

Cover Page for Protocol

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16.1.1 Protocol and protocol amendments

List of contents

Protocol version 2	Link
Protocol version 3	Link
Appendix A	Link
Attachment I and II	Link
Protocol amendment 1 Serbia	Link
Protocol amendment 2	Link
Memo analyse of antibodies	Link

*Redacted protocol
Includes redaction of personal identifiable information only.*

Protocol
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Protocol

Trial ID: NN1250-4252

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

Trial phase: 3b



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Table of contents

	Page
Table of contents	2
Table of figures	6
Table of tables	6
List of abbreviations	6
1 Summary	11
2 Flow chart	14
3 Background information and rationale for the trial	20
3.1 Background information.....	20
3.2 Rationale for the trial.....	21
4 Objective(s) and endpoint(s)	23
4.1 Objective(s).....	23
4.2 Endpoint(s).....	23
4.2.1 Primary endpoint.....	23
4.2.2 Secondary endpoints.....	23
4.2.2.1 Confirmatory secondary endpoints.....	23
4.2.3 Other endpoints.....	23
5 Trial design	25
5.1 Type of trial.....	25
5.2 Rationale for trial design.....	26
5.3 Treatment of subjects.....	26
5.4 Treatment after discontinuation of trial product.....	28
5.5 Rationale for treatment.....	28
6 Trial population	29
6.1 Number of subjects.....	29
6.2 Inclusion criteria.....	29
6.3 Exclusion criteria.....	30
6.4 Criteria for premature discontinuation of trial product.....	31
6.5 Withdrawal from trial.....	32
6.6 Subject replacement.....	33
6.7 Rationale for trial population.....	33
7 Milestones	34
8 Methods and assessments	35
8.1 Visit procedures.....	35
8.1.1 Screening visit (Visit 1).....	35
8.1.1.1 Screening failures.....	36
8.1.2 Randomisation visit (V2).....	36
8.1.3 Phone contacts.....	37
8.1.4 Fasting visits.....	37
8.1.5 End of Treatment visit (V54).....	38
8.1.6 Follow up visits.....	38

8.1.7	Unscheduled site visits.....	39
8.1.8	Premature discontinuation of trial product	39
8.1.8.1	eDiary records after premature discontinuation of trial product	41
8.1.9	Withdrawal from trial	41
8.1.10	Review of results	41
8.2	Subject related information/assessments	42
8.2.1	Demography.....	42
8.2.2	Diabetes history	42
8.2.3	Hypoglycaemia unawareness.....	42
8.2.4	Concomitant illness and medical history	42
8.2.5	Concomitant medication	43
8.2.6	Concomitant medication (Diabetes)	43
8.2.7	Childbearing potential.....	44
8.2.8	Tobacco use	44
8.3	Efficacy assessments.....	44
8.3.1	Self-measured plasma glucose	44
8.3.2	Insulin dose.....	45
8.4	Safety assessments.....	45
8.4.1	Adverse events.....	45
8.4.1.1	Medication error	45
8.4.1.2	Adverse events requiring additional data collection	46
8.4.2	Hypoglycaemic episodes	47
8.4.3	Body measurements.....	50
8.4.4	Vital signs	50
8.4.5	Physical examination	50
8.4.6	Eye examination	51
8.4.7	Electrocardiogram.....	51
8.5	Laboratory assessments	52
8.5.1	Laboratory assessments for efficacy	53
8.5.2	Laboratory assessments for safety	53
8.6	Other assessments	54
8.6.1	Training in the pen injector.....	56
8.7	Subject compliance	56
9	Trial supplies	58
9.1	Trial products.....	58
9.2	Labelling	59
9.3	Storage	59
9.4	Drug accountability and destruction	60
9.5	Auxiliary supplies	60
10	Interactive web response system.....	61
11	Randomisation procedure	62
12	Adverse events, and technical complaints and pregnancies.....	63
12.1	Definitions	63
12.1.1	Adverse event	63
12.1.2	Serious adverse event.....	64
12.1.3	Non-serious adverse event.....	65
12.1.4	Medication errors.....	66

12.1.5	Adverse events requiring additional data collection	66
12.1.6	Technical complaints	67
12.2	Reporting of adverse events	67
12.3	Follow-up of adverse events	69
12.4	Technical complaints and technical complaint samples	71
12.4.1	Reporting of technical complaints	71
12.4.2	Collection, storage and shipment of technical complaint samples	71
12.5	Pregnancies in female subjects	72
12.6	Precautions and/or overdose	73
12.7	Committees related to safety	74
12.7.1	Novo Nordisk safety committee	74
12.7.2	Event adjudication committee	74
13	Case report forms	77
13.1	Corrections to case report forms	77
13.2	Case report form flow	78
13.3	eDiary	78
14	Monitoring procedures	79
15	Data management	81
16	Computerised systems	81
17	Statistical considerations	81
17.1	General considerations	81
17.2	Sample size calculation	83
17.3	Definition of analysis sets	84
17.4	Primary endpoint	85
17.4.1	Primary statistical analysis for the primary estimand	85
17.4.2	Sensitivity analyses for the primary estimand	85
17.4.3	Statistical analysis for the secondary estimand	86
17.4.4	Sensitivity analysis for the secondary estimand	86
17.5	Secondary endpoints	86
17.5.1	Confirmatory secondary endpoints	86
17.6	Other endpoints	87
17.6.1	Efficacy endpoints	87
17.6.2	Safety endpoints	87
17.7	Classification of Hypoglycaemia	89
17.8	Health economics and/or patient reported outcomes	92
18	Ethics	93
18.1	Benefit-risk assessment of the trial	93
18.2	Informed consent	94
18.3	Data handling	95
18.4	Information to subjects during trial	95
18.5	Premature termination of the trial and/or trial site	95
19	Protocol compliance	96
19.1	Protocol deviations	96
19.2	Prevention of missing data	96
20	Audits and inspections	98

21 Critical documents	98
22 Responsibilities	99
23 Reports and publications	100
23.1 Communication of results	100
23.1.1 Authorship	101
23.1.2 Site-specific publication(s) by investigator(s)	101
23.2 Investigator access to data and review of results	102
24 Retention of clinical trial documentation and human bio samples.....	103
24.1 Retention of clinical trial documentation.....	103
24.2 Retention of human bio samples.....	103
25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities.....	105
26 Indemnity statement	106
27 References	107
Appendix A Titration Guideline	
Attachment I Global list of key staff and relevant departments and suppliers	
Attachment II Country list of key staff and relevant departments, if applicable for the individual country	

Table of figures

	Page
Figure 5–1 Trial design.....	25
Figure 12–1 Reporting of AEs.....	68
Figure 13–1 eDiary data flow	79
Figure 17–1 Novo Nordisk classification of hypoglycaemia.....	90
Figure 17–2 ADA classification of hypoglycaemia.....	91

Table of tables

	Page
Table 2–1 Flow chart – phone contacts	19
Table 9–1 Trial products.....	58
Table 9–2 Storage conditions	59
Table 12–1 Adverse events requiring completion of specific event forms and/or are subject to event adjudication	66
Table 12–2 Events for adjudication.....	74
Table 17–1 Sample sizes for the primary and secondary estimand for combinations of RR and event rates to achieve a power of 80%	83
Table 17–2 Marginal power for confirmatory secondary endpoints	84

List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
BG	blood glucose
BID	Bis In Die/twice daily
CAS	completer analysis set
CCDS	Company Core Data Sheet
CFR	Code of Federal Regulations
CLAE	clinical laboratory adverse event
CRF	case report form
DPP-IVi	dipeptidyl peptidase-4 inhibitor
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPFV	first patient first visit

FPG	fasting plasma glucose
FU	follow-up
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
HbA _{1c}	glycosylated haemoglobin
hCG	human chorionic gonadotropin
IB	investigator's brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IDeg	insulin degludec
IEC	independent ethics committee
IGlar	insulin glargine
IMP	investigational medicinal product
IND	Investigational New Drug
ITT	intention-to-treat
IRB	institutional review board
IWRS	interactive voice/web response system
LI	label information
LLOQ	lower limit of quantification
LPLV	last patient last visit
MACE	major adverse cardiovascular events

NIMP	Non-Investigational Medicinal Product
NPH	insulin Neutral Protamine Hagedorn
NYHA	New York Heart Association
OAD	oral anti-diabetic drug
OD	once daily
PP	per protocol
PRO	patient reported outcome
PYE	Patient years of exposure
PX	monthly phone contact
RR	rate ratio
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SF-36v2 [®]	short-form 36 health survey version 2
SGLT2i	sodium-glucose co-transporter 2 inhibitors
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
SU	sulfonylureas
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent AE
TIA	transient ischaemic attack

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Page: 10 of 109

Novo Nordisk

TMM	trial materials manual
TRIM-D	Treatment related impact measure - diabetes
TRIM-D-Device	Treatment related impact measure - diabetes device
TZD	Thiazolidinediones
U	Units
UNL	upper normal limit
UTN	Universal Trial Number

1 Summary

Objective(s) and endpoint(s):

Primary objective

To compare the effects of insulin degludec once daily and insulin glargine 300 units/mL once daily on hypoglycaemia in subjects with type 2 diabetes mellitus, inadequately treated with basal insulin with or without oral anti-diabetic drugs.

Key secondary objectives

To compare insulin degludec and insulin glargine 300 units/mL in terms of basal insulin requirement.

To compare insulin degludec and insulin glargine 300 units/mL in terms of safety and parameters of glycaemic control.

Primary endpoint

- Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes during maintenance period (week 16-52)

Confirmatory secondary endpoints:

- Basal insulin dose (units) at 52 weeks
- Number of nocturnal, severe or blood glucose confirmed symptomatic hypoglycaemic episodes during maintenance period (week 16-52)
- Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes during 52 weeks
- Number of severe hypoglycaemic episodes during maintenance period (week 16-52)

Other efficacy endpoints:

- Change in HbA_{1c} from baseline to 52 weeks

Other safety endpoints:

- Hypoglycaemia
 - Number of nocturnal, severe or blood glucose confirmed symptomatic hypoglycaemic episodes during 52 weeks
 - Number of severe hypoglycaemic episodes during 52 weeks
- Number of adverse events during 52 weeks

Trial design:

This is a 52-week, randomised (1:1), open-label, parallel, multi-centre, multi-national, treat-to-target, active controlled trial comparing the efficacy and safety of insulin degludec 200 units/mL with insulin glargine 300 units/mL both administered once daily \pm oral anti-diabetic drugs in subjects with type 2 diabetes mellitus previously treated with basal insulin once or twice daily \pm oral anti-diabetic drugs excluding sulfonylureas/glinides. Type and dose of any pre-trial oral anti-diabetic treatment should remain unchanged throughout the trial.

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

Total trial duration for the individual subjects will be up to 58 weeks.

Trial population:

It is planned to randomise 1,590 subjects.

Key inclusion criteria:

- Male or female, age above or equal to 18 years at the time of signing informed consent.
- Subjects fulfilling at least one of the below criteria^a:
 - a. Experienced at least one severe hypoglycaemic episode within the last year (according to the ADA definition, April 2013^b).
 - b. Moderate chronic renal failure, defined as glomerular filtration rate 30 - 59 mL/min/1.73 m² per CKD-EPI by central laboratory analysis.
 - c. Hypoglycaemic symptom unawareness^c.
 - d. Treated with insulin for more than 5 years.
 - e. 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).
- Subjects diagnosed (clinically) with type 2 diabetes mellitus.
- Treated with basal only insulin (once daily or twice-daily insulin (insulin detemir; insulin glargine 100 U/mL, biosimilar of insulin glargine 100 U/mL or insulin Neutral Protamine Hagedorn)) ≥ 90 days prior to the day of screening with or without any of the following anti-diabetic drugs with stable doses for ≥ 90 days prior to screening:
 - a Metformin
 - b Dipeptidyl peptidase -4 inhibitor
 - c Sodium-glucose co-transporter 2 inhibitor
 - d Alpha-glucosidase-inhibitors (acarbose)
 - e Thiazolidinediones

f Marketed oral combination products only including the products listed in criteria 5a-5e

- $HbA_{1c} \leq 9.5\%$ (80 mmol/mol) at screening by central laboratory analysis.
- $BMI \leq 45 \text{ kg/m}^2$.

^aFor this inclusion criterion the aim is to include minimum 80% of individuals with a previous episode of hypoglycaemia (criterion e). The remaining subjects will have to fulfil at least one of criteria a-d.

^bAn 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.

^cHistory of impaired autonomic responses (tremulousness, sweating, palpitations, and hunger) during hypoglycaemia.

Key exclusion criteria

- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before the day of screening.

Key assessments:

- Hypoglycaemic episodes
- Insulin dose
- HbA_{1c}
- Adverse events

Trial products:

Investigational medicinal products:

- Test product: Insulin degludec (Tresiba[®]), 200 U/mL, 3 mL prefilled PDS290 (FlexTouch[®]) pen for subcutaneous injection
- Reference therapy: Insulin glargine (Toujeo[®]), 300 U/mL, 1.5 mL prefilled Solostar[®] pen for subcutaneous injection

Other medicinal products:

- Insulin Neutral Protamine Hagedorn (Insulatard[®]/Prothaphane[®]/Novolin NTM), 100 IU/mL, 3 mL pre-filled pen for subcutaneous injection (will be provided by sponsor to subjects during the wash-out period in order to measure insulin antibodies)

Trial NN1250-4252	Protocol section	Screening	Randomisation	Titration 16 weeks				Maintenance 36 weeks								End Of Treatment	Follow-up			Premature discontinuation			
				V1	V2	V6	V10	V14	V18	V22	V26	V30	V34	V38	V42		V46	V50	V54	V55	V56	V18A	V30A
Visit number		V1	V2	V6	V10	V14	V18	V22	V26	V30	V34	V38	V42	V46	V50	V54	V55	V56	V18A	V30A	V42A	V54A	
 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								
Timing of visit (weeks)		-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	53	56	16	28	40	52	
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5	±3	±3	±3	±3	
Vital signs	8.4.4	X														X							
Physical examination	8.4.5	X														X							
Eye examination (Fundoscopy or fundus photography)	8.4.6	X														X							
ECG	8.4.7	X														X							
Anti-insulin antibodies	8.5.2		X			X					X					X	X						
Biochemistry	8.5.2	X														X							
Haematology	8.5.2	X														X							
Pregnancy test	8.5.2	X														X							
Technical complaints	12.1.6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
OTHER ASSESSMENTS																							
SF-36v2® Standard	8.6		X				X									X							
TRIM-D	8.6		X				X									X							
TRIM-D device	8.6		X													X							
Baseline hypoglycaemic Questionnaire (BHQ)	8.6	X																					
Insulin Pen Questionnaire	8.6															X							

Trial NN1250-4252	Protocol section	Screening	Randomisation	Titration 16 weeks			Maintenance 36 weeks									End Of Treatment	Follow-up		Premature discontinuation			
				V1	V2	V6	V10	V14	V18	V22	V26	V30	V34	V38	V42		V46	V50	V54	V55	V56	V18A
Visit number		V1	V2	V6	V10	V14	V18	V22	V26	V30	V34	V38	V42	V46	V50	V54	V55	V56	V18A	V30A	V42A	V54A
 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							
Timing of visit (weeks)		-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	53	56	16	28	40	52
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5	±3	±3	±3	±3
Hypoglycaemia resource use questionnaire	8.6			X	X	X	X	X	X	X	X	X	X	X	X	X						
TRIAL MATERIAL																						
NPH dosing (Date and Dose)	8.1.5															X						
Dosing (Date, Dose and time of trial insulin), every day	8.3.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Date of first dose of investigational trial product	8.1.2		X																			
New prescribed dose of trial insulin	8.3.2		X	X	X	X	X	X	X	X	X	X	X	X	X							
Dispensing visit	9.4		X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Drug accountability	9.4		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
IWRS session	10	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
REMINDERS																						
Attend visit fasting	8.1.4		X	X	X	X	X			X	X		X			X	X					
Confirmation of unchanged OAD	8.2.6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					

Trial NN1250-4252	Protocol section	Screening	Randomisation	Titration 16 weeks				Maintenance 36 weeks								End Of Treatment	Follow-up		Premature discontinuation			
				V1	V2	V6	V10	V14	V18	V22	V26	V30	V34	V38	V42		V46	V50	V54	V55	V56	V18A
Visit number		V1	V2	V6	V10	V14	V18	V22	V26	V30	V34	V38	V42	V46	V50	V54	V55	V56	V18A	V30A	V42A	V54A
 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							
Timing of visit (weeks)		-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	53	56	16	28	40	52
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5	±3	±3	±3	±3
Training in trial product and pen handling	8.6.1 9.2		X	X																		
Hand-out direction for use for the pen injectors	9.2		X																			
Hand-out ID card	8.1.1	X																				
Hand-out and instruct in BG meter	8.1.2		X	X																		
Hand-out and instruct in eDiary	8.1.2 8.6		X																			
eDiary collection	8.6																X					X
Make appointment for eye examination	8.4.6													X								
End Of Treatment	8.1.5															X						X
End of trial	7																X					X
Sign off Casebook																	X					

Table 2-1 Flow chart – phone contacts

NN1250-4252 Phone contacts (P) Time shown in site visit flow chart	Protocol section	P3-P53	PX
Contact window (days)		± 3	± 5
Criteria for premature discontinuation of trial products	6.4	X	
Concomitant medication	8.2.5	X	
Concomitant medication (Diabetes)	8.2.6	X	X
Self-measured plasma glucose, Once daily (pre-breakfast)	8.3.1	X	
First date on trial product	8.3.2	P3	
Dosing	8.3.2	X	
New prescribed dose of trial insulin	8.3.2	X	
Adverse events	8.4.1.12	X	X
Hypoglycaemic episodes	8.4.2	X	X
Technical complaints	12.4	X	
End of Trial	7		

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP¹ and applicable regulatory requirements, and in accordance with the Declaration of Helsinki².

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

Therapeutic area

Type 2 diabetes mellitus (T2DM) is characterised by insulin resistance, impaired insulin secretion and increased hepatic glucose output due to glucagon dysregulation resulting in chronic hyperglycaemia³. A number of landmark studies have demonstrated the importance of maintaining tight glycaemic control to reduce the risk of long-term complications associated with diabetes⁴. The current treatment cascade follows a stepwise approach comprising lifestyle changes in combination with pharmacological intervention. Metformin is recommended as initial pharmacological therapy, followed by combination therapy with other oral anti-diabetic drugs (OADs), glucagon-like peptide 1 receptor agonists (GLP-1) and insulin as the disease progresses⁵.

Insulin treatment is associated with hypoglycaemia, and fear of hypoglycaemia, especially severe hypoglycaemia, is widely acknowledged as the main limiting factor for achieving tight glycaemic control. Given the impact on quality of life, the potentially life-threatening consequences of severe and nocturnal hypoglycaemia, reducing the risk of hypoglycaemia is critical to the lives of patients.

Information on the hypoglycaemia profile of insulin products is considered an important part of the information foundation for health care professionals in considering individualised treatment. Thus it is important to compare different insulin analogues in terms of efficacy and safety to be able to offer subjects with T2DM in need of insulin treatment the best possible option.

Insulin degludec

Insulin degludec (IDeg) is an insulin analogue with unique pharmacological properties and a long duration of action⁸. IDeg provides similar glycaemic control to comparators with a 14–18% lower risk of confirmed hypoglycaemia and a 23–38% lower risk of nocturnal confirmed hypoglycaemia compared to insulin glargine 100 U/mL (IGlar 100 U/mL) in T2DM (phase 3a trials)^{6,7}. Moreover, in the SWITCH 2 trial (T2DM, phase 3b trial) IDeg was associated with a 23% lower risk of overall confirmed symptomatic hypoglycaemia, a 25% lower risk of nocturnal confirmed symptomatic hypoglycaemia and a 51% lower risk of severe hypoglycaemia compared to IGlar 100 U/mL⁸. The hypoglycaemic risk reduction for IDeg compared to IGlar 100 U/mL was more pronounced in the maintenance period in all trials⁶⁻⁸.

IDeg is developed in two strengths (100 U/mL and 200 U/mL) that are bio-equivalent in clinical pharmacology trials. IDeg has been approved in more than 70 countries globally and is indicated for treatment of diabetes mellitus as monotherapy, in combination with oral anti-diabetic agents and GLP-1, and as part of a basal-bolus insulin regimen in adults and children from the age of 1 year (GLP-1 co-usage and paediatric indication <18 years is not an approved indication in all countries with market authorisation). For further details please refer to the current version of the IDeg Investigator's Brochure (IB)⁹, of the Tresiba[®] summary of product characteristics (SmPC)¹⁰, U.S. Label Information (LI)¹¹ and any updates thereof.

Insulin glargine 300 U/mL

Insulin glargine 300 U/mL (IGlar 300 U/mL), a new long-acting insulin analogue approved in USA, Canada, EU and Japan, is indicated for treatment of diabetes mellitus as monotherapy, in combination with oral anti-diabetic agents and as part of a basal-bolus insulin regimen. The development programme established comparable efficacy and safety versus IGlar 100 U/mL^{12, 13}. Furthermore, a tendency towards a reduction in the incidence of hypoglycaemia with IGlar 300 U/mL was found in subjects with T2DM. For further details, please refer to the current version of the Toujeo[®] SmPC¹⁴ or local labelling^{15, 16}.

For an assessment of benefits and risks of the trial, see Section [18.1](#).

3.2 Rationale for the trial

The overall purpose of the trial is to compare the hypoglycaemia profile and the insulin dose requirements of IDeg versus IGlar 300 U/mL in subjects with T2DM inadequately controlled on basal insulin with or without OADs.

Both IDeg and IGlar 300 U/mL used IGlar 100 U/mL as comparator during the phase 3 development programme achieving non-inferiority with respect to the glycaemic endpoint measured by the reduction in HbA_{1c} from baseline to end of trial. In T2DM patients treatment with IDeg showed a consistent hypoglycaemia benefit compared to IGlar 100 U/mL whereas a lower number of hypoglycaemic episodes for IGlar 300 U/mL compared to IGlar 100 U/mL was primarily observed during the first weeks of treatment^{13, 17}.

IGlar 300 U/mL has a lower bioavailability compared to IGlar 100 U/mL leading to higher mean pre-breakfast SMPG values and FPG levels for patients treated with IGlar 300 U/mL compared to IGlar 100 U/mL. This is most evident during the first weeks of treatment and makes assessment of a possible hypoglycaemic benefit difficult during this time period.

Across the trial programme for IGlar 300 U/mL a 12-17% higher dose usage was needed with IGlar 300 U/mL to reach the same level of glycaemic control at end of trial compared to IGlar 100 U/mL^{12, 18}. In the IDeg phase 3a program an overall higher dose of approximately 10% was seen for IGlar 100 U/mL compared to IDeg¹⁹ and in the SWITCH 2 trial a post hoc analysis

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Page:	22 of 109	

demonstrated significantly lower insulin dose with IDeg compared with IGlar 100 U/mL after 32 weeks of treatment.

The present trial seeks to confirm the safety of IDeg particularly in the assessment of overall, nocturnal and severe hypoglycaemic episodes when similar glycaemic control levels have been obtained. Moreover, the trial will provide guidance on insulin dose requirements for achieving glycaemic control.

4 Objective(s) and endpoint(s)

4.1 Objective(s)

Primary objective

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

Secondary objectives

To compare IDeg and IGlax 300 U/mL in terms of basal insulin requirement.

To compare IDeg and IGlax 300 U/mL in terms of safety and parameters of glycaemic control.

4.2 Endpoint(s)

4.2.1 Primary endpoint

- Number of severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes during maintenance period (week 16-52)

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

- Basal insulin dose (U) at 52 weeks
- Number of nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes during maintenance period (week 16-52)
- Number of severe or BG confirmed symptomatic hypoglycaemic episodes during 52 weeks
- Number of severe hypoglycaemic episodes during maintenance period (week 16-52)

4.2.3 Other endpoints

Other efficacy endpoints

- Change in HbA_{1c} from baseline to 52 weeks
- Change in fasting plasma glucose (FPG) from baseline to 52 weeks
- FPG \leq 7.2 mmol/L (130 mg/dL) at 52 weeks (yes/no)
- FPG \leq 5 mmol/L (90 mg/dL) at 52 weeks (yes/no)
- HbA_{1c} $<$ 7% (53 mmol/mol) at 52 weeks and no severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance period (week 16-52) (yes/no)
- HbA_{1c} $<$ 7% (53 mmol/mol) at 52 weeks and no nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance period (week 16-52) (yes/no)
- Change in mean pre-breakfast self-measured plasma glucose used for titration from baseline to 52 weeks

Other safety endpoints

- Hypoglycaemia
 - Number of nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes during 52 weeks
 - Number of severe hypoglycaemic episodes during 52 weeks
- Number of adverse events during 52 weeks
- Change in clinical evaluations from baseline to week 52 in terms of:
 - Vital signs (including blood pressure and pulse)
 - Dilated funduscopy or fundus photography
 - Electrocardiogram (ECG)
- Change in body weight from baseline to week 52
- Change in central laboratory assessments from baseline to 52 weeks in terms of
 - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, leucocytes)
 - Biochemistry (creatinine, alanine aminotransferase , aspartate aminotransferase , alkaline phosphatase , sodium, potassium, albumin, total bilirubin)
- Special laboratory assessment during 52 weeks in terms of
 - Anti-insulin antibodies

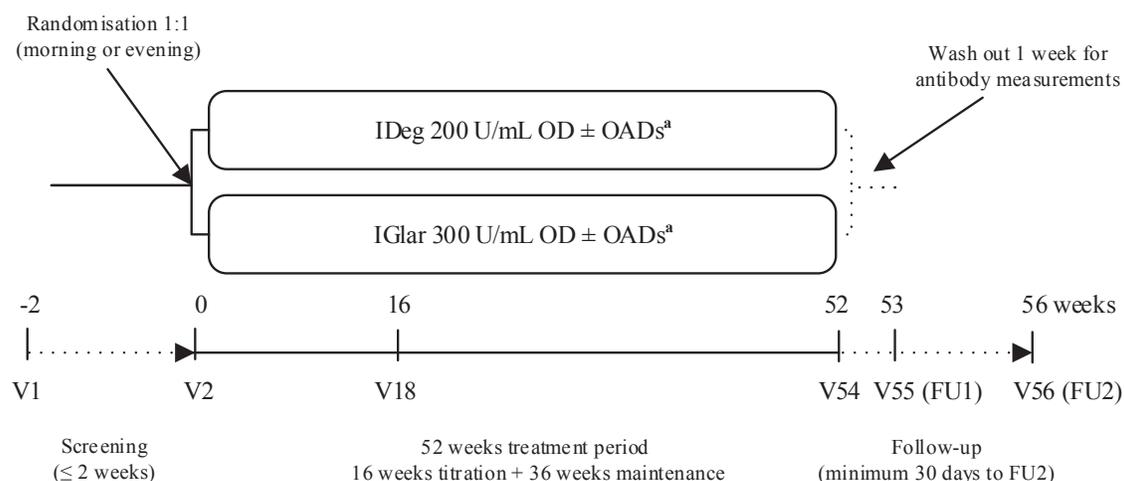
5 Trial design

5.1 Type of trial

This is a 52-week, randomised (1:1), open-label, parallel, multi-centre, multi-national, treat-to-target, active controlled trial comparing efficacy and safety of IDeg 200 U/mL with IGLar 300 U/mL both administered OD ± OADs in subjects with T2DM previously treated with basal insulin OD or twice daily (BID) ± OADs excluding sulfonylureas/glinides. Type and dose of any pre-trial OAD treatment should remain unchanged throughout the trial.

