulin. No findings related to adverse effect on the cardiovascular system have been identified in the non-clinical safety programme.

The efficacy and safety of IDeg has been evaluated in an extensive clinical development programme including over 16 therapeutic confirmatory trials with IDeg OD, both in subjects with T1DM and T2DM. The therapeutic confirmatory trials were similar in design: all the trials were randomised, controlled, parallel-group, open-label multicentre, multinational trials in which IDeg was compared to an active comparator. Trial duration was either 26 or 52 weeks, and some trials included an extension period, resulting in total trial durations of up to 104 weeks. The therapeutic confirmatory trials were designed so that all trials conducted against an insulin comparator were treat-to-target trials in which similar reductions in HbA_{1c} from baseline were targeted for IDeg and comparator insulin products, making hypoglycaemia a key differentiator in the comparison of IDeg vs. comparator. In all trials with an insulin comparator, IDeg OD was non-inferior to comparator with respect to change in HbA_{1c}. In subjects with T1DM, IDeg was associated with similar rates of both severe and confirmed hypoglycaemic episodes as for comparator products. In addition to lower FPG at end of trial, IDeg was superior to comparator products in terms of lower rates of nocturnal confirmed hypoglycaemic episodes.[8,9]

3.1.2.1 Benefits and risks

The trial population will consist of subjects with T1DM, including subjects at high risk for developing severe hypoglycaemia. For all subjects participating in this trial, the anticipated benefits include improved glycaemic control. Titration algorithms, specifying recommended adjustments of basal and bolus insulin dose at different plasma glucose levels, are used in order to ensure that subjects receive an optimal treatment. Subjects will receive intense medical care by means of close contact to the clinical sites with at least weekly contacts.

The maximum trial duration for each subject is 67 weeks and the treatment duration for a subject is planned to be 64 weeks. Subjects will be asked to perform SMPG recording and measure 9-point profiles at scheduled visits during the trial. At visits when FPG is measured the subjects need to attend fasting having consumed no food or drink except for water since midnight.

Trial products, including IAsp, will be provided by Novo Nordisk free of charge. Subjects will receive IDeg or IGlar in 10 mL vials together with syringes and needles, which can be seen as an inconvenience compared to using pen injectors or insulin pumps. IAsp will be provided in

FlexPen®, minimising the risk of medication errors. Both IAsp and IGlar are marketed products. Please refer to the local labelling of these products for a description of risks and benefits. The subjects will be provided with a glucose meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use.

Low rate of nocturnal hypoglycaemia and flexibility in the timing of insulin administration are considered to be the key benefits for IDeg in T1DM. IDeg effectively improves long-term glycaemic control and has a low rate of hypoglycaemia. Furthermore, the stable action profile of IDeg allows for flexibility in the timing of insulin administration. Hypoglycaemia, medication errors due to mix up between basal and bolus insulin, and medication errors due to mix up between the different strengths of IDeg, are considered to be the key risks for IDeg. As with any other injectable product, injection site reactions may occur. Local allergic reactions (such as redness, swelling and itching at the injection site) may occur but usually disappear after a few weeks. During the clinical development programme of IDeg, allergic reactions such as hypersensitivity and urticaria were rare. All treatments are contraindicated in case of hypersensitivity to the active substances or any of the related products.

The risks are addressed in the Investigator's Brochure (IB) and events related to the risks are monitored through post-marketing pharmacovigilance activities in approved countries.

For more detailed information, please refer to the IB for IDeg, and any updates thereof.[9]

3.1.3 Insulin glargine

Insulin glargine (Lantus®) is a long-acting insulin analogue, indicated for treatment of diabetes mellitus in combination with oral antidiabetic agents and as part of a basal-bolus insulin regimen.

An amino-acid substitution at position A21 (compared with human insulin) causes precipitation of insulin glargine upon injection, forming a depot from which it is slowly released.[10] As compared with NPH insulin, this results in a prolonged action, lower mean FPG levels and lower incidence of nocturnal hypoglycaemia, whereas within-subject variation in absorption is comparable to that observed with NPH insulin.[11-18]

For further details, please refer to the U.S. Label Information or local package insert for IGlar, and any updates thereof.[10]

3.1.4 Insulin aspart

Insulin aspart (NovoLog®) is a rapid-acting analogue indicated for the treatment of diabetes mellitus.

Insulin aspart (IAsp) is homologous to human insulin, with the exception of the substitution of proline with aspartic acid at position B28. The rapid action of IAsp is related to a weakened

tendency of the insulin molecules to self-associate due to this modification and thereby is related to faster absorption as compared with human insulin.

Compared with human insulin, IAsp has a faster onset and a shorter duration of action, resulting in superior postprandial glycaemic control by means of lowering total glucose excursion following a meal, both in subjects with T1DM and in subjects with T2DM.[19-21] IAsp should generally be given immediately (within 5−10 minutes) prior to the start of a meal.

For further details, please refer to the SmPC[22], the U.S. Label Information[23], the local package insert for IAsp, and any updates thereof.

3.2 Rationale for the trial

The overall purpose of this trial is to evaluate the hypoglycaemia profile of IDeg in subjects with T1DM.

The IDeg phase 3a treat-to-target (T-T-T) open-label trials conducted in subjects with T1DM have suggested that IDeg provides similar glycaemic control to comparators with a 25-40% lower risk of nocturnal confirmed hypoglycaemia.[8,24] The present trial seeks to confirm the safety of IDeg in the transfer from basal-bolus regimen or CSII with rapid acting insulin, in a double-blinded, cross-over design that aims to minimise potential bias, particularly in the assessment of nocturnal and overall hypoglycaemic episodes. It is expected that the concomitant bolus treatment will influence the overall hypoglycaemic risk, hence the objective is to demonstrate no increased risk in overall hypoglycaemia with IDeg + IAsp vs IGlar + IAsp. Non-inferiority margin of 1.10 is chosen as a difference less than 10% in the rate of hypoglycaemia is not considered clinical relevant. Moreover, the trial will provide guidance on a safe switch from prior insulin treatment to IDeg.

The trial will be conducted in accordance with global and local regulations.

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary objective

To compare the rates of severe or BG (blood glucose) confirmed symptomatic hypoglycaemia of IDeg once daily (OD) + IAsp to IGlar OD + IAsp, by demonstrating that the upper limit of the 95% confidence interval of the rate ratio is below or equal to a non-inferiority margin of 1.10, and if confirmed, to a superiority limit of 1.0.

4.1.2 Secondary objectives

To compare the rates of severe or BG confirmed symptomatic nocturnal hypoglycaemia with IDeg OD + IAsp to IGlar OD + IAsp, by demonstrating that the upper limit of the 95% confidence interval of the rate ratio is below or equal to a non-inferiority margin of 1.10, and if confirmed, to a superiority limit of 1.0.

To confirm superiority of IDeg OD + IAsp compared to IGlar OD + IAsp in terms of proportion of subjects with severe hypoglycaemic episodes.

To compare efficacy of IDeg OD + IAsp in controlling glycaemia with respect to change from baseline in HbA_{1c} after 32 weeks of treatment. This is done by comparing the difference in change from baseline in HbA_{1c} after 32 weeks of treatment between IDeg OD + IAsp and IGlar OD + IAsp to a non-inferiority limit of 0.4%. To compare IDeg OD + IAsp and IGlar OD + IAsp in terms of safety, other parameters of glycaemic control and patient reported outcome (PRO).

4.2 Endpoints

4.2.1 Primary endpoint

Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64).

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

- Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64).
- Proportion of subjects with one or more severe hypoglycaemic episodes during the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64).

4.2.2.2 Supportive secondary endpoints

Safety endpoints

The following safety endpoints will be assessed during 32 weeks of treatment, for each treatment period:

- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes
- Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes
- Number of treatment emergent severe hypoglycaemic episodes
- Number of treatment emergent hypoglycaemic episodes according to ADA definition*

The following safety endpoints will be assessed for the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64):

- Number of treatment emergent total hypoglycaemic (severe or BG confirmed) episodes
- Number of treatment emergent total nocturnal hypoglycaemic (severe or BG confirmed) episodes
- Number of treatment emergent severe hypoglycaemic episodes
- Number of treatment emergent hypoglycaemic episodes according to ADA definition
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes occurring during sleep in the time span between 10:01 pm and 07:59 am

The following safety endpoints will be assessed for each treatment period:

- Incidence of treatment emergent adverse events during 32 weeks of treatment*
- Change from baseline in clinical evaluations after 32 weeks of treatment:

– Vital signs (including blood pressure and pulse)
– Fundoscopy or fundus photography
– Electrocardiogram (ECG)

- Change from baseline in laboratory assessments after 32 weeks of treatment:
– Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, leucocytes)
– Biochemistry (creatinine, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase, sodium, potassium, albumin, total bilirubin)
- Change from baseline in body weight after 32 weeks of treatment
- Total daily insulin dose after 32 weeks of treatment

Efficacy endpoints

The following efficacy endpoints will be assessed for each treatment period:

- Change from baseline in HbA_{1c} after 32 weeks of treatment*
- FPG after 32 weeks of treatment*
- Self-measured plasma glucose measurements (SMPG):
– 9-point profiles:
    – Mean of the 9-point profiles after 32 weeks of treatment
– 4-point profiles (obtained for insulin dose adjustment):
    – Mean plasma glucose before breakfast after 32 weeks of treatment

Patient-reported outcomes

The following will be assessed for the Health Related Quality of Life Questionnaire (SF-36®v2) and the Treatment Related Impact Measure – Minor Hypoglycaemic Events (TRIM-HYPO), for each treatment period:

Change in score from baseline to end of treatment period, for each 32-week treatment period (Visit 2 – 34 and Visit 34− 66)

*Key supportive secondary endpoint prospectively selected for posting on clinicaltrials.gov

5 Trial design

5.1 Type of trial

This trial is a 64-week, randomised, controlled, double blind, two-period, cross-over, multi-centre, treat-to-target trial comparing the safety of IDeg and IGlar both administered once daily, in a basal-bolus regimen with IAsp as mealtime insulin in subjects with T1DM.

The trial includes a screening visit (Visit 1) and a randomisation visit (Visit 2), followed by two treatment periods in a cross-over design. Each treatment period consists of a 16-week wash-out period and a 16-week maintenance period, both with frequent visits and phone contacts. A follow-up visit (Visit 67) is scheduled after the second treatment period, no earlier than 7 days and no later than 12 days after Visit 66. Total trial duration for the individual subjects will be up to 67 weeks. The trial design is summarised schematically in Figure 5–1.

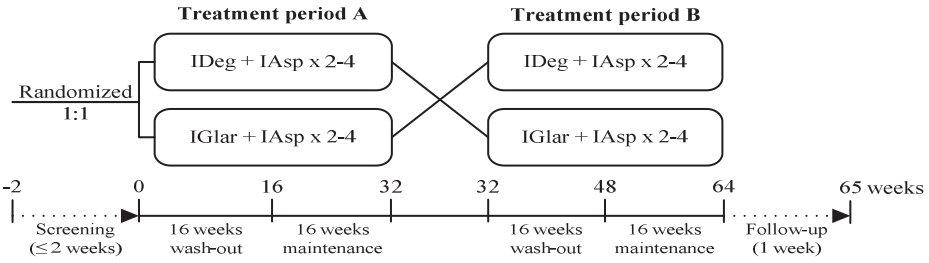

Figure 5–1 Trial design

5.2 Rationale for trial design

In this trial, a double-blinded design with the administration of both IDeg and IGlar via vial and syringe is used in order to eliminate potential reporting bias, particularly in terms of hypoglycaemia.

The cross-over design is chosen to reduce the number of subjects needed to obtain sufficient power. Wash-out periods of 16 weeks are included to avoid carryover when switching basal insulin treatment at randomisation and to ensure adequate time to achieve a stable HbA_{1c} for the evaluation of hypoglycaemia in the maintenance periods.

It is well described that subjects who switch from one insulin product to another will, in the initial switch period, experience an increased risk of hypoglycaemia compared to subjects staying on their pre-trial insulin product. To eliminate potential bias from familiarity with IGlar or IDeg dosing, only subjects previously treated with NPH insulin or IDet as basal insulin are eligible for this trial.

Subjects with recent severe and non-severe hypoglycaemia, hypoglycaemia symptom unawareness, moderate chronic renal failure or long disease duration are eligible to participate in this trial. Thus, this trial includes a broader population of subjects, compared to previous phase 3a trials with IDeg.

To reduce the risk of hypoglycaemia in the first treatment month, the overall daily dose of basal insulin is reduced by 20% at randomisation/start of treatment period A (Visit 2) and again at the start of treatment period B (Visit 34). Furthermore, subjects using bolus dosing algorithm will also reduce the bolus dose by 20% both at V2 and V34. For further details see Appendix A.

The basal insulin IDeg and IGlar will be administered in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and should be taken at the same time of day throughout the trial.

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

5.3 Treatment of subjects

At Visit 2 (randomisation), pre-trial insulin treatments will be discontinued. Eligible subjects are randomised 1:1 into one of two treatment sequences in a blinded manner:

- IDeg OD + IAsp 2-4 times daily followed by IGlar OD + IAsp 2-4 times daily
- IGlar OD + IAsp 2-4 times daily followed by IDeg OD + IAsp 2-4 times daily

Within each treatment arm subjects will be randomised 1:1 to morning or evening dosing. The dosing time will be kept throughout both treatment periods.

At randomisation, and at start of the second treatment period, the daily basal insulin dose is reduced by 20% from the doses of basal insulin taken pre-trial or at the end of treatment period A. Furthermore, subjects using bolus dosing algorithm will also reduce the bolus dose by 20% both at V2 and V34. The switch from pre-trial insulins to IDeg/IGlar + IAsp and from treatment period A to treatment period B is further described in Appendix A.

All randomised subjects are scheduled for 64 weeks of treatment with the investigational medicinal products. After 32 weeks of treatment (treatment period A) subjects will be crossed over to the other treatment (treatment period B) for 32 weeks. No additional antidiabetic treatment is allowed.

The time of insulin injection will be captured in the subject eDiary. Doses of IDeg and IGlar will be titrated individually. Weekly dose adjustments are performed on the basis of the lowest of three SMPG values measured before breakfast on the three consecutive days prior to the site visit/phone contact. The basal insulin dose adjustment should aim to reach a before breakfast SMPG target of

71–90 mg/dL (4.0–5.0 mmol/L). No maximum dose of insulin is specified. The algorithm used for titration is described in Appendix A. The investigator should always use his clinical judgement to avoid safety hazards. The investigator is responsible for the treatment of the subjects and can therefore overrule the guideline.

IAsp will be titrated individually based either on carbohydrate counting (at the investigator´s discretion) or by using sliding scale based on the lowest of three pre-meal or bedtime SMPG values measured on the three consecutive days prior to twice weekly titration, using the algorithm described in Appendix A. Throughout the trial, subjects should continue to use the same method for adjustment of bolus insulin as they did before the trial. Bolus titration should take place twice weekly for subjects who follow the pre-defined bolus dosing algorithms, while subjects using the principles of flexible dosing based on the meal carbohydrate content will adjust the dose several times daily.

During the initial eight weeks of the first period subjects are allowed to change their method of bolus titration from flexible dosing based on carbohydrate counting to adjustment based on bolus algorithm, but not vice versa. After eight weeks the bolus regimen should remain the same.

Subjects are also not allowed to change the method of bolus calculation at the cross-over between treatment period A and B.

Basal insulin should be administered subcutaneously in the abdomen, upper arm (deltoid region) or thigh. IAsp should be administered by subcutaneous injection into the abdominal region, buttocks, thigh or upper arm. Rotation of injection sites within a given region is recommended.

The investigators must document that they have trained the subject in the use of the insulin syringe and FlexPen® and that Instructions in Use for vials and Directions for Use for IAsp are given to each subject at the randomisation visit and repeated if deemed necessary by the investigator.

5.4 Treatment after end of trial

When discontinuing trial products the subject should be switched to a suitable marketed product at the discretion of the investigator. Doses of subsequent antidiabetic treatment should be carefully titrated based on blood glucose measurements, considering the stable effect and long half-life of IDeg.

If treatment with trial insulin is discontinued earlier than expected (before Visit 66) the subjects will be transferred to a marketed available diabetes treatment at the discretion of the investigator.

5.5 Rationale for treatment

Basal−bolus treatment is considered the gold standard of therapy in people with T1DM. A treat-to-target approach is used in order to optimise glycaemic control throughout the trial. To reduce the

risk of hypoglycaemia during the first treatment month, the basal insulin dose is reduced by 20% at randomisation and at start of the second treatment period. Furthermore, subjects using bolus dosing algorithm will also reduce the bolus dose by 20% both at V2 and V34. A 16 week washout period is included when switching basal insulin treatment to avoid a carryover effect. This period will also ensure adequate time to receive a stable HbA_{1c} for the evaluation of hypoglycaemia in the maintenance period. Maintenance periods of 16 weeks are included to ensure sufficient time for collection of data for comparison between treatment groups.

5.5.1 Choice of comparator

IGlar is chosen as comparator since it is a widely used basal insulin analogue world-wide, and has a well-known efficacy and safety profile. IGlar is the basal insulin product on the U.S. market that currently has the longest duration of action and is therefore regarded as the most appropriate comparator.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be randomised/started on trial products:	446
Number of subjects expected to complete the trial:	400

A screen failure rate of 30% and a withdrawal rate of randomised subjects of 10% are expected.

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. Male or female, age ≥ 18 years at the time of signing informed consent
3. Subjects fulfilling at least one of the below criteria*:
   a) Experienced at least one severe hypoglycaemic episode within the last year (according to the ADA definition, April 2013**)
   b) Moderate chronic renal failure, defined as glomerular filtration rate 30 - 59 mL/min/1.73 m^2 per CKD-Epi
   c) Hypoglycaemic symptom unawareness***
   d) Diabetes mellitus duration for more than 15 years
   e) Recent episode of hypoglycaemia (defined by symptoms of hypoglycaemia and/or episode with low glucose measurement (≤ 70 mg/dL [≤ 3.9 mmol/L])) within the last 12 weeks prior to Visit 1 (screening)
4. Type 1 diabetes mellitus (diagnosed clinically) ≥ 52 weeks prior to Visit 1
5. Current treatment with a basal−bolus regimen (consisting of NPH insulin OD / BID or IDet OD / BID plus 2-4 daily injections of any rapid acting or fast acting meal time insulin) or CSII (with rapid acting insulin) for ≥ 26 weeks prior to Visit 1
6. HbA_{1c} ≤ 10% by central laboratory analysis
7. BMI ≤ 45 kg/m^2
8. Ability and willingness to adhere to the protocol including self-measurement of plasma glucose according to the protocol

* For inclusion criteria 3 the aim is to include 20% of individuals with high risk of developing severe hypoglycaemia (a,b,c or d). The remaining subjects will have to fulfil criteria e).

** 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.
*** History of impaired autonomic responses (tremulousness, sweating, palpitations, and hunger) during hypoglycaemia.

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products
2. Previous participation in this trial. Participation is defined as having signed the informed consent form*
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice)
4. Treatment with IGlar or IDeg within the last 26 weeks prior to Visit 1 (short term use [≤ 2 weeks] is allowed, but not within 4 weeks prior to screening)
5. Use of any other anti-diabetic agent than those stated in the inclusion criteria within the last 26 weeks prior to Visit 1
6. Receipt of any investigational medicinal product within 4 weeks prior to screening
7. Any chronic disorder or severe disease which, in the opinion of the investigator, might jeopardise the subject's safety or compliance with the protocol
8. Current or past (within the last 5 years) malignant neoplasms (except basal cell and squamous cell carcinoma)
9. Stroke; decompensated heart failure New York Heart Association (NYHA) class III or IV; myocardial infarction; unstable angina pectoris; or coronary arterial bypass graft or angioplasty; all within the last 26 weeks prior to Visit 1
10. Uncontrolled or untreated severe hypertension defined as systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 100 mmHg
11. Impaired liver function defined as ALAT or ASAT ≥ 2.5 times upper limit of normal
12. Severe renal impairment defined as glomerular filtration rate <30 mL/min/1.73 m^2 per CKD-Epi
13. Proliferative retinopathy or maculopathy requiring acute treatment according to the investigator verification by fundoscopy or fundus photography performed within 12 weeks before Visit 1

* Re-screening of subjects previously failing screening due to inclusion criteria 5, 6 and/or 7 or exclusion criterion 4, who would have been eligible according to Protocol Amendment no 1 or 2 will be allowed. Before re-screening, the subjects have to be approved for re-screening by Novo Nordisk. The subjects will be randomised using the randomisation procedure described in Section 11.

6.4 Withdrawal criteria

The subject may withdraw at will at any time. The subject's request to discontinue must always be respected.

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

The subject must be withdrawn if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Pregnancy
3. Intention of becoming pregnant
4. Participation in other intervention trials throughout the trial
5. Development of any life threatening disease (e.g. cancer)
6. Unacceptable hyperglycaemia: During the maintenance part of treatment period A (Visit 18-34, both inclusive) and treatment period B (Visit 50-66, both inclusive),the subject must be withdrawn if there is:

– No reduction in HbA_{1c} calculated from the start of the treatment period (Visit 2 for treatment period A and Visit 34 for treatment period B), respectively AND
– Three pre-breakfast SMPG readings higher than 240 mg/dL (13.3 mmol/L) within a two weeks period and FPG measured at the central laboratory exceeds 240 mg/dL (13.3 mmol/L) AND
– No treatable cause for the hyperglycaemia

6.5 Subject replacement

A subject will be replaced in case of withdrawal before the maintenance period (Visit 18) during the recruitment period. The new subject will be randomised using the normal randomisation procedure (Section 11). These early withdrawals will not contribute to the primary analysis, but will contribute to the secondary supportive analysis done on the entire 32 weeks treatment periods.

6.6 Rationale for trial population

The trial population are adult male and female subjects with T1DM treated with basal bolus insulin consisting of NPH insulin or IDet plus 2−4 daily injections of any rapid acting or fast acting meal time insulin or CSII with rapid acting insulin and who have recently experienced hypoglycaemia.

This population has been chosen to eliminate potential bias from familiarity with the use of IDeg and IGlar.

A population with T1DM who have been treated with a basal bolus regimen consisting of NPH or IDet plus 2−4 daily injections of any rapid acting or fast acting meal time insulin or CSII with rapid acting insulin for at least 26 weeks and present with an $HbA_{1c} \leq 10\%$ may benefit from intensified insulin titration using a T-T-T titration algorithm. This T-T-T trial involves a rigorous protocol that

requires strict adherence on the part of investigators and subjects. Thus, good patient compliance is critical for the conduct of this trial. Amongst the T1DM population, a likely cause of elevated HbA_{1c} is poor compliance with treatment regimens. Thus individuals with an HbA_{1c} less or equal to 10% are selected in order to avoid incompliance with treatment recommendations.

A BMI limit of ≤ 45.0 kg/m^2 includes as broad a population as possible while excluding extremely obese, to avoid including subjects that are unlikely to comply with trial recommendation, as such BMI is an indication of considerable disregard to diet recommendations.

Subjects with unstable proliferative retinopathy requiring acute treatment, hepatic or severe renal impairment or uncontrolled severe hypertension and subjects who within the 26 weeks prior to screening have experienced a cardiovascular event as defined in the exclusion criteria are not eligible for inclusion in this trial due to the T-T-T approach and their need for more individualised therapy and less stringent HbA_{1c} goals.

The trial population is enriched with susceptible individuals at high risk of developing severe hypoglycaemia to be generalizable also to those most at risk.

7 Milestones

Planned duration of recruitment period (FPFV - LPFV): 20 weeks

End of trial is defined as LPLV

Recruitment:

The screening and randomisation rate will be followed closely via the interactive voice/web response system (IV/WRS) 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 IV/WRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation will be randomised.

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, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[25], the Food and Drug Administration Amendment Act (FDAAA)[26], European Commission Regulation for EudraCT[27] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail 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.

8 Methods and assessments

8.1 Visit procedures

8.1.1 Visit 1, screening

The following sections describe the assessments and procedures. These are also included in the flow chart (see section 2).

Subjects will attend a screening visit (Visit 1) in order to assess eligibility.

Before screening takes place, subjects must be provided with written information about the trial and the procedures involved. Subjects will be fully informed, orally and in writing about their responsibilities and rights while participating in the trial, as well as about possible advantages and disadvantages when participating in this trial. Subjects will have the opportunity to ask questions and have ample time to consider participation. The informed consent process may take place before the screening visit (Visit 1).

Subjects who wish to participate in the trial must sign and date the informed consent form for the trial before any trial-related procedures. All subjects must be provided with a copy of their own signed and dated informed consent form.

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.

At screening, the subjects will be assigned a unique subject number which will remain the same throughout the trial. The subject number will consist of 6 digits (the first 3 digits indicating site number and the last 3 digits are unique for the subject).

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list.

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

In- or exclusion criteria must not be ticked “Yes” or “No” in the electronic case report form (eCRF) before source data is available. In this case “Result pending” can be chosen. This is particularly relevant for lab samples and in some cases the ECG and fundoscopy or fundus photography result.

Please refer to the flow chart Table 2–1 and Table 2–2 for a description of what to perform and record in the eCRF at Visit 1.

Re-sampling is NOT allowed if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters. Re-screening is NOT allowed, except for subjects previously failing screening due to inclusion criteria 5, 6 and/or 7 or exclusion criterion 4, who would have been eligible according to Protocol Amendment no 1 or 2. Before re-screening, the subjects have to be approved for re-screening by Novo Nordisk. The subjects will be randomised using the randomisation procedure described in Section 11.

8.1.1.1 Screening failures

For screening failures the screening failure form must be completed with the reason for not continuing in the trial. Serious adverse events from screening failures must be transcribed by the investigator into the case report form (CRF). Follow-up of serious adverse events (SAEs) must be carried out according to section 12.3. A screening failure session must be made in the IV/WRS. The case book must be signed.

8.1.2 Visit 2, randomisation visit

The randomised treatment period lasts 64 weeks, see Table 2–1, Table 2–2. Subjects will be in weekly contact with the site through telephone contacts and site visits. Times of the visits are always calculated in relation to the actual date of the randomisation visit (Visit 2).

Randomisation will take place approximately one week (maximum two weeks) after the screening visit (Visit 1). The randomisation visit must not take place before all screening assessment results are available.

Eligible subjects will be randomised (1:1) into one of the two treatment sequences. At randomisation, baseline laboratory values, including HbA_{1c} will be taken.

All subjects will transfer from pre-trial insulin treatment to IDeg OD or IGlar OD in the morning, from waking up to breakfast or in the evening, between the evening meal and bedtime determined at randomisation. For the start dose of insulin (basal + bolus) prescribed at Visit 2 please refer to Appendix A.

At Visit 2, all subjects should have reinforced diabetes training. It is the investigator's responsibility to ensure that the subject has a satisfactory knowledge in:

- Recognition of carbohydrates in commonly eaten foods
- Ability to count the carbohydrate content in typical portions of simple foods
- Ability to interpret a nutrition label for carbohydrate content
- Glycaemic targets
- Preventing and treating hypoglycaemia using carbohydrate foods or glucagon
- Ability to sum up the carbohydrate content of a meal

The investigator should confirm that subjects who are capable of and willing to use the principle of flexible bolus dosing have experience in the above before the randomisation visit (Visit 2). Subjects who cannot demonstrate these skills will be allocated to follow the pre-defined algorithms described in the titration guideline (Appendix A) to adjust the bolus dose during the treatment periods.

8.1.3 Wash-out periods

The first 16-week wash-out periods starts at Visit 2 and ends at the start of the first maintenance period (Visit 18). The second wash-out period starts at Visit 34 and ends at the start of the second maintenance period (Visit 50).

During the 16-week wash-out periods, basal insulin dose should be up-titrated by the investigator in connection with the scheduled visit/phone contacts on the basis of self-measured plasma glucose as described in section 5.3 and Appendix A.