The trial design is summarised schematically in [Figure 5–1](#). The total trial duration will be approximately 58 weeks divided into the following periods:

- Screening up to two weeks
 - Screening (V1)
 - Randomisation (V2)
- 52-week treatment period consisting of
 - A 16-week titration period
 - A 36-week maintenance period
- 30 days post treatment follow-up period including two follow-up (FU) contacts
 - FU1 (V55) 7-12 days after end of treatment
 - FU2 (V56) 30-35 days after end of treatment



^aOral Anti-diabetic Drugs (OADs): Metformin, Dipeptidyl peptidase-4 inhibitor, Sodium-glucose co-transporter 2 inhibitor, Alpha-glucosidase-inhibitors (acarbose), Thiazolidinediones, marketed oral combination products only including the products listed in inclusion criteria 5a-5e.

IDeg: insulin degludec, IGLar: insulin glargine, OD: once daily, FU: follow-up

Figure 5–1 Trial design

5.2 Rationale for trial design

In this trial an open-labelled trial design is chosen to minimize inconvenience for the subjects since a blinded trial due to different pen injector systems would require a double dummy approach.

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

For subjects randomised to IDeg OD, the daily basal insulin dose should be reduced by 20% from pre-trial dose.

Subjects randomised to IGLar 300 U/mL should switch unit-to-unit, if they prior to randomisation received basal insulin once daily. For subjects that prior to randomisation received a BID basal insulin regimen, the following applies:

- US subjects that prior to randomisation received a BID basal regimen with Neutral Protamine Hagedorn (NPH) insulin should have their total daily NPH dose reduced by 20% and given once daily.
- US subjects that prior to randomisation received a BID basal regimen with other basal insulin types should have their total daily basal insulin dose added up and injected once daily.
- EU subjects that prior to randomisation received a BID basal regimen with any basal insulin type should have their total daily basal insulin dose reduced by 20% and given once daily.

The basal insulin IDeg and IGLar 300 U/mL 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 1:1 randomisation to morning or evening dosing of the basal insulin is applied to avoid any confounding from injection time on a particular time interval (such as nocturnal) during which subjects would be at highest risk of hypoglycaemic episodes.

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

5.3 Treatment of subjects

Insulin treated subjects with T2DM can enter the trial if they present with an HbA_{1c} equal to or below 9.5% (80 mmol/mol) and have been treated with basal insulin for ≥ 90 days prior to the day of screening (V1) with or without OADs (metformin, DPP-4i, SGLT2i, thiazolidinedione, alpha-

glucosidase-inhibitors or marketed oral combination products only including the products listed in inclusion criteria 5a-5e), at stable doses for ≥ 90 days prior to V1.

Pre-trial treatment with IDeg or IGlax 300 U/mL is not allowed within 90 days prior to the screening visit. Any previous use of bolus insulin, insulin pump or pre-mix insulin excludes subjects from the trial, as well as use of any GLP-1 receptor agonist (e.g., exenatide or liraglutide) or SU/glinides, all within the 90 days prior to the screening visit.

At randomisation (V2) subjects who met all inclusion criteria and no exclusion criteria will be randomly allocated 1:1 into one of two treatment arms:

- IDeg -200 U/mL OD \pm OADs
- IGlax -300 U/mL OD \pm OADs

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

Following randomisation pre-trial insulin treatment must be discontinued and the subject switched to randomised treatment.

Type and dose of any pre-trial OAD treatment should remain unchanged throughout the trial and subjects should continue pre-trial OAD treatment from screening (V1) to end of trial (V54), unless for safety reasons.

The maximum duration of treatment will be 52 weeks. No maximum trial insulin dose is specified. Doses are adjusted according to plasma glucose values (see titration guideline; [Appendix A](#)). Surveillance of insulin titration will be performed by Novo Nordisk.

At end of treatment (V54) all subjects will be switched to insulin NPH for at least one week to ensure that all IDeg/IGlax is washed out when measuring anti-insulin antibodies.

After End of treatment each subject will have a 30-day safety follow-up period including two follow-up contacts (FU1 and FU2).

FU1 (V55) will be at least 7 days after end of treatment (V54). The purpose is to collect all treatment emergent adverse events (AEs) including hypoglycaemia and antibody samples.

FU2 (V56) will be at least 30 days after end of treatment (V54). The purpose is to collect information on anti-diabetic medication and AEs including hypoglycaemia occurring in the period between the two follow-up contacts.

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

For both treatment arms diet and exercise counselling is continued as per the standard of care at the investigational site.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products, either at the scheduled end of treatment visit or if trial product is discontinued prematurely, the subject will be instructed to switch insulin treatment to the intermediate acting insulin NPH until the first follow-up visit (V55). At V55 the subject should be switched to a suitable marketed product at the discretion of the investigator. Doses of subsequent anti-diabetic treatment should be carefully titrated based on blood glucose measurements, considering the long half-life of IMPs.

5.5 Rationale for treatment

The treat-to-target design and consequent visit schedule is used in order to ensure optimal insulin titration based on self-measured plasma glucose (SMPG) values and to ensure improvement in glycaemic control. The first 16 weeks of treat-to-target is to ensure optimal time to achieve improved and stable HbA_{1c} for both treatments when entering the maintenance period (from week 16-52). A 52-week treatment period has been chosen to optimise the trial treatment regimen and to obtain sufficient data for efficacy and safety evaluation.

The switch from trial insulin treatment to the 'washout' insulin (NPH) between the end of treatment visit (V54) and the 7-day follow-up visit (V55), is done in order to provide basal insulin coverage while reducing the level of IDeg/IGlar present at antibody sampling and consequently to reduce the possibility for interference with antibody measurements.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 2,271

Number of subjects planned to be randomised: 1,590

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 above or equal to 18 years at the time of signing informed consent.
3. Subjects fulfilling at least one of the below criteria^a:
 - a. Experienced at least one severe hypoglycaemic episode within the last year (according to the ADA definition, April 2013^b)
 - b. Moderate chronic renal failure, defined as glomerular filtration rate 30 - 59 mL/min/1.73 m² per CKD-EPI^{20, 21} by central laboratory analysis
 - c. Hypoglycaemic symptom unawareness^c
 - d. Treated with insulin for more than 5 years
 - e. 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. Subjects diagnosed with type 2 diabetes mellitus.
5. Treated with basal only insulin (once daily or twice-daily insulin (insulin detemir; insulin glargine 100 U/mL, biosimilar of insulin glargine 100 U/mL or NPH)) ≥ 90 days prior to the day of screening with or without any of the following anti-diabetic drugs/regimens with stable doses for ≥ 90 days prior to screening:
 - a. Metformin
 - b. Dipeptidyl peptidase-4 inhibitor
 - c. Sodium-glucose co-transporter 2 inhibitor
 - d. Alpha-glucosidase-inhibitors (acarbose)
 - e. Thiazolidinediones
 - f. Marketed oral combination products only including the products listed in criteria 5a-5e
6. $HbA_{1c} \leq 9.5\%$ (80 mmol/mol) at screening by central laboratory analysis.
7. $BMI \leq 45$ kg/m².
8. Ability and willingness to adhere to the protocol including self-measurement of plasma glucose according to the protocol.

^aFor inclusion criterion 3 the aim is to include minimum 80% of individuals with a previous episode of hypoglycaemia (3e). The remaining subjects will have to fulfil at least one of criteria a-d.

^bAn 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.

^cHistory 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. Acute impairment of glycaemic control requiring immediate intensification of treatment to prevent severe metabolic dysregulation (e.g. diabetes ketoacidosis) \leq 90 days prior to the day of the screening.
2. Known or suspected hypersensitivity to trial product(s) or related products.
3. Previous participation in this trial. Participation is defined as signed informed consent.
4. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).

For Denmark: Contraceptive measures considered adequate include:

- a. intrauterine devices or hormonal contraception (oral contraceptive pills, implants, transdermal patches, vaginal rings or long-acting injections)

For Estonia: Contraceptive measures considered adequate include:

- a. double barrier method (a combination of male condom with either cap, diaphragm or sponge with spermicide)

For Germany: The following contraceptive measures are considered adequate:

- a. combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, transdermal or intravaginal)
 - b. progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
 - c. intrauterine device
 - d. intrauterine hormone-releasing system
 - e. sexual abstinence
 - f. vasectomised partner
 - g. double barrier method (a combination of male condom with either cap, diaphragm or sponge with spermicide)
5. Participation in any clinical trial of an approved or non-approved investigational medicinal product (IMP) within 30 days prior to screening.

6. Any of the following: myocardial infarction, stroke or hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening and between screening and randomisation.
7. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
8. Planned coronary, carotid or peripheral artery revascularization known on the day of screening.
9. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR <30 mL/min/1.73 m² as defined by KDIGO 2012 classification²² using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening.
10. Impaired liver function, defined as ALT or AST ≥ 2.5 times upper limit of normal at screening.
11. Inadequately treated blood pressure as defined as Grade 3 hypertension or higher (Systolic ≥ 180 mmHg or diastolic ≥ 110 mmHg) at screening.
12. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening.
13. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).
14. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation.
15. Presence or history of malignant neoplasms within the last 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinomas in-situ are allowed.
16. Any condition, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

6.4 Criteria for premature discontinuation of trial product

Efforts should be made so that subjects attend and complete all scheduled visit procedures. Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule or missing assessments. Only subjects who decline any further contact with the site in relation to the trial will be considered as withdrawn from the trial (see Section [6.5](#)).

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

The subject must be prematurely discontinued from trial product if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria.
2. Pregnancy.
3. Intention of becoming pregnant.
4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.
5. Initiation of concomitant medication(s) for more than 14 calendar days, which in the investigator's opinion could affect weight or glucose metabolism.
6. Lack of efficacy; if all of the fasting SMPG values taken on three consecutive days or if any of the FPG samples analysed by the central laboratory exceeds the limit of:
 - a. 13.3 mmol/L (240 mg/dL) from visit 18 to visit 26 (both inclusive)
 - b. 11.1 mmol/L (200 mg/dL) from visit 26 (not included) to visit 54 (included)and if no treatable intercurrent cause for the hyperglycaemia has been identified, the subject must be called for a confirmatory FPG measurement at a scheduled or unscheduled visit as soon as possible. A confirmatory FPG must be obtained and analysed by the central laboratory. If this FPG exceeds the limits described above, the trial product must be discontinued.

See Section [8.1.8](#) for procedures to be performed for subjects discontinuing trial product prematurely.

6.5 Withdrawal from trial

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

If the subject considers withdrawing consent the investigator must underline to the subject the importance of continuing in the trial despite trial product discontinuation. If the subject agrees to discontinue trial products but to stay in the trial, procedures described in section [8.1.8](#) must be followed.

Only subjects who decline any further contact with the site in relation to the trial, and hence do not agree to provide information concerning morbidities, which are relevant for the assessment of AEs and/or other trial endpoints at the planned end of trial, should be withdrawn from trial.

See Section [8.1.9](#) for procedures to be performed for subjects withdrawing consent.

A subject will be considered lost to follow-up if he/she repeatedly fails to attend the scheduled visits and the Investigator is unable to establish contact with the subject.

The following actions must be taken in relation to a subject who fails to attend the site for a required visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible.
- The site must re-train the subject in the importance of maintaining the scheduled visits.
- In cases in which the subject is deemed lost to follow-up the investigator must make every effort to regain contact with the subject (e.g. telephone calls to friends or family members, e-mails or certified letter to the subject as applicable). These contact attempts must be documented in the subject's medical records. Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the trial with the primary reason being "lost to follow-up".

6.6 Subject replacement

Subjects who discontinue trial product prematurely will not be replaced.

6.7 Rationale for trial population

A population of insulin-treated subjects with T2DM presenting with an HbA_{1c} equal to or below 9.5% while treated continuously with basal insulin with or without OADs for at least 90 days and who recently have experienced hypoglycaemia or have increased risk of severe hypoglycaemia has been chosen for this trial. This population reflects a general T2DM population qualifying for optimisation of basal insulin treatment. The trial is not excluding individuals at high risk of developing hypoglycaemia making the population generalizable for the T2DM population. Subjects requiring treatment with basal bolus are not included to avoid the confounding element of bolus insulin. Treatment with SUs/glinides and insulin in combination creates an increased risk of hypoglycaemia, and therefore, SU/glinides are not allowed as pre-trial, and subsequently trial treatment.

A BMI ≤ 45.0 kg/m² was chosen to include as broad a population as possible, while excluding severely insulin resistant subjects in order to secure a rather homogenous population with regard to insulin needs.

The inclusion and exclusion criteria applied in this trial should ensure relevance of trial results for a broad population of subjects with T2DM.

The 20% reduction of IDeg when transferring from pre-trial insulin regimen, is to reduce the risk of subjects experiencing hypoglycaemia in the initial treatment phase and to secure equal and comparable levels of glycaemic control initially, given that IGLar 300 U/mL has a known lower potency compared to IGLar 100 U/mL and hence also IDeg.

7 Milestones

Planned duration of recruitment period, which is from first patient first visit (FPFV) – last patient first visit (LPPFV): 24 weeks.

End of trial is defined as last patient last visit (LPLV).

Recruitment:

The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects screened during the recruitment period and found eligible for randomisation can be randomised within the timelines specified in the flow chart, see Section [2](#).

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure²³ it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)²⁴, the Food and Drug Administration Amendment Act²⁵, European Commission Requirements^{26, 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

Timing of assessments and procedures are specified in the flow chart (see Section 2). This section includes a description.

Informed consent must be obtained before any trial related activity, see Section 18.2.

8.1.1 Screening visit (Visit 1)

The subjects will attend a screening visit in order to assess eligibility.

Before any trial-related activity, the investigator must give the subject oral and written information about the trial in a form that the subject can read and understand. The informed consent process must be completed before any trial-related activity.

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 will 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 informed consent form must be signed and personally dated by the person who seeks the informed consent.

The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed. The informed consent will include permission for the investigator to obtain information from the subject and/or from his/her primary physician or other healthcare professional /next of kin on vital status. The consent will include that this information can be obtained until trial completion even if the subject stops the investigational products and/or trial procedures prematurely.

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirements and adhere to ICH GCP¹ and the Declaration of Helsinki².

The date of informed consent must be transcribed to the eCRF.

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

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. Only subjects who have signed the informed consent form should be included on the logs. The subject screening log and subject enrolment log may be combined in one log.

At screening, subjects will be provided with a card stating that they are participating in a trial and giving 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 it after the last visit.

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. The first 3 digits indicate the site number and the last 3 digits are unique for the subject.

A screening session must be performed in the IWRS, see Section [10](#).

All assessments related to the inclusion and exclusion criteria must be performed. If any inclusion criterion is answered “no” or any exclusion criterion answered “yes”, the subject is a screening failure and no further assessments should be done. Please refer to the flow chart in section [2](#) for the full list of assessments and procedures to be performed at this visit.

In- or exclusion criteria cannot not be ticked “Yes” or “No” in the electronic case report form (eCRF) before source data is available. In this case “Result pending” must be chosen. This is particularly relevant for lab samples and in some cases the ECG and eye examination result. Subjects cannot be randomized until all results are available.

The subject has to complete the Baseline Hypo Questionnaire at the screening visit.

8.1.1.1 Screening failures

For screening failures the screening failure form in the eCRF must be completed with the reason for not continuing in the trial. Serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up on serious adverse events (SAEs) must be carried out according to Section [12](#).

A screening failure session must be made in the IWRS. When data has been monitored and queries have been resolved the case book must be signed.

Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria, this includes re-sampling if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters. Re-sampling is allowed in case the sample is haemolysed, leaked during transit etc.

8.1.2 Randomisation visit (V2)

All screening including laboratory results must be available and reviewed and the subject confirmed eligible before randomisation can take place. Randomisation should take place as soon as trial products are available on site and no later than 14 days after screening visit. A randomisation session must be performed in IWRS; see Section [10](#) and trial product must be dispensed.

The Investigator should record the following in the eCRF:

- Last date on pre-trial insulin
- Total dose of pre-trial insulin administered within the last 24 hours
- Frequency of pre-trial insulin injections
- First date on trial product (registered at P3)
- First dose of trial product (registered at P3)
- Time point of trial product administered (morning or evening as specified by IWRS)

The subject must attend randomisation visit fasting. For definition of fasting, please see Section [8.1.4](#).

At randomisation baseline laboratory values of HbA_{1c} and anti-insulin antibodies will be taken. Please refer to the flow chart in section [2](#) for the full list of assessments and procedures to be performed at this visit.

A BG meter and an electronic diary (eDiary) must be provided to the subjects at V2. Subjects must be trained in the use of the BG meter. A practice eDiary must be completed before the eDiary can be used. Subject must be instructed that entries must be made according to the protocol, see Section [8.3.1](#), [8.3.2](#) and [8.4.2](#) and instructions provided.

8.1.3 Phone contacts

Before any phone contact, both the Investigator and subject should agree on the timing and direction of the call. The Investigator remains responsible for ensuring that the phone contacts occur even if it is agreed that the subject should call the site.

A phone contact may be converted to a site visit if needed. For scheduled phone contacts and their time points; see Section [2](#).

8.1.4 Fasting visits

The subjects must attend the visits specified in section [2](#) in a fasting condition. Fasting is defined as at least eight hours without drink or food intake prior to the visit except for water.

No diabetes treatment (neither trial insulin, nor any OADs) is allowed up to eight hours prior to the blood sampling. Non-anti-diabetic medication is still allowed to be taken.

If a subject attends the visit non-fasting, then the subject's blood samples should be re-scheduled preferable within the next two working days. If blood sampling has already been done before realising the subject was not fasting, only the FPG needs to be re-drawn.

8.1.5 End of Treatment visit (V54)

At the end of treatment visit (V54) the treatment with trial product must be stopped and the subjects will be instructed to switch insulin treatment to the intermediate acting insulin NPH until the first follow-up visit (V55). A completion session must be performed in IWRS, see Section [10](#). NPH will be dispensed as part of the completion session.

Last date on the randomised trial product (basal insulin) must be recorded in the eCRF.

Since NPH insulin is an intermediate acting insulin, it should be administered twice daily. To determine the dose of insulin NPH to be taken during the follow-up period, the total daily basal dose at end of the treatment period should be reduced by 20% and divided into two doses; one to be administered in the morning and one in the evening.

Date and dose of first injection of insulin NPH must be recorded in the eCRF.

Please refer to the flow chart in section [2](#) for the full list of assessments and procedures to be performed at this visit.

8.1.6 Follow up visits

The first follow up visit (V55) is a site visit and must take place 7-12 days after the end of treatment visit. Follow-up visit 2 (V56) is a site visit and must take place 30-35 days after end of treatment.

Follow-up visit 1 (V55)

At the first follow up visit (V55) treatment with insulin NPH must be stopped.

The following data will be collected:

- Date and dose of last injection of insulin NPH
- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)
- Technical complaints
- Antibody sample

The eDiary must be returned by the subject at this visit. Subjects who prematurely discontinue trial product should keep the eDiary and not return it until at V54A.

Please refer to the flow chart in section [2](#) for the full list of assessments and procedures to be performed at this visit.

Follow-up visit 2 (V56)

The following data will be collected:

- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)

8.1.7 Unscheduled site visits

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

If more trial product is needed an additional dispensing session in the IWRS must be performed.

If blood resampling is needed the laboratory requisition form must be completed with the visit number to which the sample belongs.

8.1.8 Premature discontinuation of trial product

If a subject prematurely discontinues trial product, the investigator must undertake procedures similar to those for the end of treatment visit (V54) as soon as possible including fasting blood sampling and dispensing of wash-out insulin NPH, see Section [8.1.5](#).

Treatment discontinuation must be performed in the eDiary web portal and in the IWRS.

Furthermore two follow up visits similar to V55 and V56 must be performed 7-12 and 30-35 days after discontinuation of trial product, respectively.

Follow-up visit 1 (V55)

At the first follow up visit (V55) the subject should be switched to treatment with a suitable marketed product at the discretion of the investigator.

The following data will be collected:

- Date and dose of last injection of insulin NPH prior to V55
- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)
- Technical complaints
- Antibody sample

Follow-up visit 2 (V56)

The following data will be collected:

- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)

In addition, subjects prematurely discontinued from trial product should come in for abbreviated site visits at week 16 (V18A), week 28 (V30A) and at week 40 (V42A) after randomisation depending on when the subject discontinues trial product. The abbreviated site visits can be converted to phone contacts if needed.

The following data will be collected:

- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)
- Blood sample to measure HbA_{1c} (only if site visit)

In between the abbreviated site visits listed above **monthly phone contacts (PX visits)** should be performed until the originally planned end of treatment.

The following data will be collected:

- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)

The earliest of the abbreviated site visits or monthly phone contacts (whichever comes first) should be scheduled at least 30 days after FU2. If the timing of a monthly phone contact (PX visit) is less than two weeks from a planned abbreviated site visit, the phone contact can be omitted.

Subjects prematurely discontinued from trial products should come in for a **final visit (V54A)** at the **originally planned end of treatment date** to collect:

- Date and dose of basal insulin
- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)
- Blood sample to measure HbA_{1c}

The eDiary must be returned by the subject at this visit.

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

8.1.8.1 eDiary records after premature discontinuation of trial product

Hypoglycaemic episode information (see Section [8.4.2](#)) should be recorded from V54 and to V54A in the eDiary.

8.1.9 Withdrawal from trial

If a subject withdraws consent, the investigator should aim to undertake procedures similar to those for the end of treatment visit (V54) as soon as possible. The eDiary must be returned by the subject at this visit.

If the subject agrees, the follow up visits (V55 and V56) must be performed 7-12 and 30-35 days after discontinuation of trial product.

The End-of-Treatment and End of Trial forms must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be made in the eDiary web portal and in the IWRS. The case book must be signed.

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

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

8.1.10 Review of results

Review of ECG results, eye examination report, laboratory reports, data entered in the eDiaries, etc. must be documented either on the documents, printouts, in the eDiary web portal or in the subject's medical record.

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

8.2 Subject related information/assessments

8.2.1 Demography

Demography will be recorded at screening, unless not permitted by local regulations, and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.2.2 Diabetes history

Diabetes history will be recorded at screening and consists of:

- Date of diagnosis of type 2 diabetes

8.2.3 Hypoglycaemia unawareness

Information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8²⁸.

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

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

8.2.4 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 (V1)) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Date of diagnosis of type 2 diabetes should be reported separately in the Diabetes History Form in the eCRF.

Medical history is a medical event that the subject has experienced in the past. Only 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.

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

8.2.5 Concomitant medication

A **concomitant medication** is any medication, other than the pre-trial insulin, trial products and OADs, which is taken during the trial, from the screening visit (V1) until end of treatment (V54).

Details of any concomitant medication must be recorded at V1. 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.

8.2.6 Concomitant medication (Diabetes)

Any diabetes medication other than the trial product(s) which is taken during the trial, from the screening visit (V1) until FU2 (V56) must be recorded in a separate concomitant medication (diabetes) form in the eCRF.

At V1 the pre-trial insulin and pre-trial OADs must be recorded including:

- Trade name or generic name
- Total daily dose
- Start date
- Stop date or continuation

For subjects treated with OADs it is the start date and dose of latest stable OAD dose which should be reported.

At the randomisation visit (V2) pre-trial insulin must be discontinued and a stop date recorded in the eCRF. For subjects treated with OADs, the investigator should at each weekly contact (V2 until V55), confirm with the subject that dose and frequency of OADs has been unchanged. This should be documented in the medical records.

8.2.7 Childbearing potential

It must be recorded in the eCRF whether female subjects are of childbearing potential. Reason for not being of childbearing potential must be documented in the medical records.

Pregnancy testing must be performed on female subjects of childbearing potential as described in Section [8.5.2](#). Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 1 week after end of treatment.

Female of non-childbearing potential is defined as:

- Female who has undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation
- Postmenopausal defined as no menses for 12 months without an alternative medical cause
- Other medical reasons preventing childbearing potential

8.2.8 Tobacco use

Details of tobacco use must be recorded at V1. Smoking is defined as smoking at least one cigarette or equivalent daily.