8.1.4 Maintenance periods

The first 16-week maintenance period starts after the first wash-out period (Visit 18) and ends at the cross-over to treatment period B (Visit 34). The second 16-week maintenance period starts at Visit 50 and ends at Visit 66 (end of treatment).

After the wash-out periods, it is expected that the subject has achieved a stable glycaemic control and that only minor dose adjustments are needed during the maintenance period, unless for safety reasons.

8.1.5 Visit 34, cross-over visit

Visit 34 marks the end of the first treatment period (treatment period A) and cross-over to the second treatment period (treatment period B). Results from assessments performed at the end of period A constitute the baseline for treatment period B. Subjects must be informed about the switch to a different trial product and reminded to return all unused product from treatment period A.

When the subjects cross over to a new product in treatment period B, the basal and bolus insulin doses should again be calculated in accordance with Appendix A.

At Visit 34, all subjects should repeat the diabetes training as performed at the randomisation visit (Visit 2).

8.1.6 Visit 66, end of treatment visit

At Visit 66 the treatment with trial product must be stopped (end of treatment visit). The investigator should inform the subject about his/her future antidiabetic treatment.

8.1.7 Visit 67, follow-up visit

A follow-up visit (Visit 67) should take place 7−12 days after treatment with trial products (Visit 66) has been stopped.

8.1.8 Phone contacts

A phone contact may be converted to a site visit if preferred. Scheduled phone contacts and their time points are included in Table 2–1 and Table 2–2.

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 does take place.

8.1.9 Unscheduled site visits

If the subject attends the clinic outside the visit schedule, the unscheduled visit form in the eCRF should be completed. The unscheduled visit form should not be completed if the subject attends the clinic only to obtain trial supplies or for re-scheduled visits.

If more trial product is needed an additional dispensing session in the IV/WRS must be performed. If blood sampling is needed the laboratory requisition form must be completed with the visit number to which the sample belongs.

8.1.10 Rescheduled visits

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

8.1.11 Withdrawal

If a subject is withdrawn from the trial, the investigator must aim to undertake procedures similar to those for Visit 66 as soon as possible. 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 withdrawal session must be made in the IV/WRS. The case book must be signed and drug accountability must be finalised.

Although a subject is not obliged to give his/her reason(s) for withdrawing from a trial, 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 discontinuation must be specified on the end-of-trial form in the CRF e.g.:

- Adverse events (AEs)
- Protocol violation
- Lake of efficacy
- Lost to follow up
- Withdrawal by subject
- Other (specify)
- Pregnancy

Subjects withdrawing during the follow-up period will be considered as completers.

8.2 Subject related information

8.2.1 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the first visit) or found as a result of a screening procedure.

All concomitant illnesses should be reported except T1DM.

Medical history is a medical event that the subject has experienced in the past. Relevant medical history as judged by the investigator should be reported.

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.

Smoking habit: Details of smoking habit must be recorded at the first visit. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked.

8.2.2 Concomitant medication

A **concomitant medication** is any medication, other than the trial product(s), which is taken during the trial, including the screening period.

Details of any concomitant medication must be recorded at the first visit. Changes in concomitant medication must be recorded at each visit as they occur.

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.

8.3 Assessments for efficacy

The assessments for efficacy are:

- HbA_{1c} (measured at central laboratory)
- FPG (measured at central laboratory)
- Self-measured plasma glucose (SMPG) profiles
  - 4-point profiles
  - 9-point profiles

8.3.1 Efficacy laboratory parameters

For general information on laboratory assessments please see section 8.5. Blood samples will be drawn and analysed at the central laboratory to determine levels of:

- HbA_{1c}
- FPG

8.3.2 Self-measured plasma glucose profiles

At Visit 1, subjects will be supplied with a blood glucose meter including lancets and plasma-calibrated test strips as well as instructions on use of the device including regular calibration according to the manufacturer's instructions. Subjects will also be provided with written instructions. Sites should, as necessary, repeat the instructions for use during the trial.

The blood glucose meters use 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.

Subjects should be instructed in how to record the results of the SMPGs in the eDiaries (refer to section 8.6).

4-point profile

Subjects will be asked to perform SMPG measurements before breakfast, lunch, main evening meal and bedtime on all days throughout the trial (starting at Visit 2 and ending at Visit 66), using the glucose meter provided. SMPG measurements before breakfast should preferably be performed after having consumed only water since midnight and before insulin injection. SMPG measurements before lunch, main evening meal and bedtime should be performed before insulin injection.

All measurements will be recorded in the subject's eDiary, together with the administered doses. The investigator must review the dose adjustments performed by the subject, and recommend adjustments. Both investigator and subject titration should be performed based on the Insulin Titration Guideline (Appendix A).

9-point profile

Subjects will be instructed to perform a 9-point SMPG profile with additional 4-point SMPG profiles on the three days immediately before Visit 2 (randomisation), Visit 18 (end of first washout period), Visit 34 (end of first maintenance period), Visit 50 (end of second washout period) and Visit 66 (end of second maintenance period, end of treatment).

The 9-point profiles should be started on Day 2 (two days before site visit) and end at Day 3 (the day before the visit). The SMPGs should be measured and recorded in the eDiary at the actual time points listed in Table 8–1.

The record of each SMPG for the 9-point SMPG profile must include date, actual time point and plasma glucose value.

Table 8–1 Time points for the 4-point and 9-point profiles 3 days before selected visits

Day	Day 1	Day 2	Day 3
Time point	**Three days before visit**	**Two days before visit**	**One day before visit**
Before breakfast	x	√/x	√/ x
90 min after the start of breakfast		√	
Before lunch	x	√/x	X
90 min after the start of lunch		√	
Before main evening meal	x	√/x	X
90 min after the start of main evening meal		√	
Before bedtime	x	√/x	X
At 4 am		√	

x: 4 point profile; √: 9- point profile

8.4 Assessments for safety

The following safety assessments are performed:

- Hypoglycaemic episodes
- Insulin dose
- Adverse events
- Body weight
- Physical examination
- Change from baseline in clinical evaluations
  - Vital signs (including blood pressure and pulse)
  - Fundoscopy or fundus photography
  - Electrocardiogram (ECG)
- Change from baseline in laboratory assessments
  - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, leucocytes)
  - Biochemistry (creatinine, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase, sodium, potassium, albumin, total bilirubin)

8.4.1 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) when they occur in conjunction with hypoglycaemic symptoms,

should be recorded by the subject. These must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from Visit 2 to Visit 67.

The record should, for example, include the following information:

- Date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available)
- Whether the episode was symptomatic
- Whether the subject was able to treat him/herself
- Date and time of last basal insulin dose prior to episode
- Date and time of last bolus insulin dose prior to episode
- Date and time of last main meal (breakfast, lunch or evening meal) prior to episode
- Whether the episode occurred in relation to increased physical activity
- Whether the subject was asleep when the hypoglycaemic episode occurred
- Whether the symptoms of the hypoglycaemic episodes woke up the subject

The answer to the question: "Was subject able to treat him/herself?" must be answered "No" if oral carbohydrates, glucagon or IV glucose had to be administered to the subject by another person. Oral carbohydrates should not be given if the subject is unconscious.

If oral carbohydrates, glucagon or IV glucose had to be administered to the subject by another person, the following information should be recorded in the severe hypoglycaemic episode form in the diary and transcribed into the eCRF:

- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose, other, please specify)
- Who assisted in the treatment of the hypoglycaemic episode?
  - Family/friend/co-worker or similar
  - Paramedic
  - Doctor
  - Other
- Were symptoms alleviated by the administration of treatment?
- Where was the treatment administered?
  - At home/at friends/at work or similar
  - In an ambulance
  - Emergency room or hospital (“< 24 hours stay" versus "≥ 24 hours stay”)
  - Other

- Did treatment of the hypoglycaemic episode involve transportation in an ambulance?

- If unable to treat him/herself:
– Did the subject experience any of the following symptoms: sweating, trembling, hunger, palpitations?
– Did the subject experience any of the following symptoms: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance, incoordination?
– Did the subject experience any of the following symptoms: headache, malaise?
– Did the subject experience seizure?
– Was the subject unconscious/comatose?
- Description of the hypoglycaemic episode

A hypoglycaemic episode form (and severe hypoglycaemic episode form and Event Adjudication Document Collection (Adjudication) form if applicable) must be filled in for each hypoglycaemic episode. If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a Safety Information Form must also be filled in. See section 12.1 for definition of SAE and section 12.2 for information on reporting of adverse events.

See section 17.4.2.1 for definition of hypoglycaemia.

8.4.2 Insulin dose

During the trial, starting at the randomisation visit (Visit 2), the subject will be instructed to report the date and the basal and bolus insulin doses in the diary every day as well as the actual time point of injection of basal insulin once weekly. See section 8.6 for information on data collection and eDiaries.

The recommended insulin doses will be individually calculated in the eDiary on recommendations from the Insulin Titration Guideline, described in Appendix A, or by using the principles of flexible bolus dosing based on the carbohydrate content of the meal to adjust the bolus dose.

8.4.3 Adverse events

During each contact with the trial site staff (site visits and telephone contacts) the subject must be asked about adverse events (AEs) and technical complaints. This must be documented in the subject's medical record.

AEs including those identified during review of the trial related documents such as diaries, PROs, ECGs and laboratory reports must be recorded on the AE form.

If a subject experiences an event, but this is handled at another health care clinic, the investigator must collect and report this information.

If an AE fulfils the criteria for an SAE and/or a medical event of special interest (MESI) then a Safety Information Form must also be filled in. For details about AEs see section 12.

8.4.4 Body weight and height

Body weight should be assessed without coat and shoes. Body weight will be measured in pounds (lb) or kilogram (kg) and recorded to one decimal place at Visit 1 (screening), Visit 2 (randomisation), Visit 34 and Visit 66.

Height should be assessed without shoes. At Visit 1 height is measured in inches or meters and recorded to one or two decimal places respectively.

From the body weight and height the BMI will be calculated in the eCRF.

8.4.5 Physical examination

Physical examination is performed at Visit 1, Visit 34 and Visit 66 and includes examinations of:

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

In case of "abnormal, clinically significant", the investigator must record the finding on the 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 reported as an AE.

8.4.6 Vital signs

Diastolic blood pressure, systolic blood pressure and pulse will be assessed while the subject is sitting. Vital signs will be measured at Visit 1, Visit 34 and Visit 66.

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 reported as an AE.

8.4.7 Fundoscopy or fundus photography

The procedures may be done between Visit 1 and Visit 2, as long as the results are available before Visit 2. Baseline fundoscopy or fundus photography performed within 12 weeks before Visit 1 is

acceptable if results are available at Visit 2. A subject cannot be randomised without results confirming there is no acute treatment-requiring retinopathy.

To ensure fundoscopy or fundus photography in time, the investigator is advised to assist the subject in making an appointment for the eye examination before Visit 34 and Visit 66. Fundoscopy or fundus photography performed within a period of three weeks before Visit 34 and Visit 66 is acceptable if results are available at Visit 34 and Visit 66. The procedure may be performed by the investigator or local ophthalmologist/optometrist according to local practice.

The investigator must sign and date the reports from the examinations to verify that the data have been reviewed.

The results must be transcribed to the eCRF as

- normal
- abnormal, not clinically significant
- abnormal, clinically significant

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

8.4.8 Electrocardiogram

ECG performed within 12 weeks before Visit 1 is acceptable if results are available at Visit 2. ECG performed within a period of three weeks before Visit 34 or Visit 66 is acceptable if results are available at Visit 34 or Visit 66, respectively. The investigator must sign and date ECG results to verify that the data have been reviewed. The results must be transcribed to the eCRF as

- normal
- abnormal, not clinically significant
- abnormal, clinically significant

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

8.4.9 Safety laboratory parameters

For general information on laboratory assessments please see section 8.5. Blood samples will be drawn and analysed at the central laboratory for:

- Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes)
- Biochemistry (creatinine, ALAT, ASAT, alkaline phosphatase, sodium, potassium, albumin, total bilirubin)
- Serum pregnancy test (human chorionic gonadotropin (hCG))

8.5 Laboratory assessments

Laboratory samples should be taken at specific visits according to the flowchart (see section 2). If blood samples are clotted or missed re-sampling should be performed if relevant. Re-sampling of baseline samples (visit 2 or 34) after trial drug exposure should not be performed. The subjects must attend Visits 2, 18, 34, 50 and 66 fasting having consumed only water and taken no diabetes medication since midnight. Non-antidiabetic treatments are to be taken. The fasting state is due to blood sampling for FPG. All laboratory analyses will be performed at the central laboratory assigned for this trial.

The laboratory parameters include:

- HbA_{1c}
- FPG
- Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes)
- Biochemistry (creatinine, glomerular filtration rate*, ALAT, ASAT, alkaline phosphatase, sodium, potassium, albumin, total bilirubin)
- Serum pregnancy test (human chorionic gonadotropin (hCG))

* Only at Visit 1 to determine if inclusion criterion 3b) was fulfilled.

If the laboratory FPG result is ≤ 3.9 mmol/L (70 mg/dL) then a hypoglycaemic episode form has to be entered in the eCRF and as many details as possible should be filled in. Date and time of the hypoglycaemic episode would be the date and time of the blood sample taken. See section 8.4.1 .

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 must be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol (see section 12.2).

All analyses will be listed in the trial specific laboratory manual. Description of the procedures for obtaining samples, handling conditions including coding in order to keep subject identity confidential, storage, assay methods and destruction of laboratory samples will also be included in the laboratory manual.

To verify that the data have been reviewed the investigator must sign and date the laboratory reports. All laboratory reports must be retained at the site as source data.

8.6 Diaries

In this trial both paper diaries and eDiary will be used.

At each site visit, the subjects will be provided with a new paper diary. The paper diary must be collected at the next site visit, and retained at the site as source data in accordance with section 14. The subjects should be instructed to record the following in the paper diary:

- Date and dose for first dose and last dose of IDeg/IGlar
- Hypoglycaemic episodes (please refer to section 8.4.1)
- Medical problems (please refer to section 8.2.1)
- Changes in concomitant medication (please refer to section 8.2.2)

At randomisation, the subjects will be provided with an eDiary (refer to section 13.3). Subjects must be trained in the device and complete a practise diary.

The subjects should be instructed to ensure that the following information is electronically transmitted daily from the BG meter to the eDiary:
Date, actual time point and value of all SMPG measurements (4-, and 9-point SMPG profiles)

The subjects should be instructed to record the following in the eDiary:

- Date and doses of IDeg/IGlar insulin each day during the trial
- Actual time point of IDeg/IGlar insulin injection once weekly
- Date and dose of IAsp insulin at each meal (breakfast, lunch, main evening meal or extra bolus insulin) each day during the trial as well as reason for deviation from the recommended dose

Subjects who use the principles of flexible dosing based on the meal carbohydrate content should also record the following: Carbohydrate content per meal

The investigator is allowed to record the following in the eDiary or on the webportal:

- Subject ID and actual time point to start up the eDiary
- Initial and new I:Carb ratio and PG correction factor (sensitivity factor) if applicable
- Prescribed doses of trial products

The investigator is allowed to record the following in the paper diary:

- Time and date of next visit and/or phone contact
- Subject ID and site contact details

Hypoglycaemic episodes must be transcribed to the eCRF by site staff within 24 hours after each site visit/phone contact. The temporary transferral of data between the subject and the investigator can be performed electronically, e.g. by sending a picture file or a scanned copy of the relevant diary pages by email. The diary will act as source at any time. If there is a discrepancy between the data in the diary and the transferred data, the eCRF should be updated accordingly. The entries made in the eDiary will be reviewed by the investigator to ensure consistency and compliance.

Review of the diaries must be documented either on the front page of the documents and/or in the subject's medical record. If clarification of entries or discrepancies in the diary is needed then the subject should be questioned and a conclusion made in the medical record.

8.7 Other assessments

8.7.1 Patient-reported outcome

Two patient-reported outcome (PRO) questionnaires, one generic and one disease-specific, will be used to investigate the health-related quality of life and the treatment-related impacts of minor hypoglycaemic episodes on patient daily life and functioning

The PRO questionnaires are to be completed by the subject without assistance of the site personnel, and should preferably be completed after all fasting-related activities are completed, but before any other visit related procedures are conducted. Written instructions on how to complete the questionnaires will be provided to the subject. Subjects who cannot complete the questionnaires themselves due to physical limitations may receive assistance with completion of the questionnaires. After completion, the PROs must be reviewed by any medically qualified site staff for potential AEs, including any overall change in health and concomitant medication. When reviewing the PRO questionnaires for AEs care should be taken not to influence or question the subject on the content of the subject's response to PRO questions. Potential AEs must be reported according to section 12. Review of the PROs must be documented either on the front page of the documents and/or in the subject's medical record. If clarification of entries in the PRO questionnaires is needed, the subject should be questioned and a conclusion made in the medical record. The completed questionnaires must be transcribed into the eCRF and filed at site as source documents.

The following PROs will be used in the trial:

- SF-36v2®
- TRIM-HYPO

The questionnaires should be completed as specified in the flow chart, see section 2.

SF-36® v2

The 'Short-Form 36 Health Survey version 2 (SF-36® v2): Your Health and Well-Being' questionnaire concerning various health-related quality of life questions will be used at Visits 2, 34 and 66. The SF-36® v2 is a sensitive, validated and widely used instrument which will allow direct comparison with other trials including subjects with T1DM.

TRIM-HYPO

TRIM-HYPO measures the impact of minor hypoglycaemia on patients' daily lives, emotional well-being, diabetes management, sleep disruption, and work productivity. The TRIM-HYPO instrument has 33 items and is scored so that a lower score indicates a better health state. Scoring of the instrument is done in three steps including a weighting of items. TRIM-HYPO will be used at Visits 2, 34 and 66. The data collected from the TRIM-HYPO will provide information to be used in health economic analyses. The data will not be included in the clinical trial report.

8.7.2 Hypoglycaemic episode – Interview questionnaire

A hypoglycaemic episode – Interview questionnaire must be completed at all site visits during the trial (Visit 2−66), but only if the subject reports to have experienced one or more hypoglycaemic episodes (symptomatic or asymptomatic) since LAST CONTACT (phone or site visit). The questionnaire only asks questions about the LAST episode since the LAST CONCTACT (phone or visit). The questionnaire will be completed in an interview by the investigator or a study coordinator.

The data collected from the hypoglycaemic episode – Interview questionnaires will provide information to be used in health economic analyses. The data will not be included in the clinical trial report.

8.8 Subject compliance

To encourage subject compliance, the investigator will at each site visit/phone contact emphasise the necessity for the subject to adhere to trial procedures. To ensure subject compliance, the investigator will at each visit assess the subject's compliance by evaluating the glycaemic control, adherence to the visit schedule and completion of the subject's diary, including the SMPG profiles. In addition, trial product accountability will be performed. If a subject is being non-compliant then the investigator must discuss this with the subject and emphasise the importance of following the instructions given including taking the trial products as prescribed.

During the trial, the titration data and HbA_{1c} will be monitored by a Novo Nordisk representative or designated person for titration surveillance purposes.

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 product must not be used, if it does not appear clear and colourless.

IDeg and IGlar are visually identical (blinded). IAsp is open-label.

9.1 Trial products

The following trial products will be provided by Novo Nordisk:

Table 9–1 Trial products

Trial products	Strength	Dosage form	Route of administration	Blinding
Insulin degludec	100 units/ml	10 ml vial	s.c.	Blinded
Insulin glargine (Lantus®)	100 units/ml	10 ml vial	s.c.	Blinded
Investigational medicinal products (IMP)				
Insulin aspart (NovoLog®)	100 units/ml	Pre-filled pen (FlexPen®)	s.c.	Open-label
Non-Investigational medicinal product (NIMP)				

9.2 Labelling

Labelling of the trial products will be in accordance with Annex 13, local regulations and trial requirements.[28]

Each investigator site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IV/WRS. Dispensing unit numbers (DUNs) will be distributed to the sites according to enrolment and randomisation.

Directions for use describing the use of insulin aspart FlexPen® and Instruction in Use of vials will be provided at Visit 2.

The investigator must document that Direction for Use and Instruction in Use is given to the subject orally and/or in writing.

9.3 Storage

Table 9–2 Storage of trial products

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
Insulin degludec and insulin glargine (Lantus®)	• Store in a refrigerator 36°F to 46°F (+2°C to +8°C) • Do not freeze • Store in outer carton to protect from light	• Do not refrigerate • Store in outer carton to protect from light • Do not store above 77ºF (+25ºC)	• Use within 26 days
Insulin aspart (NovoLog®)	• Store in a refrigerator 36°F to 46°F (+2°C to +8°C) • Do not freeze • Store in outer carton to protect from light	• Do not refrigerate. • Do not freeze • To protect from light, the cap should be kept on the pen when not in use • Store below 86°F (+30°C)	• Use within 28 days

* In-use time starts when first dose is taken

Insulin products must be kept away from the cooling element. Trial products must not be used after the expiration date.

The investigator must ensure the availability of proper storage conditions, 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).

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

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator.

Returned trial product (used/partly used or unused including empty packaging material) can be stored at room temperature and must be stored separately from non-allocated trial product.

Trial product accountability will be performed in the IV/IWRS drug accountability module. The accountability will include the number of allocated, returned and lost pen devices and vials.

Responsibility for trial product accountability at the trial site rests with the investigator. The tasks can be delegated to a study nurse or a pharmacist.

Destruction of used and unused trial product(s) will be done according to local procedures after accountability is finalised and verified by the monitor. Destruction of products must be documented.

9.5 Auxiliary supplies

Auxiliary supplies provided by Novo Nordisk include:

- needles for FlexPen®
- blood glucose meters
- lancets
- plasma-calibrated test strips
- control solutions
- instructions in use for vials
- directions for use for IAsp
- syringes and needles

10 Interactive voice/web response system

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

IV/WRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Withdrawal
- Completion
- Drug accountability
- Data change
- Code break

At randomisation the investigator will answer "yes/no" in the IV/WRS whether the subject has high risk of developing severe hypoglycaemia.

At any time during the trial only DUNs allocated by the IV/WRS are allowed to be dispensed to a subject. By doing this it will be ensured that:

- stock available at a site needed for the subjects
- no allocation of trial product that will expire before the next dispensing visit
- drug accountability can be made in the IV/WRS

If a subject needs trial product between dispensing visits, the investigator must make an additional dispensing.

IV/WRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

The IV/WRS is used for randomisation. Subjects, complying with the inclusion- and exclusion criteria, will be randomised 1:1 into one of the two treatment sequences in a blinded manner. Within each treatment arm subjects will be randomised 1:1 to morning or evening dosing."

In IV/WRS this means that there will be four different treatment regimens:

- IDeg OD morning dosing +IAsp / IGlar OD morning dosing +IAsp
- IDeg OD evening dosing +IAsp / IGlar OD evening dosing +IAsp
- IGlar OD morning dosing +IAsp / IDeg OD morning dosing +IAsp
- IGlar OD evening dosing +IAsp / IDeg OD evening dosing +IAsp

Due to the double blinding of the trial, all involved parties will be blinded to IDeg/IGlar treatment allocation throughout the trial.

11.1 Breaking of blinded codes

The IV/WRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

The code for a particular subject may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Whenever a code is broken the person breaking the code must print the Code Break Confirmation Notification generated by the IV/WRS, record the reason, and sign and date the document.

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IV/WRS is not accessible at the time of code break the IV/WRS vendor helpdesk should be contacted. Contact details are listed in Attachment I.

Subjects can continue after the code is broken.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a subject administered a 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.

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 procedures (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 (a hypoglycaemic episode that does not meet the definition of a serious adverse event) is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see section 8.4.1.

The following three definitions are used when assessing an AE:

- **Severity assessment**
  - **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 assessment**
  The following terms are used when assessing the 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 of an AE**

– **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 he/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.

Serious adverse event

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

- Death.
- A life-threatening[a] experience.
- In-patient hospitalisation[b] or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity[c].
- A congenital anomaly or birth defect.
- 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].

Suspicion of transmission of infectious agents via the trial product must always be considered an SAE.

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

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 his/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 dyscrasiasis or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

Non-serious adverse event

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

Medical event of special interest

A medical event of special interest (MESI) is an event which, in the evaluation of safety, has a special focus. A MESI is an AE (SAE or non-serious AE) which fulfils one or more of the below defined MESI criteria.

1. Medication errors concerning trial products:
– 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)
– Accidental administration of a lower or higher dose than intended, 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 not necessarily did happen.
2. Neoplasm
– Benign, malignant and unspecified, should always be reported to the department responsible for global safety on an AE form and a Safety Information Form irrespective of seriousness. Medical history and important follow-up data includes information about malignancy versus non-malignancy, preferably histologically verified

Technical complaint

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)
- The packaging material (e.g. leakage, cracks, rubber membrane issues or errors in labelling text)
- 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 (Visit 67, 7−12 days after end of treatment). The events must be recorded in the applicable CRF forms in a timely manner.

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. Novo Nordisk assessment of expectedness is performed according to the following reference documents: IB for IDeg, Summary of Product Characteristics (SPC)/US prescribing information for Lantus® (IGlar), and CCDS for IAsp.

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

For SAEs that could have resulted from hypoglycaemia (for example sudden death, seizure, trauma, fractures, fall, motor vehicle accident etc.), the narrative should include information on whether hypoglycaemia could have contributed to these events.

MESIs, regardless of seriousness, must be reported using both the AE form and the Safety Information Form. For medication errors, also a MESI medication error form must be filled out.

For AEs fulfilling criteria for adjudication, the specific Event Adjudication Document Collection (ACS/cerebrovascular/fatal adjudication) form and ACS/cerebrovascular/fatal form should be used.

For events fulfilling the criteria for adjudication as severe hypoglycaemia (although not necessarily AEs) or hypoglycaemic episodes reported as an SAE, the specific Event Adjudication Document Collection (Hypoglycaemic adjudication) form should be used

The AE form for a non-serious AE should be signed when the event is resolved or at the end of the trial.

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 Safety Information Form **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.
- **SAEs fulfilling the MESI medication error criteria:** In addition to the above, the MESI medication error form **within 14 calendar days** of the investigator's first knowledge of the AE.
- **Non-serious AE fulfilling the MESI criteria:** The AE form, Safety Information Form and if applicable MESI medication error form **within 14 calendar days** of the investigator's first knowledge of the event.
- **SAEs fulfilling criteria for adjudication (see** Table 12–1**):** In addition to the AE form and Safety Information Form (SIF), the Event Adjudication Document Collection (ACS/cerebrovascular/fatal adjudication) form and ACS/cerebrovascular/fatal form **within 5 calendar days** of the investigator's first knowledge of the AE**.**
- **Non-serious AEs fulfilling criteria for adjudication (see** Table 12–1**):** The AE form, the Event Adjudication Document Collection (ACS/cerebrovascular adjudication) form and ACS/cerebrovascular form **within 5 calendar days** of the investigator's first knowledge of the AE.
- **Severe hypoglycaemia fulfilling criteria for adjudication (see** Table 12–1**):** The hypoglycaemia and severe hypoglycaemia forms and the Event Adjudication Document Collection (Hypoglycaemia adjudication) form **within 5 calendar days** of the investigator's first knowledge of the severe hypoglycaemic episode.

If the eCRF is unavailable, the concerned AE information must be reported on paper forms and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must re-enter the information on the appropriate forms in the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator's trial file.

Reporting of trial product-related SUSARs by the sponsor:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and 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 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 GCP[1], unless locally this is an obligation of the investigator.

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 on-going 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.
- **Non-serious AEs fulfilling the MESI criteria:** Follow up information on MESIs should only include new (e.g. corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the MESI criteria.

The investigator must ensure that 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.

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 glargine (IGlar) 100 units/ml 10 mL vial (Lantus®, Sanofi)
- Insulin degludec (IDeg) 100 units/mL, 10 mL vial (Novo Nordisk)
- Insulin aspart (IAsp) 100 units/mL, pre-filled pen (FlexPen®), NovoLog® (Novo Nordisk)

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, e-mail and address) are provided in Attachment I to the protocol.