Smoking status:

- Never smoked
- Previous smoker
- Current smoker

8.3 Efficacy assessments

8.3.1 Self-measured plasma glucose

At V2, subjects will be provided with a BG meter including auxiliaries as well as instructions for use. The subjects will be instructed in how to use the device.

The BG 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.

Only the BG meter provided by Novo Nordisk should be used for the measurements required in the protocol.

For Serbia: The BG-meter is regarded as an investigational device and should be collected by the investigator at FU2 (Visit 56).

Subjects must be instructed to measure their pre-breakfast SMPG daily from V2 to V54 and in how to transfer the results of the SMPG values into the eDiary.

8.3.2 Insulin dose

During the trial, starting at the randomisation visit (V2), the subject should be instructed to report date, dose and actual time of basal insulin in the eDiary on a daily basis.

The recommended insulin doses will be calculated in the eDiary web portal on recommendations from the Insulin Titration Guideline (see [Appendix A](#)). At each visit/phone contact the Investigator will titrate the subjects by making prescribed dose adjustments based on the recommendation from the eDiary web portal if applicable.

The Investigator should record the following in the eDiary (through the web portal):

- Prescribed doses of trial products
- Reason for deviating in dose adjustments from the titration guideline

The subject should report the following in the eDiary:

- Date, dose and time of trial basal insulin daily

The Investigator should record the following in the eCRF:

- First date on trial product
- First dose of trial product
- Last date on trial product
- Last dose of trial product

8.4 Safety assessments

All safety assessments are outlined in the flow chart in section [2](#).

In case of an abnormal and clinically significant finding, 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.

8.4.1 Adverse events

During each contact (site visits and phone contacts) the subject must be asked about AEs and technical complaints, for example by asking: "Have you experienced any problems since the last contact?" This must be documented in the subject's medical record. AEs must be reported at each visit in accordance with the procedures outlined in Section [12](#).

8.4.1.1 Medication error

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

- Trial product(s) involved

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

For definition of medication errors, see Section [12.1.4](#).

8.4.1.2 Adverse events requiring additional data collection

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

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see Section [12](#).

Acute coronary syndrome

If an event of Acute Coronary Syndrome (ranging from unstable angina pectoris to myocardial infarction) is observed during the trial the following additional information must be reported if available on the acute coronary syndrome form:

- Duration of symptoms
- Changes in ECG
- Collection of cardiac biomarkers
- Cardiac imaging
- Cardiac stress testing
- Angiography
- Use of thrombolytic drugs
- Revascularisation procedures

Cerebrovascular events

If a cerebrovascular event (e.g. transient ischaemic attack (TIA), stroke, and haemorrhage) is observed during the trial the following additional information must be reported if available on the cerebrovascular event form:

- Type of event (e.g. TIA, Stroke)
- Contributing condition
- Neurologic signs and symptoms
- History of neurologic disease
- Imaging supporting the event
- Treatment given for the event

Neoplasm

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

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

Events for adjudication

Severe hypoglycaemia or hypoglycaemic episodes reported as an SAE and all fatal events will be subject to external independent adjudication. For these AEs a (hypoglycaemia) Adjudication Form must be completed in the eCRF. For detailed information on event adjudication, please refer to Section [12.7.2](#).

8.4.2 Hypoglycaemic episodes

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

All plasma glucose values:

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

should be reported in the eDiary according to the instructions below throughout the trial from visit 2 to visit 56.

Upon onset of a hypoglycaemic episode the subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines²⁹.

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

prompt the subject to fill out a new hypoglycaemic episode form until a succeeding measurement is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved.

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

The e-diary will automatically link multiple values within 60 minutes to the same hypoglycaemic episode.

The record should include the following information:

- Start date and time of the hypoglycaemic episode
- The plasma glucose level before treating the episode (if available) and any follow up measurements
The lowest value measured during the hypoglycaemic episode will be reported as the plasma glucose value for the episode, the remaining values will be kept as source data in the diary.
- Whether the episode was symptomatic (Yes/No)
A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experiences symptoms later during the episode. The subject is therefore to be questioned whether there are changes to symptoms for each low SMPG value within the 60 minutes period or until the subject has confirmed that the hypoglycaemic episode is symptomatic.
- Whether the subject was able to treat him/herself
If the severity of a hypoglycaemic episode aggravates, only one hypoglycaemic episode should be reported reflecting the most severe degree of hypoglycaemia. The subject is therefore to be questioned whether he/she is able to self-treat for each low SMPG value within the 60 minutes period or until the subject respond that he/she is not able to self-treat.
- Date, time and dose of last trial product administration prior to the episode
- Date and time of last main meal (not including snacks) prior to the episode
- Whether the episode occurred in relation to physical activity
- Whether the episode related to a change in a pre-existing disease
- Any sign of fever and/or other acute disease
- Whether the subject was asleep when the episode occurred
 - If yes, whether the symptoms of the episode woke up the subject

The answer to the question: "Was the subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration²⁹.

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

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

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)?
- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by another person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet change, medication error (i.e. overdose, mix-up between products, incorrect use of device), miscalculation of dose of anti-diabetic medication, other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms³⁰ (layman term used in the diary is specified in brackets if different from the protocol term)?
 - Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
 - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
 - General malaise: headache or malaise (feeling discomfort/unease)
- Other symptoms.

The investigator must review the diary data for correct reporting of SMPGs and hypoglycaemic episodes. In case of incomplete or incorrect data in the diary, the subject must be questioned whether there have been any severe hypoglycaemic episodes since the last visit, i.e. any hypoglycaemic episodes where the subject was not able to self-treat. Any severe hypoglycaemic episodes must be reported.

In case a subject is not able to fill in the eDiary e.g. in case of a fatal event, the investigator will be allowed to report the hypoglycaemic episode in the eDiary web portal.

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the start date, SMPG value, if any symptoms were present and whether the subject was able to self-treat due to decreased validity of such data^{31, 32}.

The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies unreported hypoglycaemic episodes.

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

8.4.3 Body measurements

Body weight should be measured in kilogram (kg) or pounds (lb) without coat and shoes wearing only light clothing. Body weight will be recorded to one decimal. The body weight should be assessed on the same weighing scale equipment throughout the trial, if possible.

Height should be assessed without shoes. Height is measured in inches or meters at visit 1 (screening) and recorded to one decimal place (inches) or two decimal places (meters) respectively.

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

8.4.4 Vital signs

Diastolic blood pressure, systolic blood pressure and pulse will be assessed following standard clinical practice. Abnormal and clinically significant findings must be recorded as described in Section [8.4](#).

8.4.5 Physical examination

Physical examination will include:

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

The evaluation must follow the categories:

- Normal
- Abnormal
 - Was the result clinically significant? (Yes/No)

Abnormal and clinically significant findings must be recorded as described in Section [8.4](#).

8.4.6 Eye examination

Fundus photography or dilated funduscopy must be performed by the investigator or local ophthalmologist, or an optometrist according to local practice. The result of the fundus photography/dilated funduscopy will be interpreted by the investigator. To document this, the Investigator must sign and date the interpretation in the subject's medical records.

The evaluation must follow the categories:

- Normal
- Abnormal
 - Was the result clinically significant? (Yes/No)

Abnormal and clinically significant findings must be recorded as described in Section [8.4](#).

If a fundus photography/dilated funduscopy have been performed within 90 days prior to V2, and if the results are available at V2, then the procedure do not need to be repeated. If performed before the subject consents to participate in the trial, it must also be stated in the subject's medical records that this procedure was not performed in relation to the trial.

A subject cannot be randomised without results confirming there is no acute treatment-requiring retinopathy.

Eye examination performed within a period of three weeks before end of treatment visit (V54) is acceptable, if results are available at the end of treatment visit.

8.4.7 Electrocardiogram

A 12-lead ECG must be performed at the trial site. The ECG must be interpreted by the investigator, and documented by Investigator signature and date on the ECG print-out. .

The evaluation must follow the categories:

- Normal
- Abnormal
 - Was the result clinically significant? (Yes/No)

The baseline ECG must be performed at screening (V1) or in the period between screening (V1) and randomisation (V2). The result must be available prior to randomisation.

ECGs at the end of treatment visit (V54) should be performed at the day of the visit.

Abnormal and clinically significant findings must be recorded as described in Section [8.4](#)

8.5 Laboratory assessments

Laboratory analyses will be performed at laboratories contracted by Novo Nordisk. A central laboratory will provide all laboratory supplies for the sampling and transportation of all blood samples taken during the trial.

A detailed description of the procedures for obtaining the samples, handling, storage, and shipment of the samples are specified in a trial-specific laboratory manual provided to the sites by the central laboratory. Information regarding laboratory materials such as tubes and labels are also described.

If laboratory samples need to be retaken due to missing result(s) (e.g. haemolysed, sample leaked during transit, sample not being conclusive, lost in transit, etc.), the subject should be called in for resampling. Please see the laboratory manual for further guidance.

Samples will be coded in order to keep subject's identity anonymous.

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to Section [8.2.4](#) and Section [12](#). Review of laboratory reports must be documented either on the documents and/or in the subject's medical record.

Antibody results will not be provided to the investigator on an ongoing basis, as these results will not be used for any clinical evaluation during the trial.

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

Laboratory samples will be destroyed no later than at end of trial or no later than at finalisation of the clinical trial report.

Antibody samples will be stored as described in Section [24.2](#).

8.5.1 Laboratory assessments for efficacy

Glucose metabolism

FPG is measured in order to evaluate metabolic control. The subject must attend these visits fasting. For definition of fasting, see Section [8.1.4](#).

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

Low plasma or blood glucose values (e.g. FPG) reported by a laboratory in connection to trial related visits should NOT be reported as hypoglycaemic episodes; these should be reported as AEs related to the procedure at the discretion of the investigator.

Blood samples will be drawn to determine the HbA_{1c} level in order to evaluate metabolic control.

8.5.2 Laboratory assessments for safety

Haematology

Blood samples for haematology will be analysed to determine:

- Haematocrit
- Haemoglobin
- Leucocytes
- Erythrocytes
- Thrombocytes

Biochemistry

Blood samples for biochemistry will be analysed to determine:

- ALT
- Albumin
- AST
- Alkaline phosphatase
- Bilirubins, total
- Creatinine
- Potassium
- Sodium

eGFR will be calculated (at screening) by the central laboratory based on the creatinine value using the CKD-EPI equation^{20, 21} in order to assess inclusion criteria 3b.

Pregnancy testing

For females of childbearing potential (see Section [8.2.7](#)) a blood human Chorion Gonadotropin (hCG) test will be performed at screening (V1) and V54. In addition, urine pregnancy tests will be performed locally during the trial if pregnancy is suspected or if required by local law. A positive urine test should be followed by a confirmatory serum-hCG (central laboratory).

The central laboratory will provide the pregnancy kits for urine testing performed locally at the site.

Anti-insulin antibodies

Antibody samples may be retained and used for further characterisation of antibody responses towards drug if required by health authorities, for safety reasons or in relation to exploratory analysis, see Section [24.2](#).

Serum samples will be analysed at a special lab for anti-insulin degludec or anti-insulin glargine antibodies. Anti-degludec antibodies and anti-glargine antibodies will be tested for cross-reactivity to human insulin.

- Blood samples will be drawn for determination of antibodies to insulin degludec or insulin glargine (including cross-reacting antibodies to human insulin).

The subjects must attend the antibody sampling visits specified in section [2](#) in a fasting condition. Fasting is defined as at least eight hours without drink or food intake prior to the visit except for water.

No diabetes treatment (neither trial insulin, nor any OADs) is allowed up to eight hours prior to the blood sampling. Non-anti-diabetic medication is still allowed to be taken.

8.6 Other assessments

Patient reported outcome questionnaires

The patient reported outcome (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. Instructions on how to complete the questionnaires will be provided to the subject. The questionnaires will be used to investigate the health related quality of life, hypoglycaemic episode experience as well as treatment and device satisfaction.

The following PRO questionnaires will be supplied in the site based eDiary in a linguistically validated version in all languages relevant for this trial:

- **SF-36v2[®]** The ‘Short-Form 36 Health Survey version 2 is a questionnaire concerning various health-related quality-of-life questions. It is a sensitive, validated and widely used

instrument which will allow direct comparison with other trials including subjects with T2DM. SF-36v2 consists of 36 items grouped into 8 domains

- **TRIM-D** measures treatment related impact on subjects of diabetes medication across the spectrum of pharmacological treatment over the past two weeks. The TRIM-D consists of 28 items grouped into five domains. The domains are treatment burden, daily life, diabetes management, compliance and psychological health
- **TRIM-DD** measures the impact of the treatment delivery system as an eight-item instrument. The instrument consists of eight items grouped into two domains: Device Function and Device Bother
- **Insulin Pen questionnaire** measures how easy or difficult it is to reach the dose button when injecting insulin, how easy or difficult it is to use the pen and whether or not the subject will recommend the pen to others
- **Baseline Hypo Questionnaire** measures the subjects experience with hypoglycaemic episodes

Besides the five subject completed questionnaires an investigator interview questionnaire is to be completed in the site based eDiary if the subject has reported any hypoglycaemic episode(s) since the last visit:

- **Hypoglycaemia resource use** is collected as an interview administered questionnaire regarding resource use of the latest hypoglycaemic episode within the last four weeks. The questionnaire includes questions regarding the length of the hypoglycaemic episode, the number of extra blood monitoring, contact to health care professionals, and time missed at work

The questionnaires should be completed as specified in the flow chart, see Section [2](#).

eDiary

An eDiary will be used to capture patient reported data, see Sections [8.3.1](#), [8.3.2](#) and [8.4.2](#). The Investigator must carefully instruct the subject in how to use the eDiary. All data entered in the eDiary is considered source data. All data from the eDiary will be transferred electronically to the PRO database. The investigator must review all the data for the subjects belonging to the site through the eDiary web portal. Review of hypoglycaemic episode confirmation must be documented in the web portal, while review of remaining data must be documented in the subject's medical record. The review of data must be performed before or during each visit/phone contact.

The Investigator should record the following administrative information in the eDiary/web portal:

- Subject ID
- Visit confirmation
- Hypoglycaemic episode confirmation
- Prescribed doses of trial products or confirm recommended dose
- Reason for deviation from the recommended dose, if needed
- Evaluate if a hypoglycaemic episode qualifies as an SAE

Selected titration data (e.g. certain SMPGs and dose data) will only be used during the trial for central titration surveillance, to ensure compliance with the titration guideline ([Appendix A](#)), and will not be reported in the clinical trial report (CTR). All data will be stored by Novo Nordisk (see [Section 24](#)).

The eDiary should be collected by the Investigator at FU2 (V56).

Subjects who prematurely discontinue trial product should keep the eDiary and not return it until at V54A.

8.6.1 Training in the pen injector

The subjects must be trained in how to handle the pen injector when handed out the first time. Training must be repeated at V6 in order to ensure correct use of the device. The following should be emphasised:

- Always use a new needle for each injection as this will prevent contamination and blocked needles
- Priming the pen to ensure product flow
- Injection technique as per DFU

8.7 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance.

To ensure treatment 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 eDiary including the SMPG measurements, hypoglycaemia reporting and PRO questionnaire completion. In addition, subject compliance will be assessed by monitoring of drug accountability at specified visits, please refer to the flow chart, see [Section 2](#). The unused amount IMP will be assessed against the dispensed amount and, in case of discrepancies, the subject must be asked.

If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

Protocol
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~~CONFIDENTIAL~~

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Page:	57 of 109	

Treatment compliance: It is important to ensure subjects adhere to treatment. Therefore, during the treatment period the investigator must at each weekly contact (visit or phone contact), evaluate if the subject has adhered to trial treatment since last contact.

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 insulin products (Investigational medicinal product (IMPs)) must not be used, if they do not appear clear and colourless.

Insulin NPH product (Non-Investigational Medicinal Product (NIMP)) must not be used if it does not appear uniformly white and cloudy after re-suspension.

9.1 Trial products

The following trial products will be provided by Novo Nordisk A/S, Denmark:

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/delivery device
Insulin degludec (Tresiba [®]) (IMP)	200 U/mL	Solution for injection	Subcutaneous	3 mL PDS290 pre-filled pen injector (FlexTouch [®])
Insulin glargine (Toujeo [®]) (IMP)	300 U/mL	Solution for injection	Subcutaneous	1.5 mL pre-filled pen injector (SoloStar [®])
Human isophane insulin (NPH) (Insulatard [®] /Prothaphane [®] /Novolin [®] N) (NIMP)	100 IU/mL	Suspension for injection	Subcutaneous	3 mL pre-filled pen injector (FlexPen [®])

The following Non-Investigational Medicinal Products (NIMPs) will not be provided by Novo Nordisk:

- Metformin, tablets for oral use
- DPP-4i, tablets for oral use
- SGLT2i, tablets for oral use
- Thiazolidinedione, tablets for oral use
- Alpha-glucosidase-inhibitor, tablets for oral use
- Marketed oral combination products only including the products listed above, tablets for oral use

However, metformin, DPP-IVi, SGLTi, Thiazolidinedione, Alpha-glucosidase-inhibitor or marketed combination products only including the products listed in inclusion criteria 5a-5e will be reimbursed if required by the country's regulatory authority or IRB/IEC.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13³³, local regulations and trial requirements.

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

The investigator must document that direction for use is given to the subject orally and in writing at the first dispensing visit (V2). Direction for use can be provided as needed at the following dispensing visits.

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time ^a
Insulin degludec (Tresiba [®]) (IMP)	<ul style="list-style-type: none"> Store in refrigerator (2°C - 8°C) Protect from light Do not freeze 	<ul style="list-style-type: none"> Do not store above 30°C Protect from light Can be stored in refrigerator (2°C - 8°C) Do not freeze 	Use within 8 weeks
Insulin glargine (Toujeo [®]) ^b (IMP)	<ul style="list-style-type: none"> Store in refrigerator (2°C - 8°C) Protect from light Do not freeze 	<ul style="list-style-type: none"> Store below 30°C Protect from light Do not refrigerate Do not freeze For CA: Store at room temperature (15°C – 30°C)	Use within 26 days
Insulin NPH (Insulatard [®] /Prothaphane [®] /Novolin [®] N) (NIMP)	<ul style="list-style-type: none"> Store in refrigerator (2°C - 8°C) Protect from light Do not freeze 	<ul style="list-style-type: none"> Store below 30°C Protect from light Do not refrigerate Do not freeze 	For US: Use within 14 days For CA: Use within 4 weeks For EU: Use within 6 weeks

^aIn-use time starts when first dose is taken.

^bBefore first use, the Toujeo[®] pre-filled pen injector must be stored at room temperature at least 1 hour.

The investigator must ensure that trial product is kept under proper storage conditions and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial

product has been stored outside specified conditions (e.g. outside temperature range). Additional details regarding handling of temperature deviations can be found in the TMM.

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

9.4 Drug accountability and destruction

Drug accountability of all trial products received at site is the responsibility of the investigator.

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

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

Subjects are instructed to return all used, partly used and unused trial product at each dispensing visit after V2. Please refer to the flowchart, see Section [2](#) for timing of the dispensing visits.

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

9.5 Auxiliary supplies

The following will be provided by Novo Nordisk:

- Direction for use for the pen injectors
- Novo Nordisk needles for prefilled systems
- MyGlucoHealth Wireless Meter (CE approved) and strips, lancets and control solution for BG meters
- eDiary

Only needles provided by Novo Nordisk must be used for administration of trial product.

For Serbia: The BG-meter is regarded as an investigational device. Technical complaints regarding the BG-meter should be reported to the manufacturer of the device (Entra Health Systems). This device has been selected in order to have automatic transfer of SMPG data to the eDiary and thereby increase the accuracy of SMPG values. It is expected that the better accuracy in SMPG data will facilitate an improvement in the insulin titration efforts during the trial.

Please refer to the TMM for further auxiliary supplies' details.

10 Interactive web response system

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

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing and Additional Dispensing between scheduled visits
- Dispensing Verification (when barcode scanner is used)
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

Notifications generated as a result of sessions performed in the IWRS should be archived in the investigator trial file or together with other source documents for the subject.

At any time during the trial only dispensing unit numbers (DUN) allocated by the IWRS are allowed to be dispensed to a subject. By doing this it will be ensured that:

- correct trial product is dispensed to subject
- stock is available at sites as needed for the subjects
- no trial product that will expire before the next dispensing visit will be allocated
- drug accountability can be made in the IWRS

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure

The IWRS is used for randomisation. Subjects complying with the inclusion- and exclusion criteria will be randomised 1:1 into one of the two treatment arms. Within each treatment arm, subjects will be randomised 1:1 to morning or evening dosing.

In IWRS this means that there will be four different treatment regimens:

- IDeg 200 U/mL OD morning dosing \pm OADs
- IDeg 200 U/mL OD evening dosing \pm OADs
- IGlax 300 U/mL OD morning dosing \pm OADs
- IGlax 300 U/mL OD evening dosing \pm OADs

Recruitment will be closed as soon as the total number of planned subjects to be randomised is achievable, taking the number of screened subjects and the screening failure rate into account. All investigators will be notified immediately when the recruitment period ends (estimated to be 24 weeks), after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation can be randomised.

12 Adverse events, and technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

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

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

An AE includes:

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

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is from V2 until FU1 reported on a hypoglycaemic episode form instead of on an AE form, see Section [8.4.2](#). However, FPG results ≤ 3.9 mmol/L (70 mg/dL) should not be reported as hypoglycaemic episodes but as a CLAE at the discretion of the investigator.

The following three definitions are used when assessing an AE:

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

- **Causality**

Relationship between an AE and the relevant trial product(s):

- **Probable** - Good reason and sufficient documentation to assume a causal relationship.
- **Possible** - A causal relationship is conceivable and cannot be dismissed.
- **Unlikely** - The event is most likely related to aetiology other than the trial product.

- **Final outcome**

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

12.1.2 Serious adverse event

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

- Death.
- 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.

^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 dyscrasia or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

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

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

12.1.3 Non-serious adverse event

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

12.1.4 Medication errors

A medication error concerning trial products is defined as:

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

Medication errors must be reported on an AE form and a specific event form, see Section [8.4.1.1](#).

12.1.5 Adverse events requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the product safety.

Some events in this trial will be adjudicated by an independent external committee as described in Section [12.7.2](#).

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

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

Event	<i>Specific event form</i>	<i>Event adjudication</i>
Fatal event	No	Yes ^a
Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)	Yes	No
Cerebrovascular event (stroke or transient ischaemic attack)	Yes	No
Neoplasm	Yes	No
Severe hypoglycaemia or hypoglycaemic episodes reported as an SAE	No ^b	Yes

Event	<i>Specific event form</i>	<i>Event adjudication</i>
Medication error	Yes	No

^aFatal events will be adjudicated as potential hypoglycaemic episodes (Hypoglycaemia Adjudication form to be completed).

^bHypoglycaemia will be captured in the eDiary by the subject.

For details about specific event forms, see Section [8.4.1](#).

12.1.6 Technical complaints

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

Examples of technical complaints:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (V56). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and [Figure 12-1](#).

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

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

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

Timelines for initial reporting of AEs:

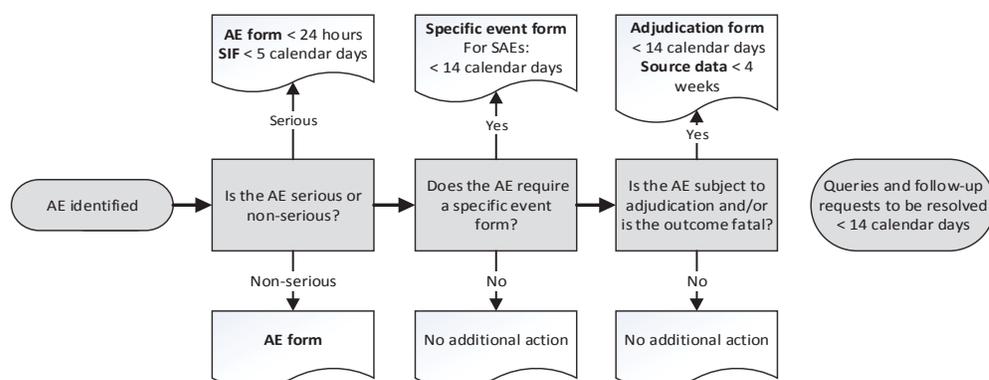
The investigator must complete the following forms in the eCRF within the specified timelines:

- **SAEs:** The AE form **within 24 hours** and the 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.

For SAEs requiring reporting on a specific event form: In addition to the above the specific event form within **14 calendar days** from the investigator's first knowledge of the AE.

- **Events for Adjudication:** The adjudication form should be completed within **14 calendar days** of the investigator's first knowledge of the AE, see Section [12.7.2](#). The investigator should provide copies of the source documentation preferably within **4 weeks** of event identification.

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



Timelines are for the completion of forms from the time of investigator's awareness
 AEs requiring specific event forms are described in Section 12.1.4 and 12.1.5
 AEs for adjudication are described in Section 12.7.2

AE: Adverse event SIF: Safety information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the current versions and any updates of the following reference documents:

- IDeg IB⁹
- IGlax 300 U/mL SmPC¹⁴ or local labelling^{15, 16}

Reporting of trial product-related SUSARs by Novo Nordisk:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP¹. 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 ICH GCP¹, unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication or non-investigational medicinal product:

If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as non-investigational medicinal product (Insulatard[®]/Prothaphane[®]/Novolin NTM) or concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

12.3 Follow-up of adverse events

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

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

- **SAEs:** All SAEs must be followed until the outcome of the event is “recovered/resolved”, “recovered/resolved with sequelae” or “fatal”, and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome “recovering/resolving” or “not recovered/not resolved”. Cases can be closed with the outcome of “recovering/resolving” when the subject has completed the follow-up period and is expected by the investigator to recover.