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

Technical complaints must be reported on a separate technical complaint form for each product listed. If the technical complaint involves more than one batch number or more than one DUN, a technical complaint form for each batch number or for each DUN 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, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above.

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 print or copy of the technical complaint form must be sent with the sample.

The investigator must ensure that the technical complaint sample contains the batch number and, if available, the DUN.

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 prescribed for the product. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (see section 9).

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the trial. The investigator must report any pregnancy in subjects who have received trial product(s).

The investigator must follow the pregnancy until the pregnancy outcome and the new-born infant is one month of age.

The investigator must report information about the pregnancy, pregnancy outcome, and health of the new-born infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and new-born infant.

The following must be collected and reported by the investigator to Novo Nordisk – electronically (e.g. in PDF format), or by fax or courier:

1. **Reporting of pregnancy information**
   Information about the pregnancy and pregnancy outcome/health of the new-born infant(s) has to be reported on Maternal Form 1A and 1B, respectively.

   When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

   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.

2. **Reporting of AE information**
   The investigator has to report AEs in connection with the pregnancy as well as in the foetus and new-born infant(s). The SAEs that must be reported include abnormal outcome, such as foetal death (including spontaneous abortion), and congenital anomalies (including those observed at gross examination or during autopsy of the foetus), as well as other pregnancy complications fulfilling the criteria of an SAE.

Forms and timelines for reporting AEs:

Non-serious AEs:

– Paper AE form* **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

SAEs:

– Paper AE form* **within 24 hours** of the investigator's first knowledge of the SAE.
– Paper Safety Information Form **within 5 calendar days** of the investigator's first knowledge of the SAE.
– **SAE follow-up information** to the AE form and/or Safety Information Form **within 24 hours** of the investigator's first knowledge of the follow-up information.

* It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or new-born infant.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

The administration of insulin or overdose may result in hypoglycaemia. Symptoms may occur suddenly and include cold sweat, nervousness or tremor, anxious feelings, unusual tiredness, confusion, difficulty in concentrating, excessive hunger, temporary vision changes, headache, nausea and palpitation. Prolonged or severe hypoglycaemia can lead to a loss of self-control, spasms, and/or unconsciousness and, in extreme cases, death.

Asymptomatic hypoglycaemia and symptoms of hypoglycaemia should be treated with carbohydrates. Mild to moderate symptoms can be treated by ingestion of carbohydrate (for example juice). Severe hypoglycaemia resulting in loss of consciousness should be treated with parenteral glucose, glucagon or dextrose at the investigator’s discretion.

Detailed information is available in the current edition of the IB for IDeg and in the local labelling for IGlar and IAsp.

12.7 Novo Nordisk safety committee

Novo Nordisk will constitute an internal IDeg safety committee to perform on-going safety surveillance. The IDeg safety committee may recommend un-blinding 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 trial personnel.

12.8 Event adjudication

Adjudication is a validation of an event based on collection of predefined data related to the specific event.

An external independent event adjudication committee (EAC) is constituted for this trial to perform adjudication in a blinded manner of events as described in Table Table 12–1 . The EAC is composed of members covering required medical specialities. EAC members must disclose potential conflicts of interest. The EAC will have no authorisation to impact on trial conduct, trial protocol or amendments.

The EAC can evaluate an event not initially reported as an event for adjudication to be adjudicated. In this case the investigator must provide medical documentation as soon as possible, when they receive the request from Novo Nordisk or the EAC. The adjudication vendor will ensure that the EAC has access to relevant documentation required. Additional information from the investigator may be requested by the EAC.

The outcomes of adjudication by the EAC will be kept in the clinical trial database and will be included in the clinical trial report together with assessments made by the investigator.

Table Table 12–1 includes a list of events that are to be reported for adjudication.

Table 12–1 Description of events to be adjudicated

Event	Definition
Acute coronary syndrome	All types of myocardial infarction (MI): • Spontaneous MI (including re-infarction) • MI secondary to ischemia due to imbalance between oxygen demand and supplies • Percutaneous coronary intervention (PCI) related MI (including MI associated with stent thrombosis) • Coronary artery bypass graft surgery related MI • Silent MI Hospitalisation for unstable angina pectoris All events with symptoms of myocardial ischemia requiring hospitalisation
Cerebrovascular event	• Any acute episode of focal or global neurological dysfunction caused by brain, spinal cord or retinal vascular injury as a result of haemorrhage or infarction
Fatal event	All-cause death
Severe hypoglycaemia or hypoglycaemic episodes reported as an SAE	Severe hypoglycaemia is defined as 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

The adjudication of cardiovascular events is done to meet FDA requirements for new antidiabetic therapies.[29] The adjudication of severe hypoglycaemic events is done to increase validity of these important endpoints.

13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be supplied by a vendor.

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.

Pregnancy forms will be provided as paper CRFs.

In addition, paper AE forms and safety information forms will be provided. These must be used when access to the eCRF is revoked.

On the paper CRF forms print 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.

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

13.1 Corrections to case report forms

Corrections to the CRF data may be made by the investigator or the investigator's authorised staff. An audit trail will be maintained in the CRF 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 authorised staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

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 or phone contact. During the trial, titration data and data from the hypoglycaemic episode form should be recorded within 24 hours. At the end of the trial at the site all data should be recorded no later than 24 hours after the last subject’s last visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

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.

13.3 13.3 eDiaries

Novo Nordisk will provide subjects with an eDiary with BG meter integration for electronic recording of details of their SMPG and insulin doses (refer to section 8.6). The eDiary and related support services will be supplied by a vendor that will be working under the direction and supervision of Novo Nordisk.

At Visit 2, the subjects will be provided with the eDiary and trained in the use thereof. The eDiary will be returned by the subject at Visit 66.

BG meter data will be transferred from the BG meter to the eDiary and the remaining data will be entered by the subject in the eDiary device. All data entered will be transferred automatically from the device to the electronic patient reported outcomes (ePRO) database, from where a certified copy will be saved on a CD-ROM and shipped to the sites after completion of the trial. This CD-ROM will act as source data. Data entered in the device will upon confirmation of a successful back-up be deleted from the device.

The eDiary will contain built in edit checks, to ensure that all relevant questions are answered.

The eDiary device is not intended to support the subsequent review and modification of completed entries. In case of corrections to transferred data are needed, a query flow must be initiated by the investigator. Upon review by Novo Nordisk, data will be corrected accordingly by the vendor. An audit trail will be maintained.

Data in the ePRO database will be viewable to relevant sites and Novo Nordisk personnel on a secure, password protected web portal. Data will be transferred to the Novo Nordisk trial database at defined intervals. For details on eDiary data flow, see Figure 13–1.

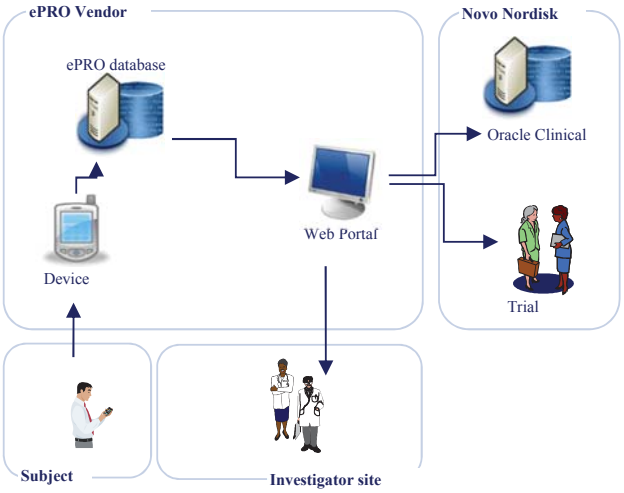

Figure 13–1 eDiary data flow

14 Monitoring procedures

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 FPFV and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the CRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks.

The monitor must be given direct access to 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 CRF. 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 diaries and/or PROs must not be removed from the trial site, unless they form part of the CRF and a copy is kept at the site.

The monitor will ensure that the CRFs are completed and that any paper CRFs are collected.

The monitor will collect CRF pages and other trial related forms containing data from screening failures. The following data must be source data verified: signed informed consent and the screening failure reason.

Monitors must review the subject's medical records and other source data (e.g. the diaries and PROs) to ensure consistency and/or identify omissions compared to the CRF. 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 addressing 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 and event adjudication committee will be transferred electronically from the laboratory performing the analyses. 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 identification number. 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.

17 Statistical considerations

Novo Nordisk will analyse and report data from all sites together.

Analyses of all endpoints will be based on the Full Analysis Set (FAS). Efficacy endpoints and patient reported outcome endpoints will be summarised using the FAS. Safety endpoints will be summarised using the Safety Analysis Set (SAS).

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

All endpoints will be summarised descriptively at each visit by treatment and in total using observed data. The endpoints are summarised by the arithmetic mean, standard deviation (SD), median, and minimum and maximum value. For endpoints assessed for each treatment period and where change from baseline is reported, the baseline value will for treatment period A be the measurement taken at Visit 2 and for treatment period B the measurement taken at Visit 34.

Presentation of results from a statistical analysis will include the estimated mean treatment effects (LSMeans) for absolute values. Estimated mean treatment ratios will be presented together with two-sided 95% confidence intervals for all endpoints analysed statistically. p-values will only be presented for the primary endpoint and confirmatory secondary endpoints for which formal statistical testing will be performed using a hierarchical (fixed sequence) testing procedure. The procedure is based on an a priori ordering of the null-hypotheses and testing them in this order using the two-sided 95% confidence interval approach until an insignificant result appears. The other endpoints are considered supportive.

For endpoints measured over time, mean values will be plotted to explore the trajectory over time. Data collected before randomisation will only be summarised descriptively.

17.1 Sample size calculation

The primary endpoint of this trial is treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance period of each treatment period.

The sample size calculation is based on showing that

IDeg OD + IAsp is non-inferior to IGlar OD + IAsp

in terms of severe or BG confirmed symptomatic hypoglycaemic episodes.

This is considered confirmed if the upper bound of the 95% confidence interval for the rate ratio (IDeg OD + IAsp/ IGlar OD + IAsp) is below or equal to 1.1 or equivalently if the p-value for the one-sided test of

H_0: RR > 1.1 against H_A: RR ≤ 1.1

is less than 2.5%, where RR is the estimated rate ratio IDeg OD + IAsp / IGlar OD + IAsp.

Assuming that conditional on the individual subject level S_i, Y_{ij} follows a Poisson distribution such that

$$\log E(Y_{ij} \mid S_i) = S_i + \tau_j + \log(t_{ij}), \quad i=1,\ldots,n \; ; \; j=1,2$$

where Y_{ij} is the number of events for subject *i* , τ_j is the effect of treatment *j*, and t_{ij} is the corresponding exposure time.

Conditioning on the total number of events for subject *i*, $y_{i\bullet} = \Sigma_j \, y_{ij}$, we have

$$Y_{ij} \mid y_{i\bullet} \sim \text{Bin}(y_{i\bullet} \, , p_{ij}), \; p_{ij} = t_{ij}e^{\tau j} / \Sigma_j \, t_{ij}e^{\tau j}$$

Introducing the notation $\rho = e^{\tau 1 - \tau 2}$ for the rate ratio of Treatment 1 over Treatment 2 we have

$$p_{i1} = t_{i1}\rho \, /(\, t_{i1}\rho + t_{i2}) = \rho \, /(\, \rho + t_{i2}/ \, t_{i1})$$

Applying the logit-transformation, we get

$$\text{logit}(p_{i1}) = \log(p_{i1}/(1- p_{i1})) = \log(\rho \, /(t_{i2}/ \, t_{i1})) = \log(\rho t_{i1}/t_{i2}) = \log(\rho) + \log(t_{i1}/t_{i2})$$

This implies that the log rate ratio can be estimated by logistic regression with the log of the relative exposure time on the two treatments as an offset.

The model described above, when conditioning on the total number of events for each subject, is a binomial with

$$\text{logit}(p_{i1}) = \log(\rho) + \log(t_{i1}/t_{i2}).$$

For the purpose of power calculations, it is assumed that the exposure time on each treatment is the same, i.e. the model reduces to a binomial with

$$\text{logit}(p_{i1}) = \log(\rho)$$

or equivalently

$$p_{i1} = \rho/(\rho+1)$$

for all subjects. Adding over all the subjects, the total number of events on treatment 1, $Y_{\bullet 1}$ is then also binomial with the same probability parameter, i.e.

$$Y_{\bullet 1} \mid y_{\bullet\bullet} \sim \text{Bin}(y_{\bullet\bullet} \; ; \; \rho/(\rho+1))$$

Under the null hypothesis of no difference between the treatments ($\rho=1$)

$Y_{\bullet 1} \mid y_{\bullet\bullet} \sim Bin(y_{\bullet\bullet}\ ;\ ½)$

The power is computed with the formula:

$P\{Z>Bin(N;½)_{0.975}\}$ where $Z \sim Bin(N\ ;\ \rho/(\rho+1))$

In the above formula when adjusting the power for the non-inferiority limit of a rate ratio of 1.1 then ρ is substituted with $\rho^*=\exp(\log(\rho) - \log(1.1)) = \rho/1.1$ such that the power is

$P\{Z>Bin(N;½)_{0.975}\}$ where $Z \sim Bin(N\ ;\ \rho^*/(\rho^*+1))$

Assuming a true rate ratio of 0.90 and a non-inferiority limit of a rate ratio of 1.1, the power for various severe or BG confirmed symptomatic hypoglycaemia rates and sample sizes are as follows (Table 17–1):

Table 17–1 Power calculation

Episodes per PYE	N=370	N=400	N=430
4.0	84.1%	87.2%	89.6%
5.0	91.8%	93.9%	95.2%
6.0	95.8%	96.7%	97.6%

PYE: patient years of exposure, RR: rate ratio

So, if up to 10% of the randomised (non-replaced) subjects do not contribute to the analysis, then 400 subjects will contribute to the analysis, if 446 subjects are randomised. With an expected rate of severe or BG confirmed symptomatic hypoglycaemic episodes of 5.0 per PYE, this will ensure around 94% power to demonstrate non-inferiority.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance.[30]

- Full Analysis Set (FAS): includes all randomised subjects. In exceptional cases subjects from the FAS may be eliminated. In such cases the elimination will be justified and documented. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation “as randomised”.

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

Before data are released for statistical analysis, a review of all data will take place to ensure a sufficient data quality and to ensure the planned statistical analyses are applicable. Any data decisions not foreseen in the protocol will be documented before database lock.

17.3 Primary endpoint

The primary endpoint is number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64).

Statistical analysis

Before the primary endpoint is tested, the secondary supportive efficacy endpoint "Change from baseline in HbA_{1c} after 32 weeks of treatment" will be tested for non-inferiority as a prerequisite for testing the primary endpoint. The analysis will be made for each treatment period separately.

All observed HbA_{1c} measurements available post randomisation, at scheduled measurement times for subjects with trial exposure in the maintenance period A will be analysed with a mixed model for repeated measurements (MMRM) with an unstructured covariance matrix. The model includes treatment, visit, sex, region, pre-trial insulin regimen and dosing time as fixed effects and age and baseline HbA_{1c} as covariates. Interactions between visit and all factors and covariates are also included in the model. For Treatment period B the analysis above will be repeated including subjects with any HbA_{1c} measurements after visit 34.

Dosing time is a factor with the following two levels: morning dosing and evening dosing.

Region is a factor with two levels: Poland and USA.

Pre-trial insulin treatment regimen is a factor with three levels: Pump users, once daily (OD) basal insulin injections or twice daily (BID) basal insulin injections.

If this model does not converge, another model will be fitted with a simplified covariance matrix.Non-inferiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval is below or equal to 0.4% or equivalent if the p-value for the one-sided test of

H_0: $D > 0.4\%$ against H_A: $D \leq 0.4\%$,

is less than 2.5%, where D is the treatment difference (IDeg OD + IAsp minus IGlar OD + IAsp).

If non-inferiority is confirmed, the primary endpoint will be tested.

The number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance period will be analysed using a Poisson model with subject as a random effect, treatment, period, sequence and dosing time as fixed effects and time exposure to trial drug in each hypoglycaemia counting period as an offset.

Non-inferiority is considered confirmed if the 95% confidence interval for the rate ratio (IDeg OD + IAsp / IGlar OD + IAsp) is below or equal to 1.1 or equivalently if the p-value for the one-sided test of

$$H_0: RR > 1.1 \text{ against } H_A: RR \leq 1.1$$

is less than 2.5%, where RR is the estimated rate ratio IDeg OD + IAsp/IGlar OD + IAsp.

If non-inferiority is confirmed the superiority of IDeg OD + IAsp over IGlar OD + IAsp will be investigated outside of the test hierarchy. Superiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval is below 1.

Sensitivity analysis
To assess the sensitivity of the result to subjects that only complete the first treatment period, the primary analysis will be repeated using the same model but with subject as fixed effect instead of random effect.

Hypoglycaemic episodes will be defined in section 17.4.2.1.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoints

Provided that non-inferiority is confirmed for the primary endpoint, two confirmatory secondary endpoints will be tested. The confirmatory secondary endpoints are given below together with the direction of the test. The order of the endpoints defines the testing sequence.

The following safety endpoints will be assessed: in the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64):

- Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes
  - Non-inferiority is considered confirmed if the upper limit of the 95% confidence interval of the rate ratio (IDeg OD + IAsp / IGlar OD + IAsp) is below or equal to 1.10. If non-inferiority is confirmed, the endpoint is tested outside of the test hierarchy to a superiority limit of 1.0.
- Proportion of subjects with one or more severe hypoglycaemic episodes

Hypoglycaemic episodes will be defined in section 17.4.2.1

Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the maintenance period will be tested using the same model as for the primary endpoint.

Proportion of subjects with one or more severe hypoglycaemic episodes in the maintenance period will be tested for superiority using McNemar's test.

17.4.2 Supportive secondary endpoints

17.4.2.1 Safety endpoints

The following safety endpoints will be assessed during 32 weeks of treatment, for each treatment period:

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

The following safety endpoints will also be assessed for the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64):

- Number of treatment emergent total hypoglycaemic (severe or BG confirmed) episodes
- Number of treatment emergent total nocturnal hypoglycaemic (severe or BG confirmed) episodes
- Number of treatment emergent severe hypoglycaemic episodes
- Number of treatment emergent hypoglycaemic episodes according to ADA definition
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes occurring during sleep in the time span between 10:01 pm and 07:59 am

The following safety endpoint will be assessed for each treatment period:

- Incidence of treatment emergent adverse events during 32 weeks of treatment
- Change from baseline in clinical evaluations after 32 weeks of treatment
  - Vital signs (including blood pressure and pulse)
  - Fundoscopy or fundus photography
  - Electrocardiogram (ECG)
- Change from baseline in laboratory assessments after 32 weeks of treatment
  - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, leucocytes)
  - Biochemistry (creatinine, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase, sodium, potassium, albumin, total bilirubin)
- Change from baseline in body weight after 32 weeks of treatment
- Total daily insulin dose after 32 weeks of treatment

Due to the cross-over design, hypoglycaemic episodes will be attributed to the treatment given in the period in which the event occurred. That is, events occurring in the time period from start of treatment in the first treatment period up to start of treatment in the second treatment period will be attributed to the treatment given in the first period. Events occurring between start of treatment in

the second treatment period up to the last day of randomised treatment will be attributed to the treatment given in the second treatment period.

Data on hypoglycaemic episodes are presented in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). Separate summaries are made by severity considering severe or BG confirmed symptomatic hypoglycaemic episodes, severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes, severe hypoglycaemia, total hypoglycaemia (severe or BG confirmed) episodes and total nocturnal hypoglycaemia (severe or BG confirmed) episodes. All events of severe hypoglycaemia will be prospectively adjudicated by an independent, external expert in a blinded manner. All tables are made for the maintenance period as well as for the whole treatment period.

The number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the entire treatment period, severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the entire treatment period, severe hypoglycaemic episodes during the entire treatment period, total hypoglycaemia (severe or BG confirmed) episodes during the maintenance period, total nocturnal hypoglycaemia (severe or BG confirmed) episodes during the maintenance period, severe hypoglycaemic episodes during the maintenance period, severe or BG confirmed symptomatic hypoglycaemic episodes during sleep during the maintenance period will be analysed separately using the same model as for the primary analysis, i.e. a Poisson model with subject as a random effect, treatment, period, sequence and dosing time as fixed effects, and time exposure to trial drug in each hypoglycaemia counting period as an offset.

The number of treatment emergent hypoglycaemic episodes according to ADA definition (maintenance and entire treatment period) will be summarized descriptively.

Hypoglycaemic episodes

Definition of Hypoglycaemia

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

Nocturnal hypoglycaemic episodes: episodes with time of onset between 00:01 and 05.59 both inclusive.

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL).[31] Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of BG confirmed hypoglycaemia (see Figure 17–1).

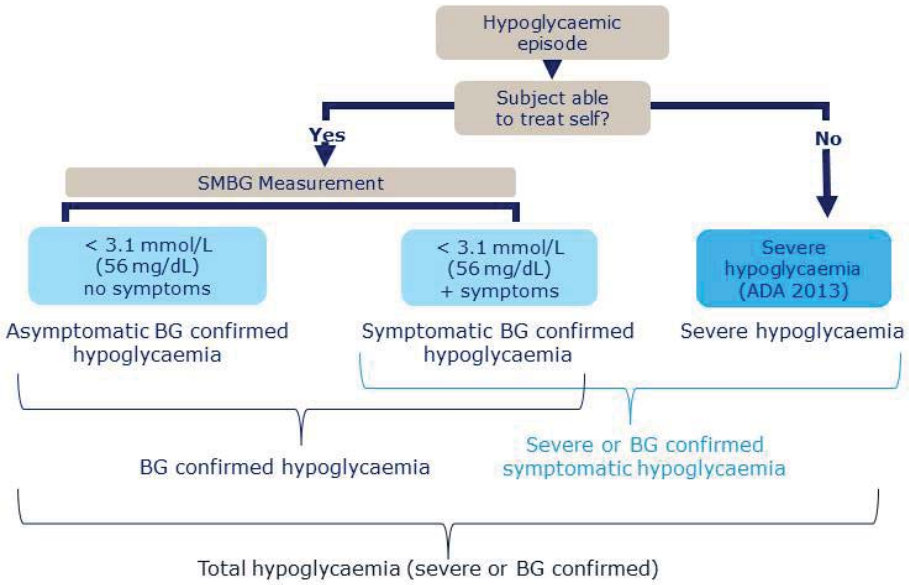

Figure 17–1 Novo Nordisk definition of hypoglycaemia to improve specificity of clinical trial episodes (in addition to ADA classification)

Total hypoglycaemia (severe or BG confirmed)

Are defined as episodes that are:

- severe (positively adjudicated according to ADA definition below) and/or
- BG confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia

Severe or BG confirmed symptomatic hypoglycaemia

Are defined as episodes that are severe and/or BG confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia.

Severe hypoglycaemia

Severe hypoglycaemic episodes are defined according to the ADA classification as stated below.

ADA classification of hypoglycaemia [32]

- 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 typical 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)

Adverse Events

Adverse Events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) coding. All adverse events will be presented based on system organ class and preferred terms.

A Treatment Emergent Adverse Event (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 the last day of randomised treatment. Due to the cross-over design adverse events will be attributed to treatment similarly as previously described for hypoglycaemic episodes.

TEAEs are summarised descriptively by treatment. TEAE data will be displayed in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). Furthermore, TEAE data are summarised by seriousness, severity, relation to insulin treatment, relation to device, withdrawal due to AEs and outcome.

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

- All TEAEs
- Serious TEAEs
- Possibly or probably related TEAEs
- Severe TEAEs
- TEAEs with preferred term that are experienced by at least 5% of the subjects in any treatment sequence or by at least 5% of all subjects

Vital Signs

The measurements and their change from baseline will be summarised descriptively by treatment.

Laboratory Assessments

Individual laboratory values will be flagged as being below or above existing relevant reference ranges. Change from baseline will be summarised descriptively by treatment.

Fundoscopy / fundus photography

Fundoscopy and fundus photography findings will be summarised descriptively by treatment including summaries of the change from baseline.

ECG

ECG findings will be summarised descriptively by treatment including summaries of the change from baseline.

Insulin dose

Prescribed and actual basal insulin dose will be recorded daily. Actual time point of basal insulin dose will be recorded once weekly. Actual bolus insulin dose will be recorded together with time (breakfast, lunch, main evening meal or extra bolus insulin) of administration.

The insulin dose will be summarised descriptively by visit and treatment as dose in units and units/kg. The summaries will also include information on time of basal insulin administration in order to document the time of the day patients inject their basal insulin and the degree to which patient shift injection times during the trial.

Body weight

Body weight will be summarised descriptively by treatment including summaries of the change from baseline.

17.4.2.2 Efficacy endpoints

The following efficacy endpoints will be assessed for each treatment period:

- Change from baseline in HbA_{1c} after 32 weeks of treatment
- FPG after 32 weeks of treatment
- Self-measured plasma glucose measurements (SMPG):
  - 9-point profiles:
    - Mean of the 9-point profiles after 32 weeks of treatment
  - 4-point profiles (obtained for insulin dose adjustment):
    - Mean plasma glucose before breakfast after 32 weeks of treatment

HbA_{1c}

See Section 17.3.

FPG

FPG will be summarised descriptively by treatment including summaries of the change from baseline.

SMPG

9-point profile (SMPG)

The endpoint from the 9-point profiles (SMPG) is:

- Mean of the 9-point profile (SMPG) after 32 weeks of treatment

The mean of the 9-point profile (SMPG) is defined as the area under the profile divided by the measurement time and is calculated using the trapezoidal method. It will be summarised descriptively by treatment including summaries of the change from baseline.

SMPG values used for dose adjustment (4-point profiles)

The endpoint from SMPG measurements obtained throughout the trial for dose adjustment will be:

- Mean plasma glucose before breakfast after 32 weeks of treatment

The mean PG before-meal will be calculated at each visit using the available data and summarised descriptively by treatment including summaries of the change from baseline.

17.5 Patient-reported outcomes

The following questionnaires will be used to asses patient reported outcomes related to treatment:

- Health Related Quality of Life Questionnaire (SF-36®v2) after 32 weeks of treatment in each treatment period
- Treatment Related Impact Measure – Minor Hypoglycaemic Events (TRIM-HYPO) after 32 weeks of treatment in each treatment period

The domain scores for the health-related quality of life questionnaire (SF-36®v2) will be summarised descriptively by treatment.

The domain scores for the Treatment Related Impact Measure for Minor Hypoglycaemic events (TRIM-HYPO) will be summarised descriptively by treatment. The data will not be included in the clinical trial report.

The following questionnaire will be used to assess costs associated with hypoglycaemia:

- Hypoglycaemia episodes – Interview questionnaire during 32 weeks of treatment in each treatment period

The data collected from the Hypoglycaemia episodes – Interview questionnaires will provide information to be used in health economic analyses. The data will not be included in the clinical trial report.

18 Ethics

18.1 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 subjects 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.

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 task may be delegated by the investigator 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 Data handling

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

- Data already collected and data collected at the end-of-trial visit will be retained by Novo Nordisk, entered into the database and used for the trial report.
- 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.

18.3 Information to subject during trial

All information to the subjects will be submitted to the health authorities and IECs/IRBs for approval according to local regulations.

18.4 Premature termination of the trial and/or trial site

Novo Nordisk, the investigator, 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 a 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 IRBs/IECs and provide a detailed written explanation. The relevant regulatory authorities must be informed.

If, after the termination of the trial, the risk/benefit 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

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 clinical database.

Documentation on protocol deviations must be kept in the investigator's trial file and Novo Nordisk trial master file.