The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator’s first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

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

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

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

SAEs after end of trial: If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product occurring to a subject after the subject has ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Insulin degludec 3ml PDS290 pen injector (FlexTouch[®])
- Insulin glargine (Toujeo[®]) 1.5ml prefilled pen (SoloStar[®])
- Insulin NPH (Insulatard[®]/Prothaphane[®]/Novolin NTM) 3ml prefilled pen (FlexPen[®])
- Novo Nordisk needles for pre-filled pen systems

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 and/or SAEs.

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

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

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

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

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

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in [Attachment I](#)) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

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

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

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

12.5 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:

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

SAEs:

- AE form^a **within 24 hours** of the investigator's first knowledge of the SAE.
- 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.

- ^a 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. If the AE occurred in the foetus or new-born infant, the AE can only be reported on paper AE and safety information form.

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

During treatment with insulin, there is a risk of hypoglycaemia (see Section [8.4.2](#)). Symptoms usually occur suddenly and may include cold sweat, nervousness or tremor, anxious feelings, unusual tiredness, confusion, difficulty in concentration, 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.

Hypoglycaemic episodes should be treated following best practice at the discretion of the investigator. As with all long-acting insulin preparations, their prolonged effect may delay recovery from a hypoglycaemic episode.

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.

For further details, please refer to current versions and any updates of the following:

- IDeg IB⁹
- IGLar 300 U/mL SmPC¹⁴ or local labelling^{15, 16}
- NPH SmPC³⁴ or local labelling^{35, 36}

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal IDeg safety committee to perform ongoing 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.

12.7.2 Event adjudication committee

An independent external event adjudication committee is established to perform validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical data related to the specific AE.

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

The AEs for adjudication are listed in [Table 12–2](#).

Table 12–2 Events for adjudication

Event	Description of events in scope for adjudication	Adjudication Outcome
Fatal event	All cause death	Severe hypoglycaemia
Severe hypoglycaemia or hypoglycaemic episodes reported as an SAE	An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an episode, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event episode was induced by a low plasma glucose concentration	Severe hypoglycaemia

Event adjudication will be performed for AEs in randomised subjects including AEs with an onset date during the screening period. Event adjudication will not be performed for AEs in screening failures.

The following describes the ways events are captured for adjudication:

Direct reporting by investigator:

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

Hypoglycaemic episodes will be reported by the subject in the eDiary. For severe hypoglycaemic episodes the adjudication form must be completed by the investigator in the eCRF. If a hypoglycaemic episode fulfils the criteria as an SAE as well as for all fatal events the AE, SIF and adjudication forms must be completed.

Screening of AEs:

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

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

EAC identified events:

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

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

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

Protocol
Trial ID: NN1250-4252
UTN: U1111-1184-8175
EudraCT no.: 2016-002801-20

~~CONFIDENTIAL~~

Date:	11 November 2016	Novo Nordisk
Version:	2.0	
Status:	Final	
Page:	76 of 109	

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

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

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 provided by an external supplier.

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

The following will be provided as paper CRFs:

- Pregnancy forms

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

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints that are not subject related (e.g. discovered at trial site before allocation))

On the paper 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 eCRF data may be made by the investigator or the investigator’s delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction.

If corrections are made by the investigator’s delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

Corrections to the data in the paper CRFs should be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that were crossed out. Each

correction must be initialled, dated and explained (if necessary) by the investigator or the investigator's authorised staff.

13.2 Case report form flow

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

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

13.3 eDiary

An eDiary will be used to capture patient reported data, see Sections [8.3.1](#), [8.3.2](#) and [8.4.2](#). The Investigator must carefully instruct the subject in how to use the eDiary. All data entered in the eDiary is considered source data. All data from the eDiary will be transferred electronically to the electronic patient reported outcomes (ePRO) database. Data in the ePRO database will be viewable to investigator and Novo Nordisk personnel on a secure, password protected eDiary web portal.

The investigator must review all the data for the subjects belonging to the site through the eDiary web portal. The review of hypoglycaemic episode confirmation must be documented in the web portal, while review of remaining data must be documented in the subject's medical record. The review of data must be performed before or during each visit/phone contact.

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.

The Investigator should record the following administrative information in the eDiary/web portal:

- Subject ID
- Visit confirmation
- Hypoglycaemic episode confirmation
- Prescribed doses of trial products or confirm recommended dose
- Reason for deviation from the recommended dose, if needed
- Evaluate if a hypoglycaemic episode qualifies as an SAE

Data will be transferred to the Novo Nordisk trial database at defined intervals. For details on eDiary data flow, see [Figure 13-1](#).

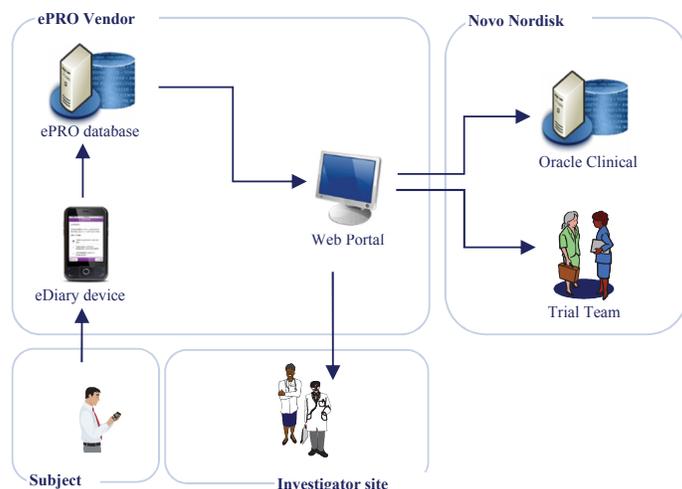


Figure 13–1 eDiary data flow

Selected titration data (e.g. certain SMPGs and dose data) will only be used during the trial for central titration surveillance, to ensure compliance with the titration guideline ([Appendix A](#)), and will not be reported in the clinical trial report (CTR). All data will be stored by Novo Nordisk (see [Section 24](#)).

The eDiary should be collected by the Investigator at FU2 (V56).

Subjects who prematurely discontinue trial product should keep the eDiary and not return it until at V54A.

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

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

All data must be verifiable in source documentation other than the eCRF, except for:

- Age and BMI which are calculated by the EDC system

During the trial the eDiary database will be considered source for data recorded directly in the eDiary/web portal.

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

The following data will be source data verified for screening failures:

- Date for obtaining informed consent.
- Screen Failure Form/Reason
- SAEs

Monitors will 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 eCRF. If discrepancies are found, the investigator must be questioned about these.

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

15 Data management

Data management is the responsibility of Novo Nordisk.

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

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

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

16 Computerised systems

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

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

The eDiary software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11 and ICH E6 (EU directive for personal data protection). After trial finalisation, Novo Nordisk and each site will be supplied with long-life DVDs. These DVDs will contain site-specific subject records including the subject's eDiary data and audit trail as well as any data additions and corrections made on each form. The eDiary vendor will furthermore retain and securely store copies of all archived documents and data for 50 years or as required by local data retention laws for trial data.

17 Statistical considerations

17.1 General considerations

For subjects withdrawing from the trial as well as for subjects not discontinuing randomised treatment prematurely, the trial period completion is at visit 54. For subjects who prematurely discontinue randomised treatment but do not withdraw, the trial period completion is at visit 54A. Treatment period completion is defined as the date when randomised treatment is discontinued.

All efficacy, PRO and hypoglycaemic endpoints will be summarised using the full analysis set (FAS) and safety endpoints excluding hypoglycaemic endpoints will be summarised using the safety analysis set (SAS).

All statistical analysis of efficacy and safety endpoints will be based on the FAS unless otherwise specified. Confirmatory analysis addressing the primary estimand will include on-treatment data and not available retrieved (V54A) data.

The primary objective is to compare the effects of IDeg OD and IGlax 300 U/mL OD on the rate of hypoglycaemia in subjects with type 2 diabetes mellitus, inadequately treated with basal insulin with or without oral anti-diabetic drugs. The primary estimand is the treatment difference between IDeg and IGlax 300 U/mL assuming that all randomised subjects adhered to the randomised treatment, that is a de jure estimand. The primary estimand addresses the treatment difference for subject that can be long-term treated with either of the two insulins. Data collected after premature treatment discontinuation will not be used when addressing the primary estimand. With the aim of comparing a safety endpoint this estimand is considered the most relevant as it compares the occurrence of a safety endpoint that is caused by the drug during exposure to the drug. The confirmatory endpoints will additionally be investigated with a de-facto estimand, other endpoints will be analysed only with a de jure estimand to support the primary analysis of the primary endpoint.

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

In accordance with guidance³⁷ endpoints will be assessed at frequent visits and also for subjects who prematurely discontinue treatment. The baseline value is defined as the value from the randomisation visit. If this value is missing the last recorded value before randomisation visit will be used.

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

Laboratory values below the lower limit of quantification (LLOQ) will be set to $\frac{1}{2}$ LLOQ.

The primary and secondary endpoints will be tested in a hierarchical order to control the family wise Type I error in the strong sense. Inferences will be based on the primary estimand.

Presentation of results from a statistical analysis will include the estimated treatment means as well as estimated mean treatment difference (or ratio) together with the two-sided 95% confidence interval and corresponding two-sided p-value.

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

1. Treatment: IDeg, IGlax 300 U/mL
2. Pre-trial 0 OADs, 1OAD, ≥ 2 OADs
3. Region: Europe , North America

4. Sex: male, female
5. Dosing time: morning, evening

17.2 Sample size calculation

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

For the sample size calculations it is assumed that the true treatment rate ratio (RR) is 0.75 corresponding to a 25% reduction in rate of hypoglycaemia in maintenance period with IDeg OD compared to IGlax 300 U/mL OD. Sample size is determined based on a negative binomial model with log-offset equal to exposure time in maintenance. The observed rate of severe or BG confirmed symptomatic hypoglycaemia for IDeg is assumed to be 1.8 per patient years of exposure (PYE) and the dispersion parameter in the negative binomial distribution is assumed to be 3.1. Furthermore it is assumed that 4% of subjects will withdraw before starting the maintenance period and therefore have no on-treatment data for the maintenance period. For these 4% the treatment ratio is set to 1. Rate assumptions are based on experience from SWITCH 2 (NN1250-3998), which has similar inclusion criteria. Dispersion parameter assumptions are based on experience from the Degludec phase 3a and 3b program. Assumptions concerning withdrawal are similarly based on the Degludec phase 3a and b program and increased focus on retention.

From these assumptions, and based on a 1:1 randomisation, the sample size is set to 795 subjects per treatment arm; in total 1,590 subjects will be randomised. This will ensure a nominal power of at least 80% for detecting a difference in favour of IDeg. The power equals 80% with 1,584 subjects and the assumptions above.

Power calculations for the secondary estimand are based on the same assumptions, except a treatment ratio of 1 is assumed for all 13% of the subjects that are assumed not to complete the trial on treatment.

Table 17–1 Sample sizes for the primary and secondary estimand for combinations of RR and event rates to achieve a power of 80%

RR	Adjusted RR	Yearly event rate					
		1.5		1.8		2.0	
		Primary	Secondary	Primary	Secondary	Primary	Secondary
0.80	0.808/0.826	2738	3412	2638	3286	2588	3224
0.75	0.76/0.7825	1642	2062	1584	1988	1556	1952
0.70	0.712/0.739	1066	1350	1030	1302	1010	1278

The marginal power for detecting a difference between IDeg OD and IGlax 300 U/mL OD with 795 subjects per treatment arm assuming a one-sided t-test at the 2.5% significance level for the

confirmatory secondary endpoints is shown below. The assumptions are based on data from NN1250-3998 with respect to hypoglycaemic episodes and the phase 3a+b program for the dose-difference.

Table 17–2 Marginal power for confirmatory secondary endpoints

Endpoint	Assumptions				
	True ratio	Adjusted RR	CV/ Over dispersion	Rate in IDeg treatment arm	Power
Number of nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes during maintenance	0.7	0.712	3.1	0.55	84%
Insulin dose (U)	0.90	0.904	0.65	-	92%
Number of severe or BG confirmed symptomatic hypoglycaemic episodes during 52 weeks	0.75	0.75	3.1	2.2	87%
Number of severe hypoglycaemic episodes during maintenance	0.6	0.616	3.1	0.03	32%

17.3 Definition of analysis sets

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

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

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

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

17.4 Primary endpoint

17.4.1 Primary statistical analysis for the primary estimand

The primary estimand will be estimated based on information from the maintenance period collected when subjects use randomised treatment (on-treatment data). Subjects that discontinue randomised treatment during the maintenance period will contribute with the available on treatment data from the maintenance period. For subjects that discontinue randomised treatment during the 16 week titration period, the number of events in the maintenance period will be imputed based on data from the same arm from the maintenance period for subjects that discontinued randomised treatment during the maintenance period. Missing data within each group will be imputed as follows:

- First 1000 samples from the posterior distribution of model parameters will be extracted. The model will be fitted to the on-treatment maintenance data for subjects that discontinued randomised treatment during the maintenance period. This will be done using a Bayes negative binomial log-link model with the factors described in section [17.1](#) (except treatment), age as covariate, and log of exposure time as offset.
- For each sample of model parameters, the total number of hypoglycaemia events for subjects that discontinued randomised treatment in the titration period will be imputed as a random number of events from a negative binomial distribution using the sampled parameters.

Having 1000 complete data sets that have maintenance period data for all randomised subjects, the mean treatment ratio will be estimated using a negative binomial model with all the factors described in section [17.1](#), age as covariate and log exposure time as offset. The estimates and standard deviations will be pooled to one estimate and associated standard deviation using Rubin's formula. From these the 95% confidence intervals for the treatment ratio and the associated p-value will be calculated.

If the above model cannot fit due to sparse data, the model in step 1 above is fitted to the on-treatment data for subjects that discontinued randomised treatment during either titration or maintenance. If this model cannot fit either, factors will be left out one by-one in the model using data from all subjects discontinuing randomised treatment in the following order, until a model fits:

- sex
- region
- previous OAD treatment

17.4.2 Sensitivity analyses for the primary estimand

To investigate missing not at random scenarios, a tipping point analysis of the hypothesis that IDeg is superior to IGlax 300 U/mL will be performed for the primary estimand. In this analysis the event rates for subjects that discontinued randomised treatment in the IDeg OD arm during either titration

or maintenance is gradually increased until the difference between the two treatments is no longer statistically significantly different. If the penalty found by this method is evaluated to be clinically plausible the sensitivity analysis does not support the primary analysis. If the penalty is not considered plausible the sensitivity analysis supports the primary analysis.

To investigate the potential influence of subjects with high number of events, the analysis of the primary estimand will be repeated on data where the maximal number of events in the maintenance period is truncated at three. The value three is based on data from SWITCH 2 (NN1250-3998) where three hypos correspond to the 95% percentile in the IDeg arm.

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

17.4.3 Statistical analysis for the secondary estimand

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

Missing data for withdrawn subjects will be imputed based on off-treatment data from the same arm from the maintenance period for subjects that discontinued randomised treatment during the maintenance period. The imputations and the analysis will be made using the same method as for the primary estimand.

17.4.4 Sensitivity analysis for the secondary estimand

The same sensitivity analysis as the sensitivity analysis for the primary estimand will be performed.

17.5 Secondary endpoints

17.5.1 Confirmatory secondary endpoints

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

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

1. Basal insulin dose (U) after 52 weeks
2. Number of nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes during maintenance, week 16-52
3. Number of severe or BG confirmed symptomatic hypoglycaemic episodes during 52 weeks
4. Number of severe hypoglycaemic episodes during maintenance, week 16-52

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

Basal insulin dose after 52 weeks will be analysed as follows: A basal insulin dose at every titration, maintenance and end of treatment visit mentioned in the flow chart will be calculated as a mean of the insulin doses in the 7 day period before the visits. These doses will be analysed on log-scale with an MMRM with the factors described in section [17.1](#) and age at baseline and pre-trial insulin dose as covariate.

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

- An analysis of covariance model for insulin dose at week 52 with the factors listed in [17.1](#) (except treatment) and pre-trial insulin dose and age at baseline as covariates will be fitted to the observed data.
- The estimated parameters will be used to impute 1000 values for insulin dose at week 52, creating 1000 complete datasets.

Having 1000 complete datasets, each of these will be analysed using an analysis of covariance model with all the factors listed in [17.1](#), pre-trial insulin dose and age at baseline as covariates. The estimates and standard deviations will be pooled to one estimate and associated standard deviation using Rubin's formula. From these the 95% confidence intervals for the treatment ratio and the associated p-value will be calculated.

17.6 Other endpoints

17.6.1 Efficacy endpoints

Continuous supportive secondary efficacy endpoints will be summarised descriptively by visits and by mean plots of observed values and observed change from baseline.

17.6.2 Safety endpoints

Adverse events during 52 weeks

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

A treatment-emergent AE (TEAE) is defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment, or has onset date before the first day of exposure on randomised treatment and increases in severity during the treatment period and until 7 days after the last drug date. Major adverse

cardiovascular events (MACEs, defined as all cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes) are considered treatment-emergent until 30 calendar days after the last day of randomised treatment.

TEAEs are summarised descriptively, whereas non-TEAEs are presented in listings. 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 of exposure (R).

Summaries of TEAEs and of serious TEAEs will be presented as an overview including all AEs, serious AEs, number of deaths, AEs by severity, AEs by relation to treatment and AEs leading to treatment discontinuation or withdrawal.

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

- All TEAEs
- Serious TEAEs
- TEAEs possibly or probably related to trial product
- Severe, moderate and mild TEAEs
- TEAEs with preferred term that are experienced by at least 5% (1%) of the subjects in any treatment arm or by at least 5% (1%) of all subjects

Summary tables of SAEs including SAEs reported for subject that discontinue trial product prematurely will be presented including summary tables based on system organ class and preferred terms.

Hypoglycaemic episodes during 52 weeks

For the definition and classification of hypoglycaemic episodes refer to section [17.7](#).

Data on treatment-emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years of exposure (R).

Separate summaries are made by severity considering severe or BG confirmed symptomatic hypoglycaemic episodes, severe hypoglycaemic episodes, and the ADA classification of hypoglycaemia. The summaries are made for all and nocturnal (between 00:01 and 05.59 both inclusive) episodes respectively and for the total treatment period (52 weeks) and maintenance period only (week 16-52).

Body weight

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

Clinical evaluation (ECG, vital signs, eye examination and physical examination) change from baseline after 52 weeks

Vital signs, physical examination, eye examination and 12-lead ECG findings will be summarised, including:

- Summaries for each visit
- Shift tables from baseline to after 52 weeks

Laboratory assessments

Biochemistry and Haematology laboratory parameters will be summarised including:

- Summaries by visit
- Shift tables from baseline to after 52 weeks
- Proportion of subjects with measurements outside reference range by treatment and week
- Box plots by time since randomisation
- Listings of individual values outside reference ranges (abnormal values)

All laboratory values will be included in listings.

Anti-insulin antibodies will be summarised by visit.

17.7 Classification of Hypoglycaemia

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

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

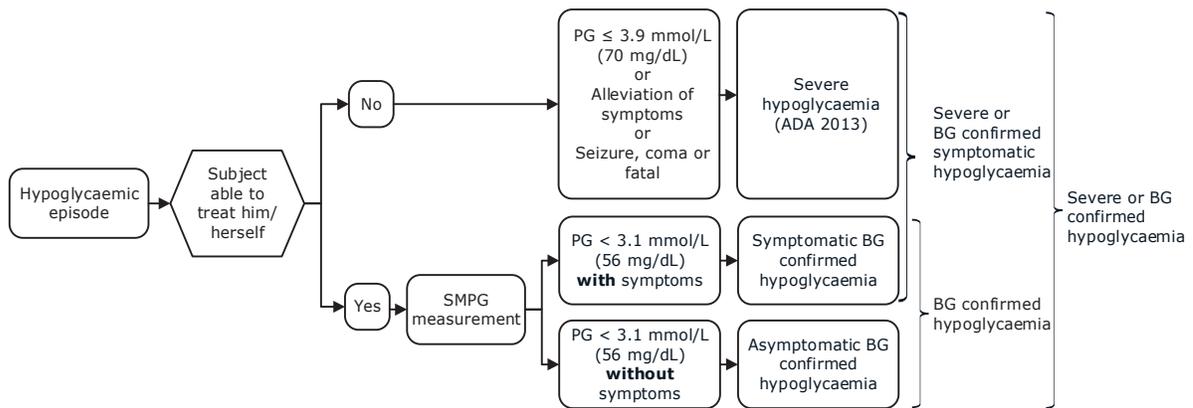
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see [Figure 17-1](#)) and the ADA classification of hypoglycaemia (see [Figure 17-2](#)).

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)³⁸. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see [Figure 17-1](#)) in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification²⁹.
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification²⁹ or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia.



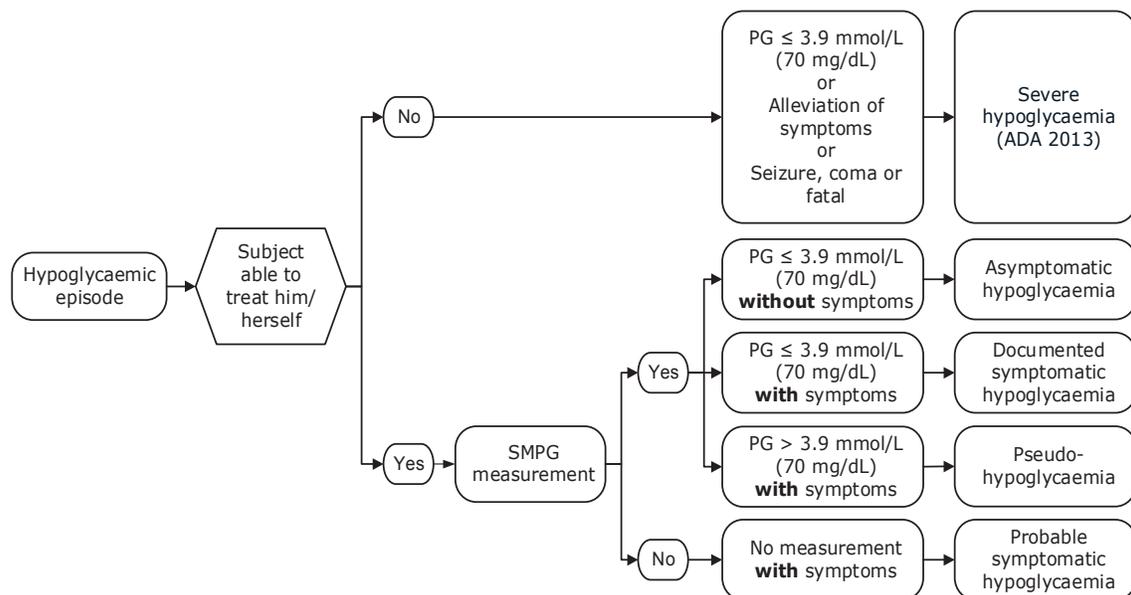
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

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

Figure 17-1 Novo Nordisk classification of hypoglycaemia

ADA classification²⁹ of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).



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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–2 ADA classification of hypoglycaemia

Protocol
Trial ID: NN1250-4252
UTN: U1111-1184-8175
EudraCT no.: 2016-002801-20

~~CONFIDENTIAL~~

Date: 11 November 2016
Version: 2.0
Status: Final
Page: 92 of 109

Novo Nordisk

17.8 Health economics and/or patient reported outcomes

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

18 Ethics

18.1 Benefit-risk assessment of the trial

The trial population will consist of insulin-treated subjects with T2DM presenting with an HbA_{1c} equal to or below 9.5% while treated continuously with basal insulin with or without OADs for at least 90 days and who recently have experienced hypoglycaemia or have increased risk of severe hypoglycaemia. For all subjects participating in this trial, the anticipated benefits include improved glycaemic control. Titration algorithms, specifying recommended adjustments of the basal 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.

Trial products will be provided by Novo Nordisk free of charge. Subjects will receive IDeg or IGLar 300 U/mL in prefilled pens and NPH during 7 days follow-up. For a description of risks and benefits please refer to current versions and any updates of the following:

- IDeg IB⁹
- IGLar 300 U/mL SmPC¹⁴ or local labelling^{15, 16}
- NPH SmPC³⁴ or local labelling^{35, 36}

The subjects will be provided with a glucose meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use.

The trial products may be associated with side effects, but relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participating in the trial. These precautions include thorough information regarding the correct administration of the trial product and in handling of low BG measurement. Furthermore, subjects will be fully informed about possible AEs and inconveniences.

Clinical benefits and risk considerations for the trial

For the individual subjects, the personal health-related benefits are related to the medical examination and the benefit from a treatment regimen anticipated being equal to or better than the treatment they receive at the time they enter the trial. However, subjects will have to spend some extra time monitoring and recording data and on additional visits to the clinic and phone contacts. The maximum trial duration for each subject is 58 weeks and the treatment duration for a subject is planned to be 52 weeks. Subjects will be asked to perform SMPG recording every day.

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

For the individual subjects, the anticipated side effects associated with the trial products are not different from what is seen with other insulins and include hypoglycaemia, hypersensitivity reactions, injection site reactions, lipodystrophy and antibody development (for more detailed description, please refer to the local labelling for each product). The side effects will be mitigated by the close supervision of the subjects and the frequent measurements of BG levels.

All treatments are contraindicated in case of hypersensitivity to the active substances or any of the excipients. The risk of hypersensitivity is partly mitigated by excluding subject with known hypersensitivity towards any trials products or related products.

Injection site reactions can occur. The nature of the injection site reactions is expected to be mild, transient, and more of a visual character and is not expected to be of concern to the subject's safety. Lipodystrophy (including lipohypertrophy, lipoatrophy) at the injection site can occur. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

Conclusion

Subjects in this trial will benefit from a basal insulin treatment in a treat-to-target setting under close supervision.