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, 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
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure
- Signed and dated agreement on the final protocol
- Signed and dated agreement on protocol amendment, if applicable
- Financial agreement(s)
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Signed and dated Investigator Agreement
- Financial disclosure form from investigator and sub-investigator(s)

- Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- FDA form 1572 must be completed and signed by each investigator

FDA form 1572:

- Intended for US sites
- Conducted under the IND
- All US investigators, as described above, will sign FDA Form 1572

Novo Nordisk will analyse and report data from all sites together.

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

By signing the protocol, each investigator also agrees to allow Novo Nordisk making 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. If any tasks are delegated, the investigator must maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties. The investigator must ensure that there is adequate 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 must ensure adequate supervision of the conduct of the trial at the trial site. 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's trial file. The documents should be kept in a secure locked facility, so no unauthorised persons can get access to the data. The subject identification code list must be kept securely and separate from the personal 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 Novo Nordisk for regulatory purposes and 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.

One Principal Investigator will be appointed to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[33].

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.

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 investigator's and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

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

Novo Nordisk maintains the right to be informed of plans by any investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to Novo Nordisk before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors (sometimes referred to as the Vancouver Criteria)[33].

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 for publication of such primary policy 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

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/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the Novo Nordisk 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 as long as the product is on the market plus 20 years.

The files from the investigator site/institution must be retained for 15 years after the completion of the trial, or longer if required by local regulations. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

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 sponsor, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to Investigator's Brochure, 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 risk/benefit 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 maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator's trial file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, updates to IBs, 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.

27 References

1 International Conference on Harmonisation. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1), Step 4. 10-6-1996.

2 World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects - Last amended by the 59th WMA General Assembly, Seoul. 2008.

3 Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353(25):2643-2653.

4 The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329(14):977-986.

5 Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: update regarding thiazolidinediones: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2008; 31(1):173-175.

6 American Diabetes Association. Standards of medical care in diabetes--2013. Diabetes Care 2013; 36 Suppl 1:S11-S66.

7 Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes Obes Metab 2012; 14(9):859-864.

8 Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379(9825):1489-1497.

9 Novo Nordisk A/S. Investigator's Brochure, Insulin degludec (8th Edition). 1-11-2012.

10 Lantus - U.S. Label information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021081s034lbl.pdf. 16-May-2013.

11 Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. Diabetes Care 2000; 23(5):644-649.

12 Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di VA et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes 2000; 49(12):2142-2148.

13 Porcellati F, Rossetti P, Fanelli G. Glargine vs NPH as basal insulin in intensive treatment of T1DM given lispro at meals: One year comparison. Diabetes 1998; 47(Suppl. 1: A 103).

14 Raskin P, Park G, Zimmerman J. For the U.S. Study Group of HOE 901 in Type 2 Diabetes Mellitus. The effect of HOE 901 in glycemic control in type 2 diabetes. Diabetes 1998; 47(Suppl 1: A103).

15 Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. Diabetes Care 2000; 23(11):1666-1671.

16 Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. Diabetes Care 2000; 23(5):639-643.

17 Rosenstock J, Schwartz SL, Clark CM, Jr., Park GD, Donley DW, Edwards MB. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care 2001; 24(4):631-636.

18 Scholtz HE, Pretorius SG, Wessels DH, Becker RHA. Pharmacokinetic and glucodynamic variability: Assessment of insulin glargine, NPH insulin and insulin ultralente in healthy volunteers using a euglycaemic clamp technique. Diabetologia 2005; 48(10):1988-1995.

19 Home PD, Lindholm A, Riis A. Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: a randomized controlled trial. Diabet Med 2000; 17(11):762-770.

20 Lindholm A, McEwen J, Riis AP. Improved postprandial glycemic control with insulin aspart. A randomized double-blind cross-over trial in type 1 diabetes. Diabetes Care 1999; 22(5):801-805.

21 Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. Diabetes Care 2000; 23(5):583-588.

22 NovoRapid - Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000258/WC500030372.pdf. 14-Sep-12 A.D.

23 NovoLog - U.S. Label information. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&searchTerm=020986&SearchType=BasicSearch. 17-Jul-2009.

24 Mathieu C, Hollander P, Miranda-Palma B, Cooper J, Franek E, Russell-Jones D et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. J Clin Endocrinol Metab 2013; 98(3):1154-1162.

25 De Angelius C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. New Engl J Med 2004; 351(12):1250-1251.

26 Food and Drug Administration Amendments Act of 2007: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm. 2007.

27 European Commission Regulation for EudraCT.http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000044.jsp&mid=WC0b01ac05800260a3. 2011.

28 The rules governing medicinal products in the European Union, volume 4, Annex 13, Manufacture of Investigational Products - Brussels. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm. 2010.

29 Guidence for Industry. Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. http://www.fda.gov. 1-Dec-2008.

30 International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials E9. International Conference on Harmonisation E9 Expert Working Group. 5-2-1998.

31 Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. J Clin Invest 1987; 79(3):777-781.

32 Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. J Clin Endocrinol Metab 2013; 98(5):1845-1859.

33 Clever L, Colaianni LA, Davidoff F, Horton R, Kassirer JP, Angell M et al. Uniform requirements for manuscripts submitted to biomedical journals. New Engl J Med 1997; 336(4):309-315.

Statistical Analysis Plan

Trial ID: NN1250-3995

A randomised, double blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, both with insulin aspart as mealtime insulin in subjects with type 1 diabetes

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

Author:
Name: [redacted]
Department: Biostatistics

Table of contents

Page

List of abbreviations

ADA	*American diabetes association*
AE	*adverse event*
ANOVA	*analysis of variance*
BG	*Blood glucose*
BID	*"Bis in die" Twice daily*
BMI	*body mass index*
CAS	*Completer analysis set*
CI	*confidence interval*
CRF	*case report form*
CTR	*clinical trial report*
EAC	*Event adjudication committee*
EoT	*end-of-text*
FAS	*full analysis set*
ITT	*intention to treat*
LOCF	*last observation carried forward*
MAR	*Missing at random*
MedDRA	*Medical Dictionary for Regulatory Activities*
MMRM	*mixed models for repeated measurement*
OD	*Once daily*
PD	*pharmacodynamics*
PK	*pharmacokinetics*
PP	*per protocol*
PRO	*Patient reported outcome*
SAE	*serious adverse event*
SAP	*statistical analysis plan*
SAS	*safety analysis set*
SD	*standard deviation*
SE	*standard error*
SMPG	*self measured plasma glucose*

1 Introduction

1.1 Trial information

Objective(s) and endpoint(s):

Primary objective

To compare the rates of severe or BG (blood glucose) confirmed symptomatic hypoglycaemia of IDeg once daily (OD) + IAsp to IGlar OD + IAsp, by demonstrating that the upper limit of the 95% confidence interval of the rate ratio is below or equal to a non-inferiority margin of 1.10, and if confirmed, to a superiority limit of 1.0

Secondary objective

To compare the rates of severe or BG confirmed symptomatic nocturnal hypoglycaemia with IDeg OD + IAsp to IGlar OD + IAsp, by demonstrating that the upper limit of the 95% confidence interval of the rate ratio is below or equal to a non-inferiority margin of 1.10, and if confirmed, to a superiority limit of 1.0.

To confirm superiority of IDeg OD + IAsp compared to IGlar OD + IAsp in terms of proportion of subjects with severe hypoglycaemic episodes.

To compare efficacy of IDeg OD + IAsp in controlling glycaemia with respect to change from baseline in HbA_{1c} after 32 weeks of treatment. This is done by comparing the difference in change from baseline in HbA_{1c} after 32 weeks of treatment between IDeg OD + IAsp and IGlar OD + IAsp to a non-inferiority limit of 0.4%.To compare IDeg OD + IAsp and IGlar OD + IAsp in terms of safety, other parameters of glycaemic control and patient reported outcome (PRO).

Trial design:

This trial is a 64-week, randomised, controlled, double blind, two-period, cross-over, multi-centre, treat-to-target trial comparing the safety and efficacy of IDeg and IGlar both administered once daily, in a basal-bolus regimen with IAsp as mealtime insulin in subjects with type 1 diabetes mellitus.

Subjects will be switched from pre-trial basal-bolus treatment and randomly allocated into one of two treatment sequences in a blinded manner:
IDeg OD + IAsp 2−4 times daily followed by IGlar OD + IAsp 2−4 times daily
IGlar OD + IAsp 2−4 times daily followed by IDeg OD + IAsp 2−4 times daily

Within each treatment arm subjects will be randomised 1:1 to morning or evening dosing. The dosing time will be kept throughout both treatment periods.

The trial includes two 32-week treatment periods in a cross-over design. Total trial duration for the individual subjects will be up to 67 weeks.

1.2 Scope of the statistical analysis plan

This statistical analysis plan (SAP) is based on the protocol ”A randomised, double blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, both with insulin aspart as mealtime insulin in subjects with type 1 diabetes”, version 5.0, and amendments no 1, 2 and 3

2 Statistical considerations

Novo Nordisk will analyse and report data from all sites together.

Analyses of all endpoints will be based on the Full Analysis Set (FAS). Efficacy endpoints and patient reported outcome endpoints will be summarised using the FAS. Safety endpoints will be summarised using the Safety Analysis Set (SAS).

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

All endpoints will be summarised descriptively at each visit by treatment and in total using observed data. The endpoints are summarised by the arithmetic mean, standard deviation (SD), median, and minimum and maximum value. For endpoints assessed for each treatment period and where change from baseline is reported, the baseline value will for treatment period A be the measurement taken at Visit 2 and for treatment period B, the measurement taken at Visit 34.

Presentation of results from a statistical analysis will include the estimated mean treatment effects (LSMeans) for absolute values. Estimated mean treatment ratios will be presented together with two-sided 95% confidence intervals for all endpoints analysed statistically. p-values will only be presented for the primary endpoint and confirmatory secondary endpoints for which formal statistical testing will be performed using a hierarchical (fixed sequence) testing procedure. The procedure is based on an a priori ordering of the null-hypotheses and testing them in this order using the two-sided 95% confidence interval approach until an insignificant result appears. The other endpoints are considered supportive.

For endpoints measured over time, mean values will be plotted to explore the trajectory over time. Adverse events and hypoglycaemic episodes collected before randomisation and during follow-up are not considered treatment emergent and will only be summarised descriptively and appear in subject listings.

AEs and hypoglycaemic episodes are summaries by actual treatment. Actual treatment is the first treatment in the randomised sequence from time of first drug date till last drug date on treatment 1.

Actual treatment is the second treatment in the randomised treatment sequence from last drug date on treatment 1 plus one day till last drug date on treatment 2.

For summaries and statistical analysis of all endpoints the first non-missing value per visit is used. The value should be taken according to protocol, e.g. a non-fasting FPG value is not used. Re-tests of non-missing values are included in subject specific listings.

2.1 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance.[30]

- Full Analysis Set (FAS): includes all randomised subjects. In exceptional cases subjects from the FAS may be eliminated. In such cases the elimination will be justified and documented. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation "as randomised".

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

- Completer analysis set (CAS): includes all subjects that complete both treatment periods, if a subject withdrew during follow-up following the second treatment period the subject is considered a completer.

Before data are released for statistical analysis, a review of all data will take place to ensure a sufficient data quality and to ensure the planned statistical analyses are applicable. Any data decisions not foreseen in the protocol will be documented before database lock.

2.2 Missing data

Subjects that withdraw or drop-out of the trial will be explored with the purpose of investigating whether in particular the population that drop out prior to first maintenance period is different from the population that is exposed in the first maintenance period and whether there are any differences in drop-out between the two treatments.

2.3 Primary endpoint

The primary endpoint is number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64).

Statistical analysis

Before the primary endpoint is tested, the secondary supportive efficacy endpoint "Change from baseline in HbA_{1c} after 32 weeks of treatment" will be tested for non-inferiority as a prerequisite for testing the primary endpoint. The analysis will be made for each treatment period separately.

All observed HbA_{1c} measurements available post randomisation, at scheduled measurement times for subjects with trial exposure in the maintenance period A will be analysed with a mixed model for repeated measurement (MMRM) with an unstructured covariance matrix. The model includes treatment, visit, sex, region, pre-trial insulin regimen and dosing time as fixed effects, and age and baseline HbA1c as covariates. Interactions between visit and all factors and covariates are also included in the model. For treatment period B the analysis above will be repeated including subjects with any HbA1c measurement after visit 34.

Dosing time is a factor with the following two levels: morning dosing and evening dosing.

Region is a factor with two levels: Poland and USA.

Pre-trial insulin treatment regimen is a factor with three levels: CSII users, once daily (OD) basal insulin injections or twice daily (BID) basal insulin injections.

If this model does not converge, another model will be fitted with a simplified covariance matrix.

Non-inferiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval is below or equal to 0.4% or equivalent if the p-value for the one-sided test of

$$H_0: D > 0.4\% \text{ against } H_A: D \leq 0.4\%,$$

is less than 2.5%, where D is the treatment difference (IDeg OD minus IGlar OD).

If non-inferiority is confirmed for both treatment periods, the primary endpoint will be tested.

The number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance period will be analysed using a Poisson model with subject as a random effect, treatment, period, sequence and dosing time as fixed effects and time exposure to trial drug in each hypoglycaemia counting period as an offset.

Non-inferiority is considered confirmed if the 95% confidence interval for the rate ratio (IDeg OD/IGlar OD) is below or equal to one or equivalently if the p-value for the one-sided test of

$$H_0: RR > 1.1 \text{ against } H_A: RR \leq 1.1$$

is less than 2.5%, where RR is the estimated rate ratio IDeg OD / IGlar OD.

If non-inferiority is confirmed the superiority of IDeg OD + IAsp /IGlar OD + IAsp will be investigated outside of the test hierarchy. Superiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval is below 1.