The safety profiles of the trial products are well established.

It is concluded that the clinical benefits from the trial outweigh the potential risks of participating in this trial.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP¹ and the requirements in the Declaration of Helsinki².

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 investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

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

18.3 Data handling

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

- Data already collected and any data collected at the end-of-trial visit including follow up visits will be retained by Novo Nordisk, entered into the database and used for the clinical 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.

18.4 Information to subjects during trial

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

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

18.5 Premature termination of the trial and/or trial site

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

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

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

19 Protocol compliance

19.1 Protocol deviations

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

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

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

19.2 Prevention of missing data

A significant proportion of missing data is a potential source of bias when analysing data in clinical trials leading to a risk of misinterpretation of the trial results. Missing data may affect both estimation of treatment effect and the confidence interval that surrounds it as well as the representativeness of the sample size in relation to the target population.

Only absolutely necessary criteria to discontinue trial drug have been stated, see Section [6.4](#), and a process has been set up to follow-up on subjects discontinuing trial drug prematurely, see section [8.1.8](#).

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

The subjects will be carefully informed about the trial procedures before signing informed consent, so that they know the implications of participating in the trial. In addition, only absolutely necessary criteria for premature discontinuation of trial products primarily focusing on subjects safety are included and thereby reducing the number of discontinuations and limiting the amount of missing data.

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

The subjects must be instructed to complete their eDiary on an ongoing basis according to the protocol. Missing data will not be recorded retrospectively due to the decreased validity of such data^{31, 32}; however a 7 days' timeline is applied for reporting of missing hypoglycaemic episode. The subject will be retrained in correct completion of the eDiary if missing data is identified.

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

20 Audits and inspections

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

21 Critical documents

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

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

- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For US sites:

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

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

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

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP¹ applicable regulatory requirements and the Declaration of Helsinki².

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

22 Responsibilities

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

A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator will follow instructions from Novo Nordisk when processing data.

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

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

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

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

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

23 Reports and publications

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

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

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

One investigator will be appointed by Novo Nordisk to review and sign the 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 publications³⁹.

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 Disclosure²³.

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

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

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

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

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 Editors³⁹ (sometimes referred to as the Vancouver Criteria).

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

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

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

23.2 Investigator access to data and review of results

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

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

24 Retention of clinical trial documentation and human bio samples

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 provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

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

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

24.2 Retention of human bio samples

Antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug if required by health authorities, for safety reasons or in relation to exploratory analysis.

Remaining anti-insulin antibody samples may be used for exploratory investigation of antibodies. The analyses will be performed by Immunogenicity Assessment, Novo Nordisk A/S or a laboratory assigned by Novo Nordisk A/S. Results will be reported under a separate study and the data documented independently from the clinical trial report.

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Page:	104 of 109	

The samples will be stored at a central bio-repository after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.

The subject's identity will remain confidential and the antibody samples will be identified only by subject number, visit number and trial identification number. No direct identification of the subject will be stored together with the samples.

Only Novo Nordisk staff and bio-repository personnel will have access to the stored antibody samples.

Subjects can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

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

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to 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 benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the clinical trial report synopsis to the 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 trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

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

26 Indemnity statement

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

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

For Poland only: Novo Nordisk carries liability for the trial exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal of Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the trial, Novo Nordisk and the investigators are covered by the insurance policy issued according to applicable Polish law.

27 References

1. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1), Step 4. 10 June 1996.
2. World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.
3. Leahy JL. Pathogenesis of type 2 diabetes mellitus. *Arch Med Res.* 2005;36(3):197-209.
4. Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal TP, Hemmingsen C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2013(11):CD008143.
5. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia.* 2015;58(3):429-42.
6. Garber AJ, King AB, Del Prato S, Sreenan S, Balci MK, Munoz-Torres M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet.* 2012;379(9825):1498-507.
7. Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care.* 2012;35(12):2464-71.
8. Wysham H, Carol, Bhargava A, Chaykin BL, Rosa RDL, Handelsman Y, Troelsen NL, et al. SWITCH 2: Reduced Hypoglycemia with Insulin Degludec (IDeg) vs. Insulin Glargine (IGlar), Both U100, in Patients with T2D at High Risk of Hypoglycemia: A Randomized, Double-Blind, Crossover Trial. *Diabetes.* 2016;65 (Supplement 1):90-LB.
9. Novo Nordisk A/S. Investigator's Brochure, insulin degludec (11th edition). December 2015.
10. Novo Nordisk A/S. Tresiba[®] (insulin degludec) EU Summary of Product Characteristics (SmPC). 2015.
11. Novo Nordisk A/S. Tresiba[®] U.S. Label information. 2015.
12. Ritzel R, Roussel R, Bolli GB, Vinet L, Brulle-Wohlhueter C, Glezer S, et al. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. *Diabetes Obes Metab.* 2015;17(9):859-67.
13. Yki-Järvinen H, Bergenstal R, Ziemien M, Wardecki M, Muehlen-Bartmer I, Boelle E, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care.* 2014;37(12):3235-43.
14. European Medicines Agency. Toujeo[®] - Summary of Product Characteristics. 4/24/ 2015.
15. Food and Drug Administration. Toujeo[®] - U.S. Label information. 2015.
16. Health Canada. Toujeo[™] SoloSTAR[®], CA Prescribing Information (PI). 15-July-2015 2015.

17. Yki-Järvinen H, Bergenstal RM, Bolli GB, Ziemien M, Wardecki M, Muehlen-Bartmer I, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus insulin glargine 100 U/ml in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension. *Diabetes Obes Metab.* 2015;17(12):1142-9.
18. Home PD, Bergenstal RM, Bolli GB, Ziemien M, Rojas M, Espinasse M, et al. New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 1 Diabetes: A Randomized, Phase 3a, Open-Label Clinical Trial (EDITION 4). *Diabetes Care.* 2015.
19. Vora J, Christensen T, Rana A, Bain SC. Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: a meta-analysis of endpoints in phase 3a trials. *Diabetes Ther.* 2014;5(2):435-46.
20. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-12.
21. Stevens LA, Schmid CH, Zhang YL, Coresh J, Manzi J, Landis R, et al. Development and validation of GFR-estimating equations using diabetes, transplant and weight. *Nephrol Dial Transplant.* 2010;25(2):449-57.
22. Lamb EJ, Levey AS, Stevens PE. The Kidney Disease Improving Global Outcomes (KDIGO) guideline update for chronic kidney disease: evolution not revolution. *Clin Chem.* 2013;59(3):462-5.
23. Novo Nordisk A/S. <http://www.novonordisk-trials.com/website/content/how-we-disclose-trial-information.aspx>.
24. De Angelis 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. *N Engl J Med.* 2004;351(12):1250-1.
25. U.S. Department of Health and Human Services, Food and Drug Administration. Food and Drug Administration Amendments Act of 2007. 27 September 2007.
26. The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, article 11. *Official Journal of the European Communities.* 1 May 2001.
27. The European Parliament and the Council of the European Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. *Official Journal of the European Communities.* 2004.
28. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care.* 1995;18(4):517-22.
29. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care.* 2013;36(5):1384-95.

30. McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. *Diabet Med.* 2001;18(9):690-705.
31. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009.
32. Stull DE, Leidy NK, Parasuraman B, Chassany O. Optimal recall periods for patient-reported outcomes: challenges and potential solutions. *Curr Med Res Opin.* 2009;25(4):929-42.
33. Rewers MJ, Pillay K, de Beaufort C, Craig ME, Hanas R, Acerini CL, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and monitoring of glycemic control in children and adolescents with diabetes. *Pediatr Diabetes.* 2014;15 Suppl 20:102-14.
34. Novo Nordisk A/S. Insulatard[®] (human isophan insulin), EU Summary of Product Characteristics. SEP 2015.
35. Novo Nordisk A/S. NOVOLIN[®] N, US Prescribing Information (PI). 01-August-2016 2016.
36. Novo Nordisk A/S. Novolin[®] ge, CA prescribing Information (PI). 11-March-2016 2016.
37. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1). 2 Jul 2010.
38. Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. *J Clin Invest.* 1987;79(3):777-81.
39. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals; current version available at www.icmje.org.

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Protocol

Trial ID: NN1250-4252

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

**Updated protocol including:
Protocol, final version 2.0 dated 11 November 2016
Local Protocol Amendment no. 1 in Serbia version 1.0 dated 25 July 2017
Global Protocol Amendment no. 2, version 1.0 dated 22 February 2018**

Trial phase: 3b



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Table of contents

	Page
Table of contents	2
Table of figures	6
Table of tables	6
List of abbreviations	6
1 Summary	11
2 Flow chart	14
3 Background information and rationale for the trial	24
3.1 Background information.....	24
3.2 Rationale for the trial.....	25
4 Objective(s) and endpoint(s)	27
4.1 Objective(s)	27
4.2 Endpoint(s)	27
4.2.1 Primary endpoint	27
4.2.2 Secondary endpoints	27
4.2.2.1 Confirmatory secondary endpoints	27
4.2.3 Other endpoints.....	27
5 Trial design	29
5.1 Type of trial	29
5.2 Rationale for trial design	30
5.3 Treatment of subjects	31
5.4 Treatment after discontinuation of trial product	32
5.5 Rationale for treatment.....	32
6 Trial population	33
6.1 Number of subjects	33
6.2 Inclusion criteria	33
6.3 Exclusion criteria	34
6.4 Criteria for premature discontinuation of trial product	35
6.5 Withdrawal from trial.....	36
6.6 Subject replacement	37
6.7 Rationale for trial population.....	37
7 Milestones	38
8 Methods and assessments	39
8.1 Visit procedures	39
8.1.1 Screening visit (Visit 1)	39
8.1.1.1 Screening failures.....	40
8.1.2 Randomisation visit (V2).....	40
8.1.3 Phone contacts	41
8.1.4 Fasting visits.....	41
8.1.5 Maintenance 2 initiation visit (V57)	41
8.1.6 End of Treatment visit (V54 or V93).....	42

8.1.7	Follow up visits	43
8.1.8	Unscheduled site visits	43
8.1.9	Premature discontinuation of trial product	44
8.1.10	Withdrawal from trial	45
8.1.11	Review of results	46
8.2	Subject related information/assessments	46
8.2.1	Demography	46
8.2.2	Diabetes history	46
8.2.3	Hypoglycaemia unawareness	46
8.2.4	Concomitant illness and medical history	46
8.2.5	Concomitant medication	47
8.2.6	Concomitant medication (Diabetes)	47
8.2.7	Childbearing potential	48
8.2.8	Tobacco use	48
8.3	Efficacy assessments	48
8.3.1	Self-measured plasma glucose	48
8.3.2	Insulin dose	49
8.4	Safety assessments	49
8.4.1	Adverse events	50
8.4.1.1	Medication error	50
8.4.1.2	Adverse events requiring additional data collection	50
8.4.2	Hypoglycaemic episodes	51
8.4.3	Body measurements	54
8.4.4	Vital signs	54
8.4.5	Physical examination	54
8.4.6	Eye examination	54
8.4.7	Electrocardiogram	55
8.5	Laboratory assessments	55
8.5.1	Laboratory assessments for efficacy	56
8.5.2	Laboratory assessments for safety	57
8.6	Other assessments	58
8.6.1	Training in the pen injector	59
8.7	Subject compliance	60
9	Trial supplies.....	61
9.1	Trial products	61
9.2	Labelling	62
9.3	Storage	62
9.4	Drug accountability and destruction	63
9.5	Auxiliary supplies	63
10	Interactive web response system.....	64
11	Randomisation procedure.....	65
12	Adverse events, and technical complaints and pregnancies	66
12.1	Definitions	66
12.1.1	Adverse event	66
12.1.2	Serious adverse event	67
12.1.3	Non-serious adverse event	68
12.1.4	Medication errors	68

12.1.5	Adverse events requiring additional data collection	69
12.1.6	Technical complaints	69
12.2	Reporting of adverse events.....	70
12.3	Follow-up of adverse events.....	72
12.4	Technical complaints and technical complaint samples	73
12.4.1	Reporting of technical complaints	73
12.4.2	Collection, storage and shipment of technical complaint samples	73
12.5	Pregnancies in female subjects	74
12.6	Precautions and/or overdose	75
12.7	Committees related to safety	76
12.7.1	Novo Nordisk safety committee	76
12.7.2	Event adjudication committee	76
13	Case report forms	78
13.1	Corrections to case report forms	78
13.2	Case report form flow	79
14	Monitoring procedures	79
15	Data management	81
16	Computerised systems	81
17	Statistical considerations	81
17.1	General considerations	81
17.2	Power calculation.....	83
17.3	Definition of analysis sets.....	84
17.4	Primary endpoint.....	85
17.4.1	Primary statistical analysis for the primary estimand	85
17.4.2	Sensitivity analyses for the primary estimand.....	85
17.4.3	Statistical analysis for the secondary estimand.....	86
17.4.4	Sensitivity analysis for the secondary estimand	86
17.5	Secondary endpoints	86
17.5.1	Confirmatory secondary endpoints	86
17.6	Other endpoints.....	87
17.6.1	Efficacy endpoints	87
17.6.2	Safety endpoints	87
17.7	Classification of Hypoglycaemia	89
17.8	Health economics and/or patient reported outcomes.....	92
18	Ethics.....	93
18.1	Benefit-risk assessment of the trial	93
18.2	Informed consent	94
18.3	Data handling.....	95
18.4	Information to subjects during trial.....	95
18.5	Premature termination of the trial and/or trial site	95
19	Protocol compliance.....	96
19.1	Protocol deviations.....	96
19.2	Prevention of missing data	96
20	Audits and inspections	97
21	Critical documents.....	97

22	Responsibilities.....	98
23	Reports and publications	99
23.1	Communication of results.....	99
23.1.1	Authorship.....	100
23.1.2	Site-specific publication(s) by investigator(s).....	100
23.2	Investigator access to data and review of results	101
24	Retention of clinical trial documentation and human bio samples.....	102
24.1	Retention of clinical trial documentation	102
24.2	Retention of human bio samples.....	102
25	Institutional Review Boards/Independent Ethics Committees and regulatory authorities	104
26	Indemnity statement	105
27	References	106
	Appendix A Titration Guideline	
	Attachment I Global list of key staff and relevant departments and suppliers	
	Attachment II Country list of key staff and relevant departments, if applicable for the individual country	

Table of figures

	Page
Figure 5–1 Trial design	30
Figure 12–1 Reporting of AEs	71
Figure 17–1 Novo Nordisk classification of hypoglycaemia	90
Figure 17–2 ADA classification of hypoglycaemia.....	91

Table of tables

	Page
Table 2–1 Flowchart – titration and maintenance 1	14
Table 2–2 Flowchart – maintenance 2	19
Table 2–3 Flow chart – phone contacts during titration and maintenance 1	23
Table 2–4 Flow chart – phone contacts during maintenance 2	23
Table 9–1 Trial products	61
Table 9–2 Storage conditions	62
Table 12–1 Adverse events requiring completion of specific event forms and/or are subject to event adjudication	69
Table 12–2 Events for adjudication.....	76
Table 17–1 Power for the primary estimand for combinations of RR and event rates.....	83
Table 17–2 Marginal power for confirmatory secondary endpoints	83

List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
BG	blood glucose
BID	Bis In Die/twice daily
CAS	completer analysis set
CCDS	Company Core Data Sheet
CFR	Code of Federal Regulations
CLAE	clinical laboratory adverse event
CRF	case report form
DPP-IVi	dipeptidyl peptidase-4 inhibitor
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPFV	first patient first visit

FPG	fasting plasma glucose
FU	follow-up
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
HbA _{1c}	glycosylated haemoglobin
hCG	human chorionic gonadotropin
IB	investigator's brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IDeg	insulin degludec
IEC	independent ethics committee
IGlar	insulin glargine
IMP	investigational medicinal product
IND	Investigational New Drug
ITT	intention-to-treat
IRB	institutional review board
IWRS	interactive voice/web response system
LI	label information
LLOQ	lower limit of quantification
LPLV	last patient last visit
MACE	major adverse cardiovascular events

NIMP	Non-Investigational Medicinal Product
NPH	insulin Neutral Protamine Hagedorn
NYHA	New York Heart Association
OAD	oral anti-diabetic drug
OD	once daily
PP	per protocol
PRO	patient reported outcome
PYE	Patient years of exposure
PX	monthly phone contact
RR	rate ratio
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SF-36v2 [®]	short-form 36 health survey version 2
SGLT2i	sodium-glucose co-transporter 2 inhibitors
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
SU	sulfonylureas
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent AE
TIA	transient ischaemic attack

Protocol
Trial ID: NN1250-4252
UTN: U1111-1184-8175
EudraCT no.: 2016-002801-20

~~CONFIDENTIAL~~

Date: 23 February 2018
Version: 3.0
Status: Final
Page: 10 of 108

Novo Nordisk

TMM	trial materials manual
TRIM-D	Treatment related impact measure - diabetes
TRIM-D-Device	Treatment related impact measure - diabetes device
TZD	Thiazolidinediones
U	Units
UNL	upper normal limit
UTN	Universal Trial Number

1 Summary

Objective(s) and endpoint(s):

Primary objective

To compare the effects of insulin degludec once daily and insulin glargine 300 units/mL once daily on hypoglycaemia in subjects with type 2 diabetes mellitus, inadequately treated with basal insulin with or without oral anti-diabetic drugs.

Key secondary objectives

To compare insulin degludec and insulin glargine 300 units/mL in terms of basal insulin requirement.

To compare insulin degludec and insulin glargine 300 units/mL in terms of safety and parameters of glycaemic control.

Primary endpoint

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

Confirmatory secondary endpoints:

- Basal insulin dose (units) at end of treatment (up to 88 weeks)
- Number of nocturnal, severe or blood glucose confirmed symptomatic hypoglycaemic episodes during maintenance 2 (36 weeks)
- Number of severe hypoglycaemic episodes during maintenance 2 (36 weeks)

Other efficacy endpoints:

- Change in HbA_{1c} from baseline to end of treatment (up to 88 weeks)

Other safety endpoints:

- Hypoglycaemia
 - Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes during treatment (up to 88 weeks)
 - Number of nocturnal, severe or blood glucose confirmed symptomatic hypoglycaemic episodes during treatment (up to 88 weeks)
 - Number of severe hypoglycaemic episodes during treatment (up to 88 weeks)
- Number of adverse events during treatment (up to 88 weeks)

Trial design:

This is a up to 88-week, randomised (1:1), open-label, parallel, multi-centre, multi-national, treat-to-target, active controlled trial comparing the efficacy and safety of insulin degludec 200 units/mL

with insulin glargine 300 units/mL both administered once daily \pm oral anti-diabetic drugs in subjects with type 2 diabetes mellitus previously treated with basal insulin once or twice daily \pm oral anti-diabetic drugs excluding sulfonylureas/glinides. Type and dose of any pre-trial oral anti-diabetic treatment should remain unchanged throughout the trial.

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

Total trial duration for the individual subjects will be up to 94 weeks.

Trial population:

It is planned to randomise 1,590 subjects.

Key inclusion criteria:

- Male or female, age above or equal to 18 years at the time of signing informed consent.
- Subjects fulfilling at least one of the below criteria^a:
 - a. Experienced at least one severe hypoglycaemic episode within the last year (according to the ADA definition, April 2013^b)
 - b. Moderate chronic renal failure, defined as glomerular filtration rate 30 - 59 mL/min/1.73 m² per CKD-EPI by central laboratory analysis
 - c. Hypoglycaemic symptom unawareness^c
 - d. Treated with insulin for more than 5 years
 - e. 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)
- Subjects diagnosed (clinically) with type 2 diabetes mellitus.
- Treated with basal only insulin (once daily or twice-daily insulin (insulin detemir; insulin glargine 100 U/mL, biosimilar of insulin glargine 100 U/mL or insulin Neutral Protamine Hagedorn)) ≥ 90 days prior to the day of screening with or without any of the following anti-diabetic drugs with stable doses for ≥ 90 days prior to screening:
 - a. Metformin
 - b. Dipeptidyl peptidase -4 inhibitor
 - c. Sodium-glucose co-transporter 2 inhibitor
 - d. Alpha-glucosidase-inhibitors (acarbose)
 - e. Thiazolidinediones
 - a. Marketed oral combination products only including the products listed in criteria 5a-5e
- HbA_{1c} $\leq 9.5\%$ (80 mmol/mol) at screening by central laboratory analysis.
- BMI ≤ 45 kg/m².

^aFor this inclusion criterion the aim is to include minimum 80% of individuals with a previous episode of hypoglycaemia (criterion e). The remaining subjects will have to fulfil at least one of criteria a-d.

^bAn 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.

^cHistory of impaired autonomic responses (tremulousness, sweating, palpitations, and hunger) during hypoglycaemia.

Key exclusion criteria

- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before the day of screening.

Key assessments:

- Hypoglycaemic episodes
- Insulin dose
- HbA_{1c}
- Adverse events

Trial products:

Investigational medicinal products:

- Test product: Insulin degludec (Tresiba[®]), 200 U/mL, 3 mL prefilled PDS290 (FlexTouch[®]) pen for subcutaneous injection
- Reference therapy: Insulin glargine (Toujeo[®]), 300 U/mL, 1.5 mL prefilled Solostar[®] pen for subcutaneous injection

Other medicinal products:

- Insulin Neutral Protamine Hagedorn (Insulatard[®]/Prothaphane[®]/Novolin N[™]), 100 IU/mL, 3 mL pre-filled pen for subcutaneous injection (will be provided by sponsor to subjects during the wash-out period in order to measure insulin antibodies)

Trial NN1250-4252	Protocol section	Screening	Randomisation	Titration 16 weeks			Maintenance 1 Up to 36 weeks										End Of Treatment	Follow-up			Premature discontinuation		
				V6	V10	V14	V18	V22	V26	V30	V34	V38	V42	V46	V50	V54		V55	V56	V18A	V30A	V42A	V54A
Visit number		V1	V2	V6	V10	V14	V18	V22	V26	V30	V34	V38	V42	V46	V50	V54	V55	V56	V18A	V30A	V42A	V54A	
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								
Timing of visit (weeks)		-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	53	56	16	28	40	52	
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5	±3	±3	±3	±3	
	12																						
Hypoglycaemic episodes	8.4.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body weight	8.4.3	X	X				X				X					X							
Height	8.4.3	X																					
Vital signs	8.4.4	X														X							
Physical examination	8.4.5	X														X							
Eye examination (Fundoscopy or fundus photography)	8.4.6	X														X							
ECG	8.4.7	X														X							
Anti-insulin antibodies	8.5.2		X			X					X					X	X						
Biochemistry	8.5.2	X														X							
Haematology	8.5.2	X														X							
Pregnancy test	8.5.2	X														X							
Technical complaints	12.1.6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
OTHER ASSESSMENTS																							
SF-36v2® Standard	8.6		X				X									X							
TRIM-D	8.6		X				X									X							

Trial NN1250-4252	Protocol section	Screening	Randomisation	Titration 16 weeks			Maintenance 1 Up to 36 weeks									End Of Treatment	Follow-up		Premature discontinuation			
				V6	V10	V14	V18	V22	V26	V30	V34	V38	V42	V46	V50		V54	V55	V56	V18A	V30A	V42A
Visit number		V1	V2	V6	V10	V14	V18	V22	V26	V30	V34	V38	V42	V46	V50	V54	V55	V56	V18A	V30A	V42A	V54A
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							
Timing of visit (weeks)		-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	53	56	16	28	40	52
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5	±3	±3	±3	±3
REMINDERS																						
Attend visit fasting	8.1.4		X	X	X	X	X			X	X		X		X	X						
Confirmation of unchanged OAD	8.2.6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Training in trial product and pen handling	8.6.1 9.2		X	X																		
Hand-out direction for use for the pen injectors	9.2		X																			
Hand-out ID card	8.1.1	X																				
Hand-out and instruct in BG meter	8.1.2		X	X																		
Hand-out and instruct in eDiary	8.1.2 8.6		X																			
eDiary collection	8.6																X				X	
Make appointment for eye examination	8.4.6												X									
End Of Treatment	8.1.6														X						X	
End of trial	7																X				X	
Sign off Casebook																	X					

Table 2–2 Flowchart – maintenance 2

Applicable from when the new glycaemic data collection system (an Abbott BG-meter and paper diary) is available.

Trial NN1250-4252	Protocol section	Maintenance 2 36 weeks									End Of Treatment	Follow-up			Premature discontinuation			
		V57	V61	V65	V69	V73	V77	V81	V85	V89		V93	V94	V95	V57A	V69A	V81A	V93A
Weekly Phone Contact number (P) (For details see separate flow chart below)		P58 P59 P60	P62 P63 P64	P66 P67 P68	P70 P71 P72	P74 P75 P76	P78 P79 P80	P82 P83 P84	P86 P87 P88	P90 P91 P92								
Timing of visit (maintenance weeks)		0	4	8	12	16	20	24	28	32	36	37	40	0	12	24	36	
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5					
SUBJECT RELATED																		
Informed consent	18.2	X												X				
Premature discontinuation of trial products	6.4 8.1.9		X	X	X	X	X	X	X	X	X	X	X					
Withdrawal from trial	6.5 8.1.10		X	X	X	X	X	X	X	X	X	X	X					
Concomitant medication	8.2.5	X	X	X	X	X	X	X	X	X	X							
Concomitant medication (Diabetes)	8.2.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EFFICACY ASSESSMENTS																		
Self-measured plasma glucose Once daily (pre-breakfast)	8.3.1	X	X	X	X	X	X	X	X	X	X							
Fasting plasma glucose	8.5.1		X		X			X			X							
HbA _{1c}	8.5.1	X	X	X	X	X	X	X	X	X	X			X	X	X	X	
SAFETY																		

Trial NN1250-4252	Protocol section	Maintenance 2 36 weeks									End Of Treatment	Follow-up	Premature discontinuation				
		V57	V61	V65	V69	V73	V77	V81	V85	V89			V93	V94	V95	V57A	V69A
Visit number																	
Weekly Phone Contact number (P) (For details see separate flow chart below)		P58 P59 P60	P62 P63 P64	P66 P67 P68	P70 P71 P72	P74 P75 P76	P78 P79 P80	P82 P83 P84	P86 P87 P88	P90 P91 P92							
Timing of visit (maintenance weeks)		0	4	8	12	16	20	24	28	32	36	37	40	0	12	24	36
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5				
ASSESSMENTS																	
Adverse events	8.4.1 12	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	8.4.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	8.4.3	X				X					X						
Vital signs	8.4.4										X						
Physical examination	8.4.5										X						
Eye examination (Fundoscopy or fundus photography)	8.4.6										X						
ECG	8.4.7										X						
Anti-insulin antibodies	8.5.2										X	X					
Biochemistry	8.5.2										X						
Haematology	8.5.2										X						
Pregnancy test	8.5.2										X						
Technical complaints	12.1.6	X	X	X	X	X	X	X	X	X	X	X					
OTHER ASSESSMENTS																	
SF-36v2® Standard	8.6										X						
TRIM-D	8.6										X						

Trial NN1250-4252	Protocol section	Maintenance 2 36 weeks									End Of Treatment	Follow-up		Premature discontinuation			
		V57	V61	V65	V69	V73	V77	V81	V85	V89		V93	V94	V95	V57A	V69A	V81A
Visit number																	
Weekly Phone Contact number (P) (For details see separate flow chart below)		P58 P59 P60	P62 P63 P64	P66 P67 P68	P70 P71 P72	P74 P75 P76	P78 P79 P80	P82 P83 P84	P86 P87 P88	P90 P91 P92							
Timing of visit (maintenance weeks)		0	4	8	12	16	20	24	28	32	36	37	40	0	12	24	36
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5				
TRIM-D device	8.6										X						
Insulin Pen Questionnaire	8.6										X						
Hypoglycaemia resource use questionnaire	8.6	X	X	X	X	X	X	X	X	X	X						
TRIAL MATERIAL																	
NPH dosing (Date and Dose)	8.1.6										X						
Dosing (Date, Dose and time of trial insulin), every day	8.3.2	X	X	X	X	X	X	X	X	X	X						
New prescribed dose of trial insulin	8.3.2	X	X	X	X	X	X	X	X	X							
Dispensing visit	9.4	X	X	X	X	X	X	X	X	X	X						
Drug accountability	9.4	X	X	X	X	X	X	X	X	X	X	X					
IWRS session	10	X	X	X	X	X	X	X	X	X	X						
REMINDERS																	
Attend visit fasting	8.1.4		X		X			X			X	X					
Confirmation of unchanged OAD	8.2.6	X	X	X	X	X	X	X	X	X	X	X					
Hand-out and instruct	8.1.2	X															

Protocol
Trial ID: NN1250-4252

UTN: U1111-1184-8175
EudraCT no.: 2016-002801-20

Date:
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23 February 2018
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Status:
Page:

Final
22 of 108

Novo Nordisk

Trial NN1250-4252	Protocol section	Maintenance 2 36 weeks									End Of Treatment	Follow-up	Premature discontinuation					
		V57	V61	V65	V69	V73	V77	V81	V85	V89			V93	V94	V95	V57A	V69A	V81A
Weekly Phone Contact number (P) (For details see separate flow chart below)		P58 P59 P60	P62 P63 P64	P66 P67 P68	P70 P71 P72	P74 P75 P76	P78 P79 P80	P82 P83 P84	P86 P87 P88	P90 P91 P92								
Timing of visit (maintenance weeks)		0	4	8	12	16	20	24	28	32	36	37	40	0	12	24	36	
Visit window (days) in Abbott BG meter			±3	±3	±3	±3	±3	±3	±3	±3	±3	+5	+5					
Hand-out diary		X	X	X	X	X	X	X	X	X	X	X						
Collect diary		X	X	X	X	X	X	X	X	X	X	X		X	X	X		
Make appointment for eye examination	8.4.6								X									
End Of Treatment	8.1.6										X						X	
End of trial	7											X					X	
Sign off Casebook												X					X	

Table 2–3 Flow chart – phone contacts during titration and maintenance 1

ONLY applicable until the new glycaemic data collection system (an Abbott BG-meter and paper diary) is available. As soon as the new glycaemic data collection system is available the subject should come for a visit 57 and enter maintenance 2 (Table 2–2) irrespectively of their current visit.

NN1250-4252 Phone contacts during titration and maintenance 1 (P) Time shown in site visit flow chart	Protocol section	P3-P53	PX
Contact window (days)		± 3	± 5
Criteria for premature discontinuation of trial products	6.4	X	
Concomitant medication	8.2.5	X	
Concomitant medication (Diabetes)	8.2.6	X	X
Self-measured plasma glucose, Once daily (pre-breakfast)	8.3.1	X	
First date on trial product	8.3.2	P3	
Dosing	8.3.2	X	
New prescribed dose of trial insulin	8.3.2	X	
Adverse events	8.4.1 12	X	X
Hypoglycaemic episodes	8.4.2	X	X
Technical complaints	12.4	X	
End of Trial	7		

Table 2–4 Flow chart – phone contacts during maintenance 2

NN1250-4252 Phone contacts during maintenance period 2 (P) Time shown in site visit flow chart	Protocol section	P58-P92	PX
Contact window (days)		± 3	± 5
Criteria for premature discontinuation of trial products	6.4	X	
Concomitant medication	8.2.5	X	
Concomitant medication (Diabetes)	8.2.6	X	X
Self-measured plasma glucose, Once daily (pre-breakfast)	8.3.1	X	
Dosing	8.3.2	X	
New prescribed dose of trial insulin	8.3.2	X	
Adverse events	8.4.1 12	X	
Hypoglycaemic episodes	8.4.2	X	X
Technical complaints	12.4	X	X
End of Trial	7		

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP¹ and applicable regulatory requirements, and in accordance with the Declaration of Helsinki².

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

Therapeutic area

Type 2 diabetes mellitus (T2DM) is characterised by insulin resistance, impaired insulin secretion and increased hepatic glucose output due to glucagon dysregulation resulting in chronic hyperglycaemia³. A number of landmark studies have demonstrated the importance of maintaining tight glycaemic control to reduce the risk of long-term complications associated with diabetes⁴. The current treatment cascade follows a stepwise approach comprising lifestyle changes in combination with pharmacological intervention. Metformin is recommended as initial pharmacological therapy, followed by combination therapy with other oral anti-diabetic drugs (OADs), glucagon-like peptide 1 receptor agonists (GLP-1) and insulin as the disease progresses⁵.

Insulin treatment is associated with hypoglycaemia, and fear of hypoglycaemia, especially severe hypoglycaemia, is widely acknowledged as the main limiting factor for achieving tight glycaemic control. Given the impact on quality of life, the potentially life-threatening consequences of severe and nocturnal hypoglycaemia, reducing the risk of hypoglycaemia is critical to the lives of patients.

Information on the hypoglycaemia profile of insulin products is considered an important part of the information foundation for health care professionals in considering individualised treatment. Thus it is important to compare different insulin analogues in terms of efficacy and safety to be able to offer subjects with T2DM in need of insulin treatment the best possible option.

Insulin degludec

Insulin degludec (IDeg) is an insulin analogue with unique pharmacological properties and a long duration of action⁸. IDeg provides similar glycaemic control to comparators with a 14–18% lower risk of confirmed hypoglycaemia and a 23–38% lower risk of nocturnal confirmed hypoglycaemia compared to insulin glargine 100 U/mL (IGlar 100 U/mL) in T2DM (phase 3a trials)^{6,7}. Moreover, in the SWITCH 2 trial (T2DM, phase 3b trial) IDeg was associated with a 23% lower risk of overall confirmed symptomatic hypoglycaemia, a 25% lower risk of nocturnal confirmed symptomatic hypoglycaemia and a 51% lower risk of severe hypoglycaemia compared to IGlar 100 U/mL⁸. The hypoglycaemic risk reduction for IDeg compared to IGlar 100 U/mL was more pronounced in the maintenance period in all trials⁶⁻⁸.

IDeg is developed in two strengths (100 U/mL and 200 U/mL) that are bio-equivalent in clinical pharmacology trials. IDeg has been approved in more than 70 countries globally and is indicated for treatment of diabetes mellitus as monotherapy, in combination with oral anti-diabetic agents and

GLP-1, and as part of a basal-bolus insulin regimen in adults and children from the age of 1 year (GLP-1 co-usage and paediatric indication <18 years is not an approved indication in all countries with market authorisation). For further details please refer to the current version of the IDeg Investigator's Brochure (IB)⁹, of the Tresiba[®] summary of product characteristics (SmPC)¹⁰, U.S. Label Information (LI)¹¹ and any updates thereof.

Insulin glargine 300 U/mL

Insulin glargine 300 U/mL (IGlar 300 U/mL), a new long-acting insulin analogue approved in USA, Canada, EU and Japan, is indicated for treatment of diabetes mellitus as monotherapy, in combination with oral anti-diabetic agents and as part of a basal-bolus insulin regimen. The development programme established comparable efficacy and safety versus IGLar 100 U/mL^{12, 13}. Furthermore, a tendency towards a reduction in the incidence of hypoglycaemia with IGLar 300 U/mL was found in subjects with T2DM. For further details, please refer to the current version of the Toujeo[®] SmPC¹⁴ or local labelling^{15, 16}.

For an assessment of benefits and risks of the trial, see Section [18.1](#).

3.2 Rationale for the trial

The overall purpose of the trial is to compare the hypoglycaemia profile and the insulin dose requirements of IDeg versus IGLar 300 U/mL in subjects with T2DM inadequately controlled on basal insulin with or without OADs.

Both IDeg and IGLar 300 U/mL used IGLar 100 U/mL as comparator during the phase 3 development programme achieving non-inferiority with respect to the glycaemic endpoint measured by the reduction in HbA_{1c} from baseline to end of trial. In T2DM patients treatment with IDeg showed a consistent hypoglycaemia benefit compared to IGLar 100 U/mL whereas a lower number of hypoglycaemic episodes for IGLar 300 U/mL compared to IGLar 100 U/mL was primarily observed during the first weeks of treatment^{13, 17}.

IGlar 300 U/mL has a lower bioavailability compared to IGLar 100 U/mL leading to higher mean pre-breakfast SMPG values and FPG levels for patients treated with IGLar 300 U/mL compared to IGLar 100 U/mL. This is most evident during the first weeks of treatment and makes assessment of a possible hypoglycaemic benefit difficult during this time period.

Across the trial programme for IGLar 300 U/mL a 12-17% higher dose usage was needed with IGLar 300 U/mL to reach the same level of glycaemic control at end of trial compared to IGLar 100 U/mL^{12, 18}. In the IDeg phase 3a program an overall higher dose of approximately 10% was seen for IGLar 100 U/mL compared to IDeg¹⁹ and in the SWITCH 2 trial a post hoc analysis demonstrated significantly lower insulin dose with IDeg compared with IGLar 100 U/mL after 32 weeks of treatment.

The present trial seeks to confirm the safety of IDeg particularly in the assessment of overall, nocturnal and severe hypoglycaemic episodes when similar glycaemic control levels have been

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~~CONFIDENTIAL~~

Date:	23 February 2018	Novo Nordisk
Version:	3.0	
Status:	Final	
Page:	26 of 108	

obtained. Moreover, the trial will provide guidance on insulin dose requirements for achieving glycaemic control.

4 Objective(s) and endpoint(s)

4.1 Objective(s)

Primary objective

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

Secondary objectives

To compare IDeg and IGlax 300 U/mL in terms of basal insulin requirement.

To compare IDeg and IGlax 300 U/mL in terms of safety and parameters of glycaemic control.

4.2 Endpoint(s)

4.2.1 Primary endpoint

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

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

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

4.2.3 Other endpoints

Other efficacy endpoints

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

Other safety endpoints

- Hypoglycaemia
 - Number of severe or BG confirmed symptomatic hypoglycaemic episodes during treatment (up to 88 weeks)
 - Number of nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes during treatment (up to 88 weeks)
 - Number of severe hypoglycaemic episodes during treatment (up to 88 weeks)
- Number of adverse events during treatment (up to 88 weeks)
- Change in clinical evaluations from baseline to end of treatment (up to 88 weeks) in terms of:
 - Vital signs (including blood pressure and pulse)
 - Dilated funduscopy or fundus photography
 - Electrocardiogram (ECG)
- Change in body weight from baseline to end of treatment (up to 88 weeks)
- Change in central laboratory assessments from baseline to end of treatment (up to 88 weeks) in terms of
 - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes, leucocytes)
 - Biochemistry (creatinine, alanine aminotransferase , aspartate aminotransferase , alkaline phosphatase , sodium, potassium, albumin, total bilirubin)
- Special laboratory assessment during treatment (up to 88 weeks)in terms of
 - Anti-insulin antibodies

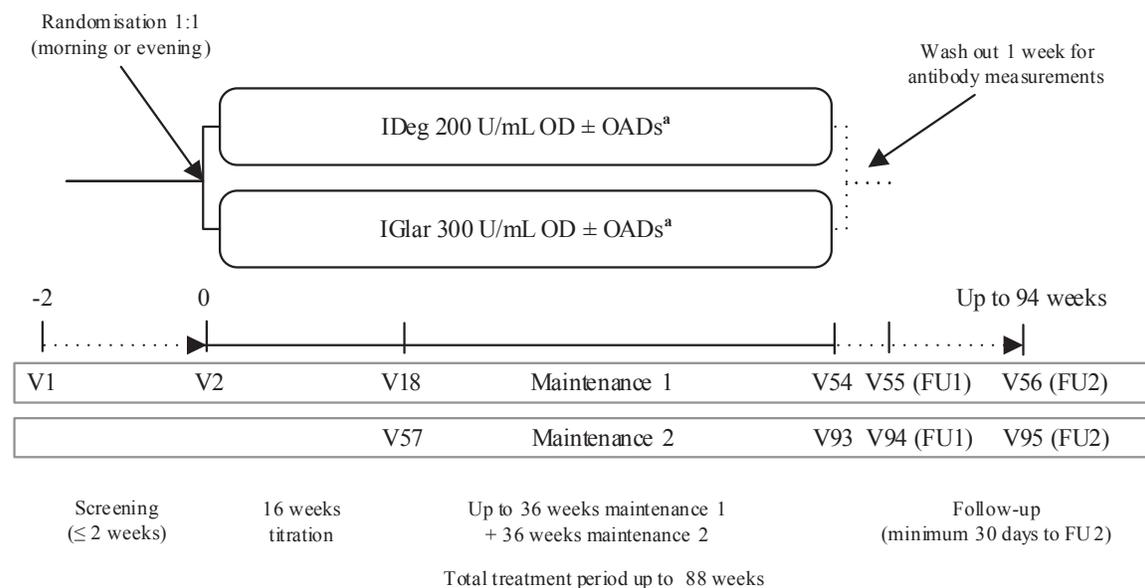
5 Trial design

5.1 Type of trial

This is a up to 88-week, randomised (1:1), open-label, parallel, multi-centre, multi-national, treat-to-target, active controlled trial comparing efficacy and safety of IDeg 200 U/mL with IGLar 300 U/mL both administered OD ± OADs in subjects with T2DM previously treated with basal insulin OD or twice daily (BID) ± OADs excluding sulfonylureas/glinides. Type and dose of any pre-trial OAD treatment should remain unchanged throughout the trial.

The trial design is summarised schematically in [Figure 5–1](#). The total trial duration will be up to 94 weeks divided into the following periods:

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



^aOral Anti-diabetic Drugs (OADs): Metformin, Dipeptidyl peptidase-4 inhibitor, Sodium-glucose co-transporter 2 inhibitor, Alpha-glucosidase-inhibitors (acarbose), Thiazolidinediones, marketed oral combination products only including the products listed in inclusion criteria 5a-5e.

IDeg: insulin degludec, IGLar: insulin glargine, OD: once daily, FU: follow-up, EOT: End of Treatment

Figure 5–1 Trial design

5.2 Rationale for trial design

In this trial an open-labelled trial design is chosen to minimize inconvenience for the subjects since a blinded trial due to different pen injector systems would require a double dummy approach.

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

For subjects randomised to IDeg OD, the daily basal insulin dose should be reduced by 20% from pre-trial dose.

Subjects randomised to IGLar 300 U/mL should switch unit-to-unit, if they prior to randomisation received basal insulin once daily. For subjects that prior to randomisation received a BID basal insulin regimen, the following applies:

- US subjects that prior to randomisation received a BID basal regimen with Neutral Protamine Hagedorn (NPH) insulin should have their total daily NPH dose reduced by 20% and given once daily.
- US subjects that prior to randomisation received a BID basal regimen with other basal insulin types should have their total daily basal insulin dose added up and injected once daily.
- EU subjects that prior to randomisation received a BID basal regimen with any basal insulin type should have their total daily basal insulin dose reduced by 20% and given once daily.

The basal insulin IDeg and IGLar 300 U/mL 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 1:1 randomisation to morning or evening dosing of the basal insulin is applied to avoid any confounding from injection time on a particular time interval (such as nocturnal) during which subjects would be at highest risk of hypoglycaemic episodes.

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

Due to an unusual data reporting pattern of hypoglycaemia and glycaemic values being linked to the glycaemic data collection system (the combined use of MyGlucoHealth with the electronic diary) it

was decided on 13 February 2018 to apply a new data collecting system consisting of an Abbott BG-meter and a paper diary.

To accommodate changes in the data collection system and to ensure sufficient data collection with respect to the confirmatory endpoints a new maintenance period (maintenance 2) of 36 weeks duration was included in the trial.

5.3 Treatment of subjects

Insulin treated subjects with T2DM can enter the trial if they present with an HbA_{1c} equal to or below 9.5% (80 mmol/mol) and have been treated with basal insulin for ≥ 90 days prior to the day of screening (V1) with or without OADs (metformin, DPP-4i, SGLT2i, thiazolidinedione, alpha-glucosidase-inhibitors or marketed oral combination products only including the products listed in inclusion criteria 5a-5e), at stable doses for ≥ 90 days prior to V1.

Pre-trial treatment with IDeg or IGlax 300 U/mL is not allowed within 90 days prior to the screening visit. Any previous use of bolus insulin, insulin pump or pre-mix insulin excludes subjects from the trial, as well as use of any GLP-1 receptor agonist (e.g., exenatide or liraglutide) or SU/glinides, all within the 90 days prior to the screening visit.

At randomisation (V2) subjects who met all inclusion criteria and no exclusion criteria will be randomly allocated 1:1 into one of two treatment arms:

- IDeg -200 U/mL OD \pm OADs
- IGlax -300 U/mL OD \pm OADs

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

Following randomisation pre-trial insulin treatment must be discontinued and the subject switched to randomised treatment.

Type and dose of any pre-trial OAD treatment should remain unchanged throughout the trial and subjects should continue pre-trial OAD treatment from screening (V1) to end of treatment (V54 or V93), unless for safety reasons.

The maximum duration of treatment will be 88 weeks. No maximum trial insulin dose is specified. Doses are adjusted according to plasma glucose values (see titration guideline; [Appendix A](#)). Surveillance of insulin titration will be performed by Novo Nordisk.

At end of treatment (V54 or V93) all subjects will be switched to insulin NPH for at least one week to ensure that all IDeg/IGlax is washed out when measuring anti-insulin antibodies.

After End of treatment each subject will have a 30-day safety follow-up period including two follow-up contacts (FU1 and FU2).

FU1 (V55 or V94) will be at least 7 days after end of treatment (V54 or V93). The purpose is to collect all treatment emergent adverse events (AEs) including hypoglycaemia and antibody samples.

FU2 (V56 or V95) will be at least 30 days after end of treatment (V54 or V93). The purpose is to collect information on anti-diabetic medication and AEs including hypoglycaemia occurring in the period between the two follow-up contacts.

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

For both treatment arms diet and exercise counselling is continued as per the standard of care at the investigational site.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products, either at the scheduled end of treatment visit or if trial product is discontinued prematurely, the subject will be instructed to switch insulin treatment to the intermediate acting insulin NPH until the first follow-up visit FU1. At FU1 the subject should be switched to a suitable marketed product at the discretion of the investigator. Doses of subsequent anti-diabetic treatment should be carefully titrated based on blood glucose measurements, considering the long half-life of IMPs.

5.5 Rationale for treatment

The treat-to-target design and consequent visit schedule is used in order to ensure optimal insulin titration based on self-measured plasma glucose (SMPG) values and to ensure improvement in glycaemic control. The 16 week titration period is applied to ensure optimal time to achieve improved and stable HbA_{1c} for both treatments before entering maintenance period 1. The second maintenance period is applied to obtain sufficient data for efficacy and safety evaluation after including the new data collecting system.

The switch from trial insulin treatment to the 'washout' insulin (NPH) between the end of treatment visit (V54 or V93) and the 7-day follow-up visit (FU1), is done in order to provide basal insulin coverage while reducing the level of IDeg/IGlar present at antibody sampling and consequently to reduce the possibility for interference with antibody measurements.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 2,271

Number of subjects planned to be randomised: 1,590

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 above or equal to 18 years at the time of signing informed consent.
3. Subjects fulfilling at least one of the below criteria^a:
 - a. Experienced at least one severe hypoglycaemic episode within the last year (according to the ADA definition, April 2013^b)
 - b. Moderate chronic renal failure, defined as glomerular filtration rate 30 - 59 mL/min/1.73 m² per CKD-EPI^{20,21} by central laboratory analysis
 - c. Hypoglycaemic symptom unawareness^c
 - d. Treated with insulin for more than 5 years
 - e. 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. Subjects diagnosed with type 2 diabetes mellitus.
5. Treated with basal only insulin (once daily or twice-daily insulin (insulin detemir; insulin glargine 100 U/mL, biosimilar of insulin glargine 100 U/mL or NPH)) ≥ 90 days prior to the day of screening with or without any of the following anti-diabetic drugs/regimens with stable doses for ≥ 90 days prior to screening:
 - a. Metformin
 - b. Dipeptidyl peptidase-4 inhibitor
 - c. Sodium-glucose co-transporter 2 inhibitor
 - d. Alpha-glucosidase-inhibitors (acarbose)
 - e. Thiazolidinediones
 - f. Marketed oral combination products only including the products listed in criteria 5a-5e
6. HbA_{1c} $\leq 9.5\%$ (80 mmol/mol) at screening by central laboratory analysis.
7. BMI ≤ 45 kg/m².
8. Ability and willingness to adhere to the protocol including self-measurement of plasma glucose according to the protocol.

^aFor inclusion criterion 3 the aim is to include minimum 80% of individuals with a previous episode of hypoglycaemia (3e). The remaining subjects will have to fulfil at least one of criteria a-d.

^bAn 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.

^cHistory 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. Acute impairment of glycaemic control requiring immediate intensification of treatment to prevent severe metabolic dysregulation (e.g. diabetes ketoacidosis) \leq 90 days prior to the day of the screening.
2. Known or suspected hypersensitivity to trial product(s) or related products.
3. Previous participation in this trial. Participation is defined as signed informed consent.
4. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).

For Denmark: Contraceptive measures considered adequate include:

- a. intrauterine devices or hormonal contraception (oral contraceptive pills, implants, transdermal patches, vaginal rings or long-acting injections)

For Estonia: Contraceptive measures considered adequate include:

- a. double barrier method (a combination of male condom with either cap, diaphragm or sponge with spermicide)

For Germany: The following contraceptive measures are considered adequate:

- a. combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, transdermal or intravaginal)
 - b. progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
 - c. intrauterine device
 - d. intrauterine hormone-releasing system
 - e. sexual abstinence
 - f. vasectomised partner
 - g. double barrier method (a combination of male condom with either cap, diaphragm or sponge with spermicide)
5. Participation in any clinical trial of an approved or non-approved investigational medicinal product (IMP) within 30 days prior to screening.

6. Any of the following: myocardial infarction, stroke or hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening and between screening and randomisation.
7. Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
8. Planned coronary, carotid or peripheral artery revascularization known on the day of screening.
9. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR <30 mL/min/1.73 m² as defined by KDIGO 2012 classification²² using isotope dilution mass spectrometry (IDMS) for serum creatinine measured at screening.
10. Impaired liver function, defined as ALT or AST ≥ 2.5 times upper limit of normal at screening.
11. Inadequately treated blood pressure as defined as Grade 3 hypertension or higher (Systolic ≥ 180 mmHg or diastolic ≥ 110 mmHg) at screening.
12. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening.
13. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).
14. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within the past 90 days prior to randomisation.
15. Presence or history of malignant neoplasms within the last 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinomas in-situ are allowed.
16. Any condition, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

6.4 Criteria for premature discontinuation of trial product

Efforts should be made so that subjects attend and complete all scheduled visit procedures. Subjects should stay in the trial irrespective of lack of adherence to randomised treatment, lack of adherence to visit schedule or missing assessments. Only subjects who decline any further contact with the site in relation to the trial will be considered as withdrawn from the trial (see Section [6.5](#)).

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

The subject must be prematurely discontinued from trial product if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria.
2. Pregnancy.
3. Intention of becoming pregnant.
4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.
5. Initiation of concomitant medication(s) for more than 14 calendar days, which in the investigator's opinion could affect weight or glucose metabolism.
6. Lack of efficacy; if all of the fasting SMPG values taken on three consecutive days or if any of the FPG samples analysed by the central laboratory exceeds the limit of:
 - a. 13.3 mmol/L (240 mg/dL) from visit 18 to visit 26 (both inclusive)
 - b. 11.1 mmol/L (200 mg/dL) from visit 26 (not included) to visit 54 or visit 93 (included)

and if no treatable intercurrent cause for the hyperglycaemia has been identified, the subject must be called for a confirmatory FPG measurement at a scheduled or unscheduled visit as soon as possible. A confirmatory FPG must be obtained and analysed by the central laboratory. If this FPG exceeds the limits described above, the trial product must be discontinued.