Sensitivity analysis

In the primary analysis subjects that are not exposed in the second maintenance period contribute to the estimation of the treatment difference. This implies that these subjects are assumed to behave like subjects that are exposed in both maintenance periods, i.e. a missing completely at random (MCAR) assumption. To investigate how this assumption influences the primary results a sensitivity analysis has been added that only include patients that are exposed in both maintenance periods. This analysis follows the randomisation principle [1], in that the same subjects are analysed on both treatments. The treatment estimate from this analysis is an unbiased estimate in the subset of subjects that were exposed to the maintenance period for both treatments, under the assumption that missing data for subjects that drop-out in the second maintenance period are missing at random (MAR). Since data from subjects that were only exposed in the first maintenance period are excluded, the pragmatic effectiveness principle [1] is violated.

A secondary sensitivity analysis has been added that only includes subjects from the CAS. The estimated treatment difference from this sensitivity analysis is unbiased in the subset of subjects that complete both maintenance periods, and does not rely on any assumptions regarding missing data. This analysis follows the randomisation principle, but violates the pragmatic effectiveness principle since data from all subjects not completing both maintenance periods are excluded. This analysis estimates the principal stratum direct effect [1].

The negative binomial model will be explored on the primary endpoint and the results will be compared with the Poisson model. The specification of the model will be identical to the primary analysis except that the distribution will be a negative binomial instead of a Poisson distribution. Due to the random patient effect in the model it is likely that the negative binomial model will be over-parameterized, and hence will not converge.

Hypoglycaemic episodes will be defined in section 2.4.2.1.

2.4 Secondary endpoints

2.4.1 Confirmatory secondary endpoints

Provided that non-inferiority is confirmed for the primary endpoint, two confirmatory secondary endpoints will be tested. The confirmatory secondary endpoints are given below together with the direction of the test. The order of the endpoints defines the testing sequence.

The following safety endpoints will be assessed: in the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64):

- Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes
  - Non-inferiority is considered confirmed if the upper limit of the 95% confidence interval of the rate ratio (IDeg OD + IAsp / IGlar OD 0 IAsp) is below or equal to 1.10. If non-inferiority is confirmed, the endpoint is tested outside the test hierarchy to a superiority limit of 1.0.
- Proportion of subjects with one or more severe hypoglycaemic episodes

Hypoglycaemic episodes will be defined in section 2.4.2.1.

Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the maintenance period will be tested using the same model and sensitivity analysis as for the primary endpoint.

Proportion of subjects with one or more severe hypoglycaemic episodes in the maintenance period will be tested for superiority using McNemar's test.

2.4.2 Supportive secondary endpoints

2.4.2.1 Safety endpoints

The following safety endpoints will be assessed during 32 weeks of treatment:

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

The following safety endpoints will be assessed for the maintenance period, i.e. after 16 weeks of treatment, in each treatment period (Week 16−32 and Week 48−64):

- Number of treatment emergent total hypoglycaemic (severe or BG confirmed) episodes
- Number of treatment emergent nocturnal total hypoglycaemic (severe or BG confirmed) episodes
- Number of treatment emergent severe hypoglycaemic episodes
- Number of treatment emergent hypoglycaemic episodes according to ADA definition
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes occurring during sleep in the time span between 10:01 pm and 07:59 am

The following safety endpoints will be assessed for each 32 week treatment period:

- Incidence of treatment emergent adverse events during 32 weeks of treatment
- Change from baseline in clinical evaluations after 32 weeks of treatment
  - Vital signs (including blood pressure and pulse)
  - Fundoscopy or fundus photography
  - Electrocardiogram (ECG)
- Change from baseline in laboratory assessments after 32 weeks of treatment
  - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, leucocytes)
  - Biochemistry (creatinine, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase, sodium, potassium, albumin, total bilirubin)
- Change from baseline in body weight after 32 weeks of treatment
- Total daily insulin dose after 32 weeks of treatment

Due to the cross-over design, hypoglycaemic episodes will be attributed to the treatment given in the period in which the event occurred. That is, events occurring in the time period from start of treatment in the first treatment period up to start of treatment in the second treatment period will be attributed to the treatment given in the first period. Events occurring between start of treatment in the second treatment period up to the last day of randomised treatment will be attributed to the treatment given in the second treatment period.

Data on hypoglycaemic episodes are presented in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). Separate summaries are made by severity considering severe or BG confirmed symptomatic hypoglycaemic episodes, severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes, severe hypoglycaemia, total hypoglycaemia (severe or BG confirmed) episodes and total nocturnal hypoglycaemia (severe or BG confirmed) episodes. All events of severe hypoglycaemia will be prospectively adjudicated by an independent, external expert in a blinded manner. All tables are made for the maintenance period as well as for the whole treatment period.

The number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the entire treatment period, severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the entire treatment period, severe hypoglycaemic episodes during the entire treatment period, total hypoglycaemia (severe or BG confirmed) episodes during the maintenance period, total nocturnal hypoglycaemia (severe or BG confirmed) episodes during the maintenance period, severe hypoglycaemic episodes during the maintenance period, severe or BG confirmed symptomatic hypoglycaemic episodes during sleep during the maintenance period will be analysed separately using the same model as for the primary analysis, i.e. a Poisson model with subject as a random effect, treatment, period, sequence and dosing time as fixed effects, and time exposure to trial drug in each hypoglycaemia counting period as an offset.

The proportions of subjects with one or more treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance periods and the proportions of

subjects with one or more severe or BG confirmed symptomatic hypoglycaemic nocturnal episodes during the maintenance periods will be analysed with the McNemar's test.

The number of treatment emergent hypoglycaemic episodes according to ADA definition (maintenance and entire treatment period) will be summarized descriptively.

Hypoglycaemic episodes

Definition of Hypoglycaemia

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

Nocturnal hypoglycaemic episodes: are episodes with time of onset between 00:01 and 05.59 both inclusive.

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL).[32] Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of BG confirmed hypoglycaemia (see Figure 2–**1**).

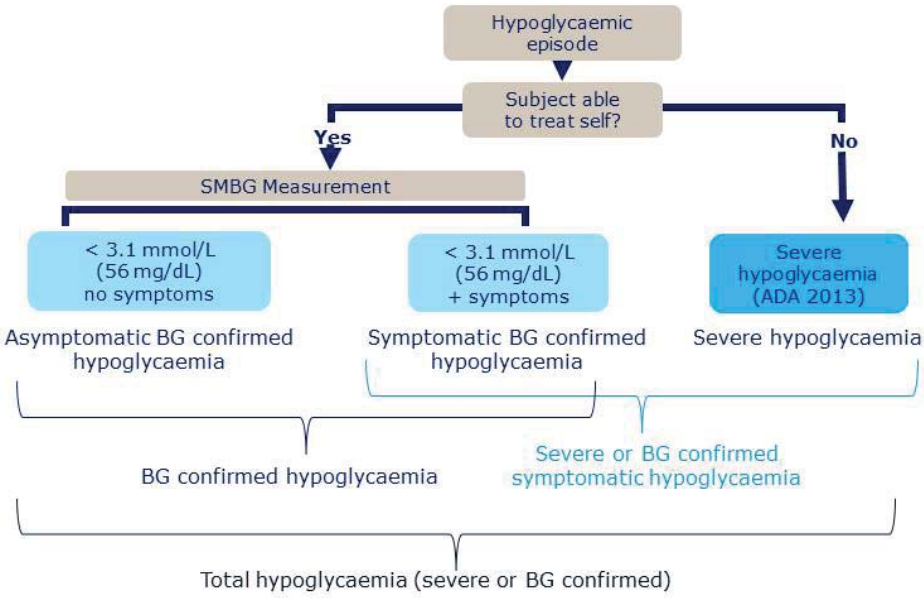

Figure 2–1 Novo Nordisk definition of hypoglycaemia to improve specificity of clinical trial episodes (in addition to ADA classification)

Total hypoglycaemia (severe or BG confirmed)

Are defined as episodes that are:
- severe (positively adjudicated according to ADA definition) and/or
- BG confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia

Severe or BG confirmed symptomatic hypoglycaemia

Are defined as episodes that are severe and/or BG confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia.

Severe hypoglycaemia

Severe hypoglycaemic episodes are defined according to the ADA classification as stated below.

ADA classification of hypoglycaemia
- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose values 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)

Hypoglycaemic episodes are classified as severe only if confirmed by the EAC.

Severe hypoglycaemic episodes reported by investigator but not confirmed by EAC are re-classified according to information on eCRF. If the BG measurement is missing or non-confirmed and presence of symptoms is unknown the episodes is re-classified as unable to selftreat – unclassifiable.

For adjudicated events the onset date is determined by the EAC. Hence, in case there is a discrepancy between the investigator-provided onset date and the EAC-provided time of onset date then the EAC date is used. For hypoglycaemic episodes that are not confirmed by the EAC the onset date is the investigator reported onset date.

Adjudicated events occurring before the date of randomisation and after the last day of treatment, as determined by the EAC, are not included in the statistical analysis or treatment emergent summary tables.

Data collected before the randomisation date and in the follow-up period will only be included in subject specific listings.

Adverse Events

Adverse Events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) coding. All adverse events will be presented based on system organ class and preferred terms.

A Treatment Emergent Adverse Event (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 the last day of randomised

treatment. This is due to the cross-over design. Adverse events will be attributed to treatment similarly as previously described for hypoglycaemic episodes.

TEAEs are summarised descriptively by treatment. TEAE data will be displayed in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). Furthermore, TEAE data are summarised by seriousness, severity, relation to insulin treatment, relation to device, withdrawal due to AEs and outcome.

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

- All TEAEs
- Serious TEAEs
- Possibly or probably related TEAEs
- Severe TEAEs
- TEAEs with preferred term that are experienced by at least 5% of the subjects in any treatment sequence or by at least 5% of all subjects

Vital Signs

The measurements and their change from baseline will be summarised descriptively by treatment .

Laboratory Assessments

Individual laboratory values will be flagged as being below or above existing relevant reference ranges. Change from baseline will be summarised descriptively by treatment.

Funduscopy / fundus photography

Funduscopy and fundus photography findings will be summarised descriptively by treatment including summaries of the change from baseline.

ECG

ECG findings will be summarised descriptively by treatment including summaries of the change from baseline.

Insulin dose

Prescribed and actual basal insulin dose will be recorded daily. Actual time point of basal insulin dose will be recorded once weekly. Actual bolus insulin dose will be recorded together with time (breakfast, lunch, main evening meal or extra bolus insulin) of administration.

The insulin dose will be summarised descriptively by visit and treatment as dose in units and units/kg. The summaries will also include information on time of basal insulin administration in

order to document the time of the day patients inject their basal insulin and the degree to which patient shift injection times during the trial.

To describe compliance to the randomised dosing times, morning dosing is defined as the time from 03:00 to 14:59 and evening dosing is from 15.00 to 02:59.

Body weight

Body weight will be summarised descriptively by treatment including summaries of the change from baseline.

2.4.2.2 Efficacy endpoints

The following efficacy endpoints will be assessed for each 32 week treatment period:

- Change from baseline in HbA_{1c} after 32 weeks of treatment
- FPG after 32 weeks of treatment
- Self-measured plasma glucose measurements (SMPG):
  - 9-point profiles:
    - Mean of the 9-point profiles after 32 weeks of treatment
  - 4-point profiles (obtained for insulin dose adjustment):
    - Mean plasma glucose before breakfast after 32 weeks of treatment

HbA_{1c}

See Section 2.3.

FPG

FPG will be summarised descriptively by treatment including summaries of the change from baseline.

SMPG

9-point profile (SMPG)

The endpoint from the 9-point profiles (SMPG) is:
Mean of the 9-point profile (SMPG) after 32 weeks of treatment

The mean of the 9-point profile (SMPG) is defined as the area under the profile divided by the measurement time and is calculated using the trapezoidal method. It will be summarised descriptively by treatment including summaries of the change from baseline.

SMPG values used for dose adjustment (4-point profiles)

The endpoints from SMPG measurements obtained throughout the trial for dose adjustment will be:

– Mean plasma glucose before breakfast after 32 weeks of treatment

The mean PG before-meal will be calculated at each visit using the available data and summarised descriptively by treatment including summaries of the change from baseline

2.5 Patient reported outcomes

The following questionnaires will be used to assess patient reported outcomes:

– Health Related Quality of Life Questionnaire (SF-36®v2) after 32 weeks of treatment in each treatment period
– Treatment Related Impact Measure – Minor Hypoglycaemic Events (TRIM-HYPO) after 32 weeks of treatment in each treatment period

The domain scores for the health-related quality of life questionnaire will be summarised descriptively by treatment. The domain scores for the Treatment Related Impact Measure for minor Hypoglycaemic events will be summarised descriptively by treatment.

The following interview questionnaire will be used to assess costs associated with hypoglycaemia:

– Hypoglycaemic episodes – Interview questionnaire during 32 weeks of treatment in each treatment period

The data collected from the Hypoglycaemic episode – Interview questionnaires will to provide information to be used in health economic analyses.

2.6 Switch from other insulin treatment regimens to IDeg

A judgement of safety will be made on the switch from pre-trial CSII and twice daily dosing (BID) to IDeg once daily (OD) dosing and on the switch from IGlar OD to IDeg OD. Subjects will be categorized based on their pre-trial insulin treatment regimen at screening or use of IGlar in first treatment sequence.

3 Changes to the statistical analyses planned in the protocol

The sensitivity analysis to the primary analysis is changed compared to the sensitivity analysis specified in final protocol version 8.0. A fixed effect model cannot be fitted if there are subjects that do no experience any hypoglycaemic episodes on both treatments.

The sensitivity analysis on the CAS is added to further investigate the missing at random assumption for subjects that drop-out in the second maintenance periods.

The sensitivity analysis exchanging the Poisson model with the negative binomial model is due to FDA expressing concerns regarding the Poisson model and suggesting the negative binomial model as a supportive analysis.

The analysis of proportions of subjects with severe or BG confirmed symptomatic hypoglycaemic episodes and proportions of subjects with nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes are added to follow the recommendation of FDA.

In addition output on the safe switch from other insulin treatment regimens and missing data are specified in the SAP. These outputs are specified for transparency, i.e. these output were intented prior to unblinding data.

4 References

[1] Permutt, T. (2015) A taxonomy of estimands for regulatory clinical trials with discontinuations. Statist. Med., doi: 10.1002/sim.6841.