See Section [8.1.9](#) for procedures to be performed for subjects discontinuing trial product prematurely.

6.5 Withdrawal from trial

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

If the subject considers withdrawing consent the investigator must underline to the subject the importance of continuing in the trial despite trial product discontinuation. If the subject agrees to discontinue trial products but to stay in the trial, procedures described in section [8.1.9](#) must be followed.

Only subjects who decline any further contact with the site in relation to the trial, and hence do not agree to provide information concerning morbidities, which are relevant for the assessment of AEs and/or other trial endpoints at the planned end of trial, should be withdrawn from trial.

See Section [8.1.10](#) for procedures to be performed for subjects withdrawing consent.

A subject will be considered lost to follow-up if he/she repeatedly fails to attend the scheduled visits and the Investigator is unable to establish contact with the subject.

The following actions must be taken in relation to a subject who fails to attend the site for a required visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible.
- The site must re-train the subject in the importance of maintaining the scheduled visits.
- In cases in which the subject is deemed lost to follow-up the investigator must make every effort to regain contact with the subject (e.g. telephone calls to friends or family members, e-mails or certified letter to the subject as applicable). These contact attempts must be documented in the subject's medical records. Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the trial with the primary reason being "lost to follow-up".

6.6 Subject replacement

Subjects who discontinue trial product prematurely will not be replaced.

6.7 Rationale for trial population

A population of insulin-treated subjects with T2DM presenting with an HbA_{1c} equal to or below 9.5% while treated continuously with basal insulin with or without OADs for at least 90 days and who recently have experienced hypoglycaemia or have increased risk of severe hypoglycaemia has been chosen for this trial. This population reflects a general T2DM population qualifying for optimisation of basal insulin treatment. The trial is not excluding individuals at high risk of developing hypoglycaemia making the population generalizable for the T2DM population. Subjects requiring treatment with basal bolus are not included to avoid the confounding element of bolus insulin. Treatment with SUs/glinides and insulin in combination creates an increased risk of hypoglycaemia, and therefore, SU/glinides are not allowed as pre-trial, and subsequently trial treatment.

A BMI ≤ 45.0 kg/m² was chosen to include as broad a population as possible, while excluding severely insulin resistant subjects in order to secure a rather homogenous population with regard to insulin needs.

The inclusion and exclusion criteria applied in this trial should ensure relevance of trial results for a broad population of subjects with T2DM.

The 20% reduction of IDeg when transferring from pre-trial insulin regimen, is to reduce the risk of subjects experiencing hypoglycaemia in the initial treatment phase and to secure equal and comparable levels of glycaemic control initially, given that IGLar 300 U/mL has a known lower potency compared to IGLar 100 U/mL and hence also IDeg.

7 Milestones

Planned duration of recruitment period, which is from first patient first visit (FPFV) – last patient first visit (LPFV): 24 weeks.

End of trial is defined as last patient last visit (LPLV).

Recruitment:

The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects screened during the recruitment period and found eligible for randomisation can be randomised within the timelines specified in the flow chart, see Section [2](#).

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure²³ it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)²⁴, the Food and Drug Administration Amendment Act²⁵, European Commission Requirements^{26, 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

Timing of assessments and procedures are specified in the flow chart (see Section [2](#)). This section includes a description.

Informed consent must be obtained before any trial related activity, see Section [18.2](#).

8.1.1 Screening visit (Visit 1)

The subjects will attend a screening visit in order to assess eligibility.

Before any trial-related activity, the investigator must give the subject oral and written information about the trial in a form that the subject can read and understand. The informed consent process must be completed before any trial-related activity.

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 will 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 informed consent form must be signed and personally dated by the person who seeks the informed consent.

The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed. The informed consent will include permission for the investigator to obtain information from the subject and/or from his/her primary physician or other healthcare professional /next of kin on vital status. The consent will include that this information can be obtained until trial completion even if the subject stops the investigational products and/or trial procedures prematurely.

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirements and adhere to ICH GCP¹ and the Declaration of Helsinki².

The date of informed consent must be transcribed to the eCRF.

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

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. Only subjects who have signed the informed consent form should be included on the logs. The subject screening log and subject enrolment log may be combined in one log.

At screening, subjects will be provided with a card stating that they are participating in a trial and giving 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 it after the last visit.

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. The first 3 digits indicate the site number and the last 3 digits are unique for the subject.

A screening session must be performed in the IWRS, see Section [10](#).

All assessments related to the inclusion and exclusion criteria must be performed. If any inclusion criterion is answered “no” or any exclusion criterion answered “yes”, the subject is a screening failure and no further assessments should be done. Please refer to the flow chart in section [2](#) for the full list of assessments and procedures to be performed at this visit.

In- or exclusion criteria cannot not be ticked “Yes” or “No” in the electronic case report form (eCRF) before source data is available. In this case “Result pending” must be chosen. This is particularly relevant for lab samples and in some cases the ECG and eye examination result. Subjects cannot be randomized until all results are available.

The subject has to complete the Baseline Hypo Questionnaire at the screening visit.

8.1.1.1 Screening failures

For screening failures the screening failure form in the eCRF must be completed with the reason for not continuing in the trial. Serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up on serious adverse events (SAEs) must be carried out according to Section [12](#).

A screening failure session must be made in the IWRS. When data has been monitored and queries have been resolved the case book must be signed.

Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria, this includes re-sampling if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters. Re-sampling is allowed in case the sample is haemolysed, leaked during transit etc.

8.1.2 Randomisation visit (V2)

All screening including laboratory results must be available and reviewed and the subject confirmed eligible before randomisation can take place. Randomisation should take place as soon as trial products are available on site and no later than 14 days after screening visit. A randomisation session must be performed in IWRS; see Section [10](#) and trial product must be dispensed.

The Investigator should record the following in the eCRF:

- Last date on pre-trial insulin
- Total dose of pre-trial insulin administered within the last 24 hours
- Frequency of pre-trial insulin injections
- First date on trial product (registered at P3)
- First dose of trial product (registered at P3)
- Time point of trial product administered (morning or evening as specified by IWRS)

The subject must attend randomisation visit fasting. For definition of fasting, please see Section [8.1.4](#).

At randomisation baseline laboratory values of HbA_{1c} and anti-insulin antibodies will be taken. Please refer to the flow chart in section [2](#) for the full list of assessments and procedures to be performed at this visit.

A BG meter and an electronic diary (eDiary) must be provided to the subjects at V2. Subjects must be trained in the use of the BG meter. A practice eDiary must be completed before the eDiary can be used. Subject must be instructed that entries must be made according to the protocol, see Section [8.3.1](#), [8.3.2](#) and [8.4.2](#) and instructions provided.

8.1.3 Phone contacts

Before any phone contact, both the Investigator and subject should agree on the timing and direction of the call. The Investigator remains responsible for ensuring that the phone contacts occur even if it is agreed that the subject should call the site.

A phone contact may be converted to a site visit if needed. For scheduled phone contacts and their time points; see Section [2](#).

8.1.4 Fasting visits

The subjects must attend the visits specified in section [2](#) in a fasting condition. Fasting is defined as at least eight hours without drink or food intake prior to the visit except for water.

No diabetes treatment (neither trial insulin, nor any OADs) is allowed up to eight hours prior to the blood sampling. Non-anti-diabetic medication is still allowed to be taken.

If a subject attends the visit non-fasting, then the subject's blood samples should be re-scheduled preferable within the next two working days. If blood sampling has already been done before realising the subject was not fasting, only the FPG needs to be re-drawn.

8.1.5 Maintenance 2 initiation visit (V57)

As soon as the new glycaemic data collection system (an Abbott BG-meter and paper diary) is available all subjects should come for a maintenance 2 initiation visit (V57) to enter maintenance 2 ([Table 2-2](#)) irrespectively of their current visit in maintenance 1. Subjects should not complete all the maintenance 1 visits.

Subjects who discontinued trial drug treatment prematurely during titration or maintenance 1 can enter maintenance 2 off treatment and continue to follow the abbreviated visit schedule as specified in section [8.1.9](#). These subjects should come for a maintenance 2 initiation visit (V57A) to enter maintenance 2 ([Table 2-2](#)) irrespectively of their current visit maintenance 1. Subjects should not complete all the maintenance 1 abbreviated visits.

At V57 the subject should stop using their own BG meter.

An Abbott BG meter and a diary must be provided to the subject. The subject must be trained in the use of the BG meter and instructed that entries must be made in the diary according to Section [8.3.1](#) and the instructions provided

8.1.6 End of Treatment visit (V54 or V93)

Subjects entering maintenance 2 should attend the V93 End of Treatment visit.

Subjects who do not re-consent to enter the maintenance period should attend the V54 End of Treatment visit as soon as possible.

At the end of treatment visit (V54 or V93) the treatment with trial product must be stopped and the subjects will be instructed to switch insulin treatment to the intermediate acting insulin NPH until the first follow-up visit (FU1). A completion session must be performed in IWRS, see Section [10](#). NPH will be dispensed as part of the completion session.

Last date on the randomised trial product (basal insulin) must be recorded in the eCRF.

Since NPH insulin is an intermediate acting insulin, it should be administered twice daily. To determine the dose of insulin NPH to be taken during the follow-up period, the total daily basal dose at end of the treatment period should be reduced by 20% and divided into two doses; one to be administered in the morning and one in the evening.

Date and dose of first injection of insulin NPH must be recorded in the eCRF.

Please refer to the flow chart in section [2](#) for the full list of assessments and procedures to be performed at this visit.

8.1.7 Follow up visits

Subjects entering maintenance 2 should attend:

- FU1 (V94) a site visit which must take place 7-12 days after the end of treatment visit (V93)
- FU2 (V95) a site visit which must take place 30-35 days after the end of treatment visit (V93)

Subjects who do not re-consent to enter maintenance 2 should attend:

FU1 (V55) a site visit which must take place 7-12 days after the end of treatment visit (V54)

FU2 (V56) a site visit which must take place 30-35 days after end of treatment (V54)

Follow-up visit FU1 (V55 or V94)

At the first follow up visit (V55 or V94) treatment with insulin NPH must be stopped.

The following data will be collected:

- Date and dose of last injection of insulin NPH
- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)
- Technical complaints
- Antibody sample

Please refer to the flow chart in section [2](#) for the full list of assessments and procedures to be performed at this visit.

Follow-up visit FU2 (V56 or V95)

The following data will be collected:

- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)

8.1.8 Unscheduled site visits

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

If more trial product is needed an additional dispensing session in the IWRS must be performed.

If blood resampling is needed the laboratory requisition form must be completed with the visit number to which the sample belongs.

8.1.9 Premature discontinuation of trial product

If a subject prematurely discontinues trial product, the investigator must undertake procedures similar to those for the end of treatment visit (V54 or V93) as soon as possible including fasting blood sampling and dispensing of wash-out insulin NPH, see Section [8.1.6](#).

Treatment discontinuation must be performed in IWRS.

Furthermore two follow up visits similar to FU1 and FU2 must be performed 7-12 and 30-35 days after discontinuation of trial product, respectively.

Subjects who discontinued trial drug treatment prematurely during titration or maintenance 1 should come for an abbreviated maintenance 2 initiation visit (V57A) to enter maintenance 2 ([Table 2-2](#)) irrespectively of their current visit. Subjects should not complete all the maintenance 1 abbreviated.

Follow-up visit FU1 (V55 or V94)

At the first follow up visit (V55 or V94) the subject should be switched to treatment with a suitable marketed product at the discretion of the investigator.

The following data will be collected:

- Date and dose of last injection of insulin NPH prior to V55
- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)
- Technical complaints
- Antibody sample

Follow-up visit FU2 (V56 or V95)

The following data will be collected:

- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)

In addition, subjects prematurely discontinued from trial product should come in for abbreviated site visits:

- V69A
- V81A

The abbreviated site visits can be converted to phone contacts if needed.

The following data will be collected:

- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)
- Blood sample to measure HbA_{1c} (only if site visit)

In between the abbreviated site visits listed above **monthly phone contacts (PX visits)** should be performed until the originally planned end of treatment.

The following data will be collected:

- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)

The earliest of the abbreviated site visits or monthly phone contacts (whichever comes first) should be scheduled at least 30 days after FU2. If the timing of a monthly phone contact (PX visit) is less than two weeks from a planned abbreviated site visit, the phone contact can be omitted.

Subjects prematurely discontinued from trial products should come in for a **final visit (V93A)** at the **originally planned end of treatment date** to collect:

- Date and dose of basal insulin
- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)
- Blood sample to measure HbA_{1c}

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

8.1.10 Withdrawal from trial

If a subject withdraws consent, the investigator should aim to undertake procedures similar to those for the end of treatment visit (V54 or V93) as soon as possible.

If the subject agrees, the follow up visits (FU1 and FU2) must be performed 7-12 and 30-35 days after discontinuation of trial product.

The End-of-Treatment and End of Trial forms must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be made in IWRS. The case book must be signed.

Although a subject is not obliged to give his/her reason(s) for withdrawing consent, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

Where the reasons are obtained, the primary reason for withdrawing consent must be specified in the End-of-Trial form in the eCRF.

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

8.1.11 Review of results

Review of ECG results, eye examination report, laboratory reports, data entered in the diaries, etc. must be documented either on the documents, printouts or in the subject's medical record.

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

8.2 Subject related information/assessments

8.2.1 Demography

Demography will be recorded at screening, unless not permitted by local regulations, and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.2.2 Diabetes history

Diabetes history will be recorded at screening and consists of:

- Date of diagnosis of type 2 diabetes

8.2.3 Hypoglycaemia unawareness

Information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8²⁸.

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

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

8.2.4 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 (V1)) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Date of diagnosis of type 2 diabetes should be reported separately in the Diabetes History Form in the eCRF.

Medical history is a medical event that the subject has experienced in the past. Only 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.

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

8.2.5 Concomitant medication

A **concomitant medication** is any medication, other than the pre-trial insulin, trial products and OADs, which is taken during the trial, from the screening visit (V1) until end of treatment (V54 or V93).

Details of any concomitant medication must be recorded at V1. 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.

8.2.6 Concomitant medication (Diabetes)

Any diabetes medication other than the trial product(s) which is taken during the trial, from the screening visit (V1) until FU2 (V56 or V95) must be recorded in a separate concomitant medication (diabetes) form in the eCRF.

At V1 the pre-trial insulin and pre-trial OADs must be recorded including:

- Trade name or generic name
- Total daily dose
- Start date
- Stop date or continuation

For subjects treated with OADs it is the start date and dose of latest stable OAD dose which should be reported.

At the randomisation visit (V2) pre-trial insulin must be discontinued and a stop date recorded in the eCRF. For subjects treated with OADs, the investigator should at each weekly contact (V2 until V55 or V94), confirm with the subject that dose and frequency of OADs has been unchanged. This should be documented in the medical records.

8.2.7 Childbearing potential

It must be recorded in the eCRF whether female subjects are of childbearing potential. Reason for not being of childbearing potential must be documented in the medical records.

Pregnancy testing must be performed on female subjects of childbearing potential as described in Section [8.5.2](#). Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 1 week after end of treatment.

Female of non-childbearing potential is defined as:

- Female who has undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation
- Postmenopausal defined as no menses for 12 months without an alternative medical cause
- Other medical reasons preventing childbearing potential

8.2.8 Tobacco use

Details of tobacco use must be recorded at V1. Smoking is defined as smoking at least one cigarette or equivalent daily.

Smoking status:

- Never smoked
- Previous smoker
- Current smoker

8.3 Efficacy assessments

8.3.1 Self-measured plasma glucose

At V2, subjects will be provided with a BG meter including auxiliaries as well as instructions for use. The subjects will be instructed in how to use the device.

As soon as the new glycaemic data collection system (an Abbott BG-meter and paper diary) is available the subject should come for a V57 or V57A to enter maintenance 2 ([Table 2-2](#)).

At V57 or V57A subjects will be provided with a new glycaemic data collection system.

The BG 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.

Only the BG meter provided by Novo Nordisk should be used for the measurements required in the protocol.

Subjects must be instructed to measure their pre-breakfast SMPG daily from V57 to End of Treatment (V93).

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

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

8.3.2 Insulin dose

After applying the new glycaemic data collection system at V57 the subjects should be instructed to report date, dose and time point of basal insulin in the diary on a daily basis.

The recommended insulin doses will be calculated in the eCRF on recommendations from the Insulin Titration Guideline (see [Appendix A](#)). At each visit/phone contact the Investigator will titrate the subjects by making prescribed dose adjustments based on the recommendation from the eCRF if applicable.

The subject should report the following in the diary:

- Date, dose and time of trial basal insulin daily

The Investigator should record the following in the eCRF:

- Prescribed doses of trial products
- Reason for deviating in dose adjustments from the titration guideline
- Actual daily dose of trial product including injection time
- Last date on trial product
- Last dose of trial product

8.4 Safety assessments

All safety assessments are outlined in the flow chart in section [2](#).

In case of an abnormal and clinically significant finding, 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.

8.4.1 Adverse events

During each contact (site visits and phone contacts) the subject must be asked about AEs and technical complaints, for example by asking: "Have you experienced any problems since the last contact?" This must be documented in the subject's medical record. AEs must be reported at each visit in accordance with the procedures outlined in Section [12](#).

8.4.1.1 Medication error

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

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

For definition of medication errors, see Section [12.1.4](#).

8.4.1.2 Adverse events requiring additional data collection

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

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see Section [12](#).

Acute coronary syndrome

If an event of Acute Coronary Syndrome (ranging from unstable angina pectoris to myocardial infarction) is observed during the trial the following additional information must be reported if available on the acute coronary syndrome form:

- Duration of symptoms
- Changes in ECG
- Collection of cardiac biomarkers
- Cardiac imaging
- Cardiac stress testing
- Angiography
- Use of thrombolytic drugs
- Revascularisation procedures

Cerebrovascular events

If a cerebrovascular event (e.g. transient ischaemic attack (TIA), stroke, and haemorrhage) is observed during the trial the following additional information must be reported if available on the cerebrovascular event form:

- Type of event (e.g. TIA, Stroke)
- Contributing condition
- Neurologic signs and symptoms
- History of neurologic disease
- Imaging supporting the event
- Treatment given for the event

Neoplasm

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

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

Events for adjudication

Severe hypoglycaemia or hypoglycaemic episodes reported as an SAE and all fatal events will be subject to external independent adjudication. For these AEs a (hypoglycaemia) Adjudication Form must be completed in the eCRF. For detailed information on event adjudication, please refer to Section [12.7.2](#).

8.4.2 Hypoglycaemic episodes

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

All plasma glucose values:

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

should be reported in the diary according to the instructions below throughout the trial from visit 2 to the End of Trial visit (V56 or V95).

Upon onset of a hypoglycaemic episode the subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is >3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines²⁹.

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

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

The record should include the following information:

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

The answer to the question: "Was the subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event,

but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration²⁹.

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

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

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)?
- Where the treatment was administered (in clinic/emergency room/hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not)
- Type of treatment provided by another person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet change, medication error (i.e. overdose, mix-up between products, incorrect use of device), miscalculation of dose of anti-diabetic medication, other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms³⁰ (layman term used in the diary is specified in brackets if different from the protocol term)?
 - Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
 - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
 - General malaise: headache or malaise (feeling discomfort/unease)
- Other symptoms.

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

All hypoglycaemic episodes must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected.

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query for additional data except for the start date, SMPG value, if any symptoms were present and whether the subject was able to self-treat due to decreased validity of such data^{31,32}.

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

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

8.4.3 Body measurements

Body weight should be measured in kilogram (kg) or pounds (lb) without coat and shoes wearing only light clothing. Body weight will be recorded to one decimal. The body weight should be assessed on the same weighing scale equipment throughout the trial, if possible.

Height should be assessed without shoes. Height is measured in inches or meters at visit 1 (screening) and recorded to one decimal place (inches) or two decimal places (meters) respectively.

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

8.4.4 Vital signs

Diastolic blood pressure, systolic blood pressure and pulse will be assessed following standard clinical practice. Abnormal and clinically significant findings must be recorded as described in Section [8.4](#).

8.4.5 Physical examination

Physical examination will include:

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

The evaluation must follow the categories:

- Normal
- Abnormal
 - Was the result clinically significant? (Yes/No)

Abnormal and clinically significant findings must be recorded as described in Section [8.4](#).

8.4.6 Eye examination

Fundus photography or dilated funduscopy must be performed by the investigator or local ophthalmologist, or an optometrist according to local practice. The result of the fundus

photography/dilated funduscopy will be interpreted by the investigator. To document this, the Investigator must sign and date the interpretation in the subject's medical records.

The evaluation must follow the categories:

- Normal
- Abnormal
 - Was the result clinically significant? (Yes/No)

Abnormal and clinically significant findings must be recorded as described in Section [8.4](#).

If a fundus photography/dilated funduscopy have been performed within 90 days prior to V2, and if the results are available at V2, then the procedure do not need to be repeated. If performed before the subject consents to participate in the trial, it must also be stated in the subject's medical records that this procedure was not performed in relation to the trial.

A subject cannot be randomised without results confirming there is no acute treatment-requiring retinopathy.

Eye examination performed within a period of three weeks before end of treatment visit (V54 or V93) is acceptable, if results are available at the end of treatment visit.

8.4.7 Electrocardiogram

A 12-lead ECG must be performed at the trial site. The ECG must be interpreted by the investigator, and documented by Investigator signature and date on the ECG print-out. .

The evaluation must follow the categories:

- Normal
- Abnormal
 - Was the result clinically significant? (Yes/No)

The baseline ECG must be performed at screening (V1) or in the period between screening (V1) and randomisation (V2). The result must be available prior to randomisation.

ECGs at the end of treatment visit (V54 or V93) should be performed at the day of the visit.

Abnormal and clinically significant findings must be recorded as described in Section [8.4](#).

8.5 Laboratory assessments

Laboratory analyses will be performed at laboratories contracted by Novo Nordisk. A central laboratory will provide all laboratory supplies for the sampling and transportation of all blood samples taken during the trial.

A detailed description of the procedures for obtaining the samples, handling, storage, and shipment of the samples are specified in a trial-specific laboratory manual provided to the sites by the central laboratory. Information regarding laboratory materials such as tubes and labels are also described.

If laboratory samples need to be retaken due to missing result(s) (e.g. haemolysed, sample leaked during transit, sample not being conclusive, lost in transit, etc.), the subject should be called in for resampling. Please see the laboratory manual for further guidance.

Samples will be coded in order to keep subject's identity anonymous.

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to Section [8.2.4](#) and Section [12](#). Review of laboratory reports must be documented either on the documents and/or in the subject's medical record.

Antibody results will not be provided to the investigator on an ongoing basis, as these results will not be used for any clinical evaluation during the trial.

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

Laboratory samples will be destroyed no later than at end of trial or no later than at finalisation of the clinical trial report.

Antibody samples will be stored as described in Section [24.2](#).

8.5.1 Laboratory assessments for efficacy

Glucose metabolism

FPG is measured in order to evaluate metabolic control. The subject must attend these visits fasting. For definition of fasting, see Section [8.1.4](#).

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

Low plasma or blood glucose values (e.g. FPG) reported by a laboratory in connection to trial related visits should NOT be reported as hypoglycaemic episodes; these should be reported as AEs related to the procedure at the discretion of the investigator.

Blood samples will be drawn to determine the HbA_{1c} level in order to evaluate metabolic control.

8.5.2 Laboratory assessments for safety

Haematology

Blood samples for haematology will be analysed to determine:

- Haematocrit
- Haemoglobin
- Leucocytes
- Erythrocytes
- Thrombocytes

Biochemistry

Blood samples for biochemistry will be analysed to determine:

- ALT
- Albumin
- AST
- Alkaline phosphatase
- Bilirubins, total
- Creatinine
- Potassium
- Sodium

eGFR will be calculated (at screening) by the central laboratory based on the creatinine value using the CKD-EPI equation^{20, 21} in order to assess inclusion criteria 3b.

Pregnancy testing

For females of childbearing potential (see Section [8.2.7](#)) a blood human Chorion Gonadotropin (hCG) test will be performed at screening (V1) and End of Treatment (V54 or V93). In addition, urine pregnancy tests will be performed locally during the trial if pregnancy is suspected or if required by local law. A positive urine test should be followed by a confirmatory serum -hCG (central laboratory).

The central laboratory will provide the pregnancy kits for urine testing performed locally at the site.

Anti-insulin antibodies

Antibody samples may be retained and used for further characterisation of antibody responses towards drug if required by health authorities, for safety reasons or in relation to exploratory analysis, see Section [24.2](#).

Serum samples will be analysed at a special lab for anti-insulin degludec or anti-insulin glargine antibodies. Anti-degludec antibodies and anti-glargine antibodies will be tested for cross-reactivity to human insulin.

- Blood samples will be drawn for determination of antibodies to insulin degludec or insulin glargine (including cross-reacting antibodies to human insulin).

The subjects must attend the antibody sampling visits specified in section [2](#) in a fasting condition. Fasting is defined as at least eight hours without drink or food intake prior to the visit except for water.

No diabetes treatment (neither trial insulin, nor any OADs) is allowed up to eight hours prior to the blood sampling. Non-anti-diabetic medication is still allowed to be taken.

8.6 Other assessments

Patient reported outcome questionnaires

The patient reported outcome (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. Instructions on how to complete the questionnaires will be provided to the subject. The questionnaires will be used to investigate the health related quality of life, hypoglycaemic episode experience as well as treatment and device satisfaction. The completed questionnaires must be transcribed into the eCRF and filed at site as source documents.

The following PRO questionnaires will be supplied in a linguistically validated version in all languages relevant for this trial:

- **SF-36v2[®]** The ‘Short-Form 36 Health Survey version 2 is a questionnaire concerning various health-related quality-of-life questions. It is a sensitive, validated and widely used instrument which will allow direct comparison with other trials including subjects with T2DM. SF-36v2 consists of 36 items grouped into 8 domains
- **TRIM-D** measures treatment related impact on subjects of diabetes medication across the spectrum of pharmacological treatment over the past two weeks. The TRIM-D consists of 28 items grouped into five domains. The domains are treatment burden, daily life, diabetes management, compliance and psychological health
- **TRIM-DD** measures the impact of the treatment delivery system as an eight-item instrument. The instrument consists of eight items grouped into two domains: Device Function and Device Bother
- **Insulin Pen questionnaire** measures how easy or difficult it is to reach the dose button when injecting insulin, how easy or difficult it is to use the pen and whether or not the subject will recommend the pen to others
- **Baseline Hypo Questionnaire** measures the subjects experience with hypoglycaemic episodes

Besides the five subject completed questionnaires an investigator interview questionnaire is to be completed if the subject has reported any hypoglycaemic episode(s) since the last visit:

- **Hypoglycaemia resource use** is collected as an interview administered questionnaire regarding resource use of the latest hypoglycaemic episode within the last four weeks. The questionnaire includes questions regarding the length of the hypoglycaemic episode, the number of extra blood monitoring, contact to health care professionals, and time missed at work

The questionnaires should be completed as specified in the flow chart, see Section [2](#).

8.6.1 Training in the pen injector

The subjects must be trained in how to handle the pen injector when handed out the first time. Training must be repeated at V6 in order to ensure correct use of the device. The following should be emphasised:

- Always use a new needle for each injection as this will prevent contamination and blocked needles
- Priming the pen to ensure product flow
- Injection technique as per DFU

8.7 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance.

To ensure treatment 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 measurements, hypoglycaemia reporting and PRO questionnaire completion. In addition, subject compliance will be assessed by monitoring of drug accountability at specified visits, please refer to the flow chart, see Section [2](#). The unused amount IMP will be assessed against the dispensed amount and, in case of discrepancies, the subject must be asked.

If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

Treatment compliance: It is important to ensure subjects adhere to treatment. Therefore, during the treatment period the investigator must at each weekly contact (visit or phone contact), evaluate if the subject has adhered to trial treatment since last contact.

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 insulin products (Investigational medicinal product (IMPs)) must not be used, if they do not appear clear and colourless.

Insulin NPH product (Non-Investigational Medicinal Product (NIMP)) must not be used if it does not appear uniformly white and cloudy after re-suspension.

9.1 Trial products

The following trial products will be provided by Novo Nordisk A/S, Denmark:

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/delivery device
Insulin degludec (Tresiba [®]) (IMP)	200 U/mL	Solution for injection	Subcutaneous	3 mL PDS290 pre-filled pen injector (FlexTouch [®])
Insulin glargine (Toujeo [®]) (IMP)	300 U/mL	Solution for injection	Subcutaneous	1.5 mL pre-filled pen injector (SoloStar [®])
Human isophane insulin (NPH) (Insulatard [®] /Prothaphane [®] /Novolin [®] N) (NIMP)	100 IU/mL	Suspension for injection	Subcutaneous	3 mL pre-filled pen injector (FlexPen [®])

The following Non-Investigational Medicinal Products (NIMPs) will not be provided by Novo Nordisk:

- Metformin, tablets for oral use
- DPP-4i, tablets for oral use
- SGLT2i, tablets for oral use
- Thiazolidinedione, tablets for oral use
- Alpha-glucosidase-inhibitor, tablets for oral use
- Marketed oral combination products only including the products listed above, tablets for oral use

However, metformin, DPP-IVi, SGLTi, Thiazolidinedione, Alpha-glucosidase-inhibitor or marketed combination products only including the products listed in inclusion criteria 5a-5e will be reimbursed if required by the country's regulatory authority or IRB/IEC.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13³³, local regulations and trial requirements.

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

The investigator must document that direction for use is given to the subject orally and in writing at the first dispensing visit (V2). Direction for use can be provided as needed at the following dispensing visits.

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time ^a
Insulin degludec (Tresiba [®]) (IMP)	<ul style="list-style-type: none"> Store in refrigerator (2°C - 8°C) Protect from light Do not freeze 	<ul style="list-style-type: none"> Do not store above 30°C Protect from light Can be stored in refrigerator (2°C - 8°C) Do not freeze 	Use within 8 weeks
Insulin glargine (Toujeo [®]) ^b (IMP)	<ul style="list-style-type: none"> Store in refrigerator (2°C - 8°C) Protect from light Do not freeze 	<ul style="list-style-type: none"> Store below 30°C Protect from light Do not refrigerate Do not freeze For CA: Store at room temperature (15°C – 30°C)	Use within 26 days
Insulin NPH (Insulatard [®] /Prothaphane [®] /Novolin [®] N) (NIMP)	<ul style="list-style-type: none"> Store in refrigerator (2°C - 8°C) Protect from light Do not freeze 	<ul style="list-style-type: none"> Store below 30°C Protect from light Do not refrigerate Do not freeze 	For US: Use within 14 days For CA: Use within 4 weeks For EU: Use within 6 weeks

^aIn-use time starts when first dose is taken.

^bBefore first use, the Toujeo[®] pre-filled pen injector must be stored at room temperature at least 1 hour.

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

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

9.4 Drug accountability and destruction

Drug accountability of all trial products received at site is the responsibility of the investigator.

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

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

Subjects are instructed to return all used, partly used and unused trial product at each dispensing visit after V2. Please refer to the flowchart, see Section [2](#) for timing of the dispensing visits.

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

9.5 Auxiliary supplies

The following will be provided by Novo Nordisk:

- Direction for use for the pen injectors
- Novo Nordisk needles for prefilled systems
- BG Meter and strips, lancets and control solution for BG meters

Only needles provided by Novo Nordisk must be used for administration of trial product.

Please refer to the TMM for further auxiliary supplies' details.

10 Interactive web response system

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

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing and Additional Dispensing between scheduled visits
- Dispensing Verification (when barcode scanner is used)
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

Notifications generated as a result of sessions performed in the IWRS should be archived in the investigator trial file or together with other source documents for the subject.

At any time during the trial only dispensing unit numbers (DUN) allocated by the IWRS are allowed to be dispensed to a subject. By doing this it will be ensured that:

- correct trial product is dispensed to subject
- stock is available at sites as needed for the subjects
- no trial product that will expire before the next dispensing visit will be allocated
- drug accountability can be made in the IWRS

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure

The IWRS is used for randomisation. Subjects complying with the inclusion- and exclusion criteria will be randomised 1:1 into one of the two treatment arms. Within each treatment arm, subjects will be randomised 1:1 to morning or evening dosing.

In IWRS this means that there will be four different treatment regimens:

- IDeg 200 U/mL OD morning dosing ± OADs
- IDeg 200 U/mL OD evening dosing ± OADs
- IGlax 300 U/mL OD morning dosing ± OADs
- IGlax 300 U/mL OD evening dosing ± OADs

Recruitment will be closed as soon as the total number of planned subjects to be randomised is achievable, taking the number of screened subjects and the screening failure rate into account. All investigators will be notified immediately when the recruitment period ends (estimated to be 24 weeks), after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation can be randomised.

12 Adverse events, and technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

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

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

An AE includes:

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

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is from V2 until FU1 reported on a hypoglycaemic episode form instead of on an AE form, see Section [8.4.2](#). However, FPG results ≤ 3.9 mmol/L (70 mg/dL) should not be reported as hypoglycaemic episodes but as a CLAE at the discretion of the investigator.

The following three definitions are used when assessing an AE:

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

Relationship between an AE and the relevant trial product(s):

- **Probable** - Good reason and sufficient documentation to assume a causal relationship.

- **Possible** - A causal relationship is conceivable and cannot be dismissed.
- **Unlikely** - The event is most likely related to aetiology other than the trial product.
- Final outcome
 - **Recovered/resolved** - The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
 - **Recovering/resolving** - The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
 - **Recovered/resolved with sequelae** - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
 - **Not recovered/not resolved** - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
 - **Fatal** - This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before 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.

12.1.2 Serious adverse event

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

- Death.
- 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.

^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 dyscrasia or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

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

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

12.1.3 Non-serious adverse event

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

12.1.4 Medication errors

A medication error concerning trial products is defined as:

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

Medication errors must be reported on an AE form and a specific event form, see Section [8.4.1.1](#).

12.1.5 Adverse events requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the product safety.

Some events in this trial will be adjudicated by an independent external committee as described in Section [12.7.2](#).

[Table 12-1](#) lists AEs that require completion of specific event forms in the eCRFs and/or are subject to event adjudication.

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

Event	<i>Specific event form</i>	<i>Event adjudication</i>
Fatal event	No	Yes ^a
Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)	Yes	No
Cerebrovascular event (stroke or transient ischaemic attack)	Yes	No
Neoplasm	Yes	No
Severe hypoglycaemia or hypoglycaemic episodes reported as an SAE	No ^b	Yes
Medication error	Yes	No

^aFatal events will be adjudicated as potential hypoglycaemic episodes (Hypoglycaemia Adjudication form to be completed).

^bHypoglycaemia will be captured in the diary by the subject.

For details about specific event forms, see Section [8.4.1](#).

12.1.6 Technical complaints

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

Examples of technical complaints:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (V56). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and [Figure 12-1](#).

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

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

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

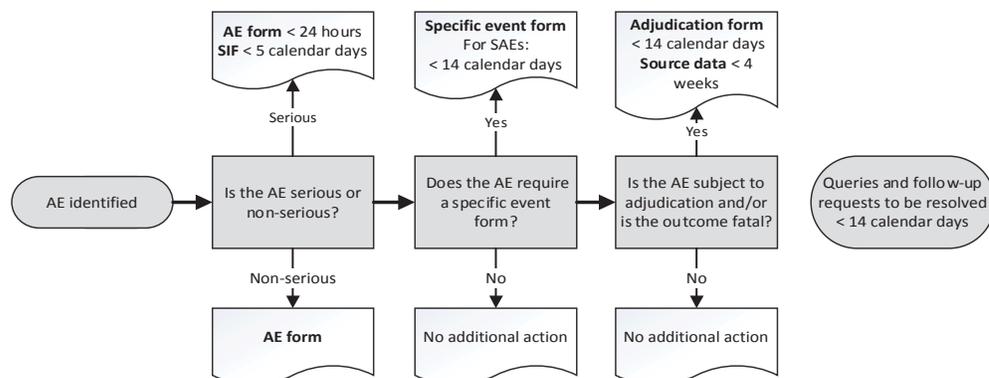
Timelines for initial reporting of AEs:

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

- **SAEs:** The AE form **within 24 hours** and the 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.
For SAEs requiring reporting on a specific event form: In addition to the above the specific event form within **14 calendar days** from the investigator’s first knowledge of the AE.
- **Events for Adjudication:** The adjudication form should be completed within **14 calendar days** of the investigator’s first knowledge of the AE, see Section [12.7.2](#). The investigator should provide copies of the source documentation preferably within **4 weeks** of event identification.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the

eCRF becomes available again, the investigator must enter the information on the form into the eCRF. Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.



Timelines are for the completion of forms from the time of investigator's awareness
AEs requiring specific event forms are described in Section 12.1.4 and 12.1.5
AEs for adjudication are described in Section 12.7.2

AE: Adverse event SIF: Safety information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the current versions and any updates of the following reference documents:

- IDeg IB⁹
- IGlar 300 U/mL SmPC¹⁴ or local labelling^{15, 16}

Reporting of trial product-related SUSARs by Novo Nordisk:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP¹. 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 ICH GCP¹, unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication or non-investigational medicinal product:

If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as non-investigational medicinal product (Insulatard[®]/Prothaphane[®]/Novolin NTM) or concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

12.3 Follow-up of adverse events

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

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

- **SAEs:** All SAEs must be followed until the outcome of the event is “recovered/resolved”, “recovered/resolved with sequelae” or “fatal”, and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome “recovering/resolving” or “not recovered/not resolved”. Cases can be closed with the outcome of “recovering/resolving” when the subject has completed the follow-up period and is expected by the investigator to recover.

The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator’s first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

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

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

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

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

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

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Insulin degludec 3ml PDS290 pen injector (FlexTouch[®])
- Insulin glargine (Toujeo[®]) 1.5ml prefilled pen (SoloStar[®])
- Insulin NPH (Insulatard[®]/Prothaphane[®]/Novolin NTM) 3ml prefilled pen (FlexPen[®])
- Novo Nordisk needles for pre-filled pen systems

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 and/or SAEs.

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

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

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

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

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

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in [Attachment I](#)) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

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

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

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

12.5 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:

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

SAEs:

- AE form^a **within 24 hours** of the investigator's first knowledge of the SAE.
- 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.

- ^a 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. If the AE occurred in the foetus or new-born infant, the AE can only be reported on paper AE and safety information form.

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

During treatment with insulin, there is a risk of hypoglycaemia (see Section [8.4.2](#)). Symptoms usually occur suddenly and may include cold sweat, nervousness or tremor, anxious feelings, unusual tiredness, confusion, difficulty in concentration, 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.

Hypoglycaemic episodes should be treated following best practice at the discretion of the investigator. As with all long-acting insulin preparations, their prolonged effect may delay recovery from a hypoglycaemic episode.

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.

For further details, please refer to current versions and any updates of the following:

- IDeg IB⁹
- IGLar 300 U/mL SmPC¹⁴ or local labelling^{15,16}
- NPH SmPC³⁴ or local labelling^{35,36}

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal IDeg safety committee to perform ongoing 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.

12.7.2 Event adjudication committee

An independent external event adjudication committee is established to perform validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical data related to the specific AE.

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

The AEs for adjudication are listed in [Table 12-2](#).

Table 12-2 Events for adjudication

Event	Description of events in scope for adjudication	Adjudication Outcome
Fatal event	All cause death	Severe hypoglycaemia
Severe hypoglycaemia or hypoglycaemic episodes reported as an SAE	An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an episode, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event episode was induced by a low plasma glucose concentration	Severe hypoglycaemia

Event adjudication will be performed for AEs in randomised subjects including AEs with an onset date during the screening period. Event adjudication will not be performed for AEs in screening failures.

The following describes the ways events are captured for adjudication:

Direct reporting by investigator:

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

Hypoglycaemic episodes will be reported by the subject in the diary. For severe hypoglycaemic episodes the adjudication form must be completed by the investigator in the eCRF. If a hypoglycaemic episode fulfils the criteria as an SAE as well as for all fatal events the AE, SIF and adjudication forms must be completed.

Screening of SAEs:

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

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

EAC identified events:

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

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

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

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

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

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 provided by an external supplier.

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

The following will be provided as paper CRFs:

- Pregnancy forms

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

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints that are not subject related (e.g. discovered at trial site before allocation))

On the paper 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 eCRF data may be made by the investigator or the investigator’s delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction.

If corrections are made by the investigator’s delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

Corrections to the data in the paper CRFs should be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that were crossed out. Each correction must be initialled, dated and explained (if necessary) by the investigator or the investigator’s authorised staff.

13.2 Case report form flow

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

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

14 Monitoring procedures

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

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

All data must be verifiable in source documentation other than the eCRF, except for:

- Age and BMI which are calculated by the EDC system

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

Protocol
Trial ID: NN1250-4252
UTN: U1111-1184-8175
EudraCT no.: 2016-002801-20

~~CONFIDENTIAL~~

Date:	23 February 2018	Novo Nordisk
Version:	3.0	
Status:	Final	
Page:	80 of 108	

The following data will be source data verified for screening failures:

- Date for obtaining informed consent.
- Screen Failure Form/Reason
- SAEs

Monitors will 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 eCRF. If discrepancies are found, the investigator must be questioned about these.

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

15 Data management

Data management is the responsibility of Novo Nordisk.

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

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

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

16 Computerised systems

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

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

The eDiary software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11 and ICH E6 (EU directive for personal data protection). After trial finalisation, Novo Nordisk and each site will be supplied with long-life DVDs. These DVDs will contain site-specific subject records including the subject's eDiary data and audit trail as well as any data additions and corrections made on each form. The eDiary vendor will furthermore retain and securely store copies of all archived documents and data for 50 years or as required by local data retention laws for trial data.

17 Statistical considerations

17.1 General considerations

For subjects withdrawing from the trial as well as for subjects not discontinuing randomised treatment prematurely, the trial period completion is at visit 54 (subject not entering maintenance 2) or visit 93 (subjects entering maintenance 2). For subjects who prematurely discontinue randomised treatment during the titration period or maintenance 1 but do not withdraw, the trial period completion is at visit 93A. Treatment period completion is defined as the date when randomised treatment is discontinued.

All efficacy, PRO and hypoglycaemic endpoints will be summarised using the full analysis set (FAS) and safety endpoints excluding hypoglycaemic endpoints will be summarised using the safety analysis set (SAS).

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

The primary objective is to compare the effects of IDeg OD and IGlax 300 U/mL OD on the rate of hypoglycaemia in subjects with type 2 diabetes mellitus, inadequately treated with basal insulin with or without oral anti-diabetic drugs. The primary estimand is the treatment difference between IDeg and IGlax 300 U/mL assuming that all randomised subjects adhered to the randomised treatment, that is a de jure estimand. The primary estimand addresses the treatment difference for subject that can be long-term treated with either of the two insulins. Data collected after premature treatment discontinuation will not be used when addressing the primary estimand. With the aim of comparing a safety endpoint this estimand is considered the most relevant as it compares the occurrence of a safety endpoint that is caused by the drug during exposure to the drug. The confirmatory endpoints will additionally be investigated with a de-facto estimand, other endpoints will be analysed only with a de jure estimand to support the primary analysis of the primary endpoint.

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

In accordance with guidance³⁷ endpoints will be assessed at frequent visits and also for subjects who prematurely discontinue treatment. The baseline value is defined as the value from the randomisation visit. If this value is missing the last recorded value before randomisation visit will be used.

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

Laboratory values below the lower limit of quantification (LLOQ) will be set to $\frac{1}{2}$ LLOQ.

The primary and secondary endpoints will be tested in a hierarchical order to control the family wise Type I error in the strong sense. Inferences will be based on the primary estimand.

Presentation of results from a statistical analysis will include the estimated treatment means as well as estimated mean treatment difference (or ratio) together with the two-sided 95% confidence interval and corresponding two-sided p-value.

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

1. Treatment: IDeg, IGlax 300 U/mL
2. Pre-trial 0 OADs, 1OAD, ≥ 2 OADs
3. Region: Europe, North America
4. Sex: male, female
5. Dosing time: morning, evening

17.2 Power calculation

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

For the power calculations it is assumed that the true treatment rate ratio (RR) is 0.75 corresponding to a 25% reduction in rate of hypoglycaemia in maintenance period with IDeg OD compared to IGlax 300 U/mL OD. Sample size is determined based on a negative binomial model with log-offset equal to exposure time in maintenance. The observed rate of severe or BG confirmed symptomatic hypoglycaemia for IDeg is assumed to be 1.8 per patient years of exposure (PYE) and the dispersion parameter in the negative binomial distribution is assumed to be 3.1. Furthermore it is assumed that 4% of subjects will withdraw before starting the maintenance period and therefore have no on-treatment data for the maintenance period. For these 4% the treatment ratio is set to 1. Rate assumptions are based on experience from SWITCH 2 (NN1250-3998), which has similar inclusion criteria. Dispersion parameter assumptions are based on experience from the Degludec phase 3a and 3b program. Assumptions concerning withdrawal are similarly based on actual withdrawal rate of the trial during titration and maintenance 1.

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

Table 17-1 Power for the primary estimand for combinations of RR and event rates

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

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

Table 17-2 Marginal power for confirmatory secondary endpoints

Endpoint	Assumptions				
	True ratio	Adjusted RR	CV/ Over dispersion	Rate in IDeg treatment arm	Power
Number of nocturnal, severe or BG confirmed symptomatic hypoglycaemic episodes during maintenance 2	0.7	0.718	3.1	0.55	82%

Insulin dose (U)	0.90	0.906	0.65	-	92%
Number of severe hypoglycaemic episodes during maintenance 2	0.6	0.624	3.1	0.03	31%

17.3 Definition of analysis sets

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

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

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

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

17.4 Primary endpoint

17.4.1 Primary statistical analysis for the primary estimand

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

- First 1000 samples from the posterior distribution of model parameters will be extracted. The model will be fitted to the on-treatment maintenance 2 data for subjects that discontinued randomised treatment during maintenance 2. This will be done using a Bayes negative binomial log-link model with the factors described in section [17.1](#) (except treatment), age as covariate, and log of exposure time as offset.
- For each sample of model parameters, the total number of hypoglycaemia events for subjects that discontinued randomised treatment in the titration period or maintenance 1 will be imputed as a random number of events from a negative binomial distribution using the sampled parameters.

Having 1000 complete data sets that have maintenance 2 data for all randomised subjects, the mean treatment ratio will be estimated using a negative binomial model with all the factors described in section [17.1](#), age as covariate and log exposure time as offset. The estimates and standard deviations will be pooled to one estimate and associated standard deviation using Rubin's formula. From these the 95% confidence intervals for the treatment ratio and the associated p-value will be calculated.

If the model in step one above cannot fit due to sparse data, factors will be left out one by-one in the model using data from all subjects discontinuing randomised treatment in the following order, until a model fits:

- sex
- region
- previous OAD treatment

If the above model cannot fit either the model is fitted to the on-treatment data for subjects that discontinued randomised treatment during either titration or maintenance periods.

17.4.2 Sensitivity analyses for the primary estimand

To investigate missing not at random scenarios, a tipping point analysis of the hypothesis that IDeg is superior to IGLar 300 U/mL will be performed for the primary estimand. In this analysis the event rates for subjects that discontinued randomised treatment in the IDeg OD arm during either titration or maintenance periods is gradually increased until the difference between the two treatments is no

longer statistically significantly different. If the penalty found by this method is evaluated to be clinically plausible the sensitivity analysis does not support the primary analysis. If the penalty is not considered plausible the sensitivity analysis supports the primary analysis.

To investigate the potential influence of subjects with high number of events, the analysis of the primary estimand will be repeated on data where the maximal number of events in maintenance 2 is truncated at three. The value three is based on data from SWITCH 2 (NN1250-3998) where three hypos correspond to the 95% percentile in the IDeg arm.

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

17.4.3 Statistical analysis for the secondary estimand

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

Missing data for withdrawn subjects will be imputed based on off-treatment data from the same arm from maintenance 2 for subjects that discontinued randomised treatment during maintenance 2. The imputations and the analysis will be made using the same method as for the primary estimand.

17.4.4 Sensitivity analysis for the secondary estimand

The same sensitivity analysis as the sensitivity analysis for the primary estimand will be performed.

17.5 Secondary endpoints

17.5.1 Confirmatory secondary endpoints

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

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

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

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

Basal insulin dose at end of maintenance 2 will be analysed as follows: A basal insulin dose at every titration, maintenance and end of treatment visit mentioned in the flow chart will be

calculated as a mean of the insulin doses in the 7 day period before the visits. These doses will be analysed on log-scale with an MMRM with the factors described in section [17.1](#) and age at baseline and pre-trial insulin dose as covariate. If this model does not converge visits and/or factors will be excluded from the analysis.

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

- An analysis of covariance model for insulin dose at week 52 with the factors listed in [17.1](#) (except treatment) and pre-trial insulin dose and age at baseline as covariates will be fitted to the observed data.
- The estimated parameters will be used to impute 1000 values for insulin dose at week 52, creating 1000 complete datasets.

Having 1000 complete datasets, each of these will be analysed using an analysis of covariance model with all the factors listed in [17.1](#), pre-trial insulin dose and age at baseline as covariates. The estimates and standard deviations will be pooled to one estimate and associated standard deviation using Rubin's formula. From these the 95% confidence intervals for the treatment ratio and the associated p-value will be calculated.

17.6 Other endpoints

17.6.1 Efficacy endpoints

Continuous supportive secondary efficacy endpoints will be summarised descriptively by visits and by mean plots of observed values and observed change from baseline.

17.6.2 Safety endpoints

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

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

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

TEAEs are summarised descriptively, whereas non-TEAEs are presented in listings. 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 of exposure (R).

Summaries of TEAEs and of serious TEAEs will be presented as an overview including all AEs, serious AEs, number of deaths, AEs by severity, AEs by relation to treatment and AEs leading to treatment discontinuation or withdrawal.

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

- All TEAEs
- Serious TEAEs
- TEAEs possibly or probably related to trial product
- Severe, moderate and mild TEAEs
- TEAEs with preferred term that are experienced by at least 5% (1%) of the subjects in any treatment arm or by at least 5% (1%) of all subjects

Summary tables of SAEs including SAEs reported for subject that discontinue trial product prematurely will be presented including summary tables based on system organ class and preferred terms.

Hypoglycaemic episodes

For the definition and classification of hypoglycaemic episodes refer to section [17.7](#).

Data on treatment-emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years of exposure (R).

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

Body weight

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

Clinical evaluation (ECG, vital signs, eye examination and physical examination) change from baseline after 52 weeks

Vital signs, physical examination, eye examination and 12-lead ECG findings will be summarised, including:

- Summaries for each visit
- Shift tables from baseline to end of treatment

Laboratory assessments

Biochemistry and Haematology laboratory parameters will be summarised including:

- Summaries by visit
- Shift tables from baseline to end of treatment
- Proportion of subjects with measurements outside reference range by treatment and visit
- Box plots by visit
- Listings of individual values outside reference ranges (abnormal values)

All laboratory values will be included in listings.

Anti-insulin antibodies will be summarised by visit.

17.7 Classification of Hypoglycaemia

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

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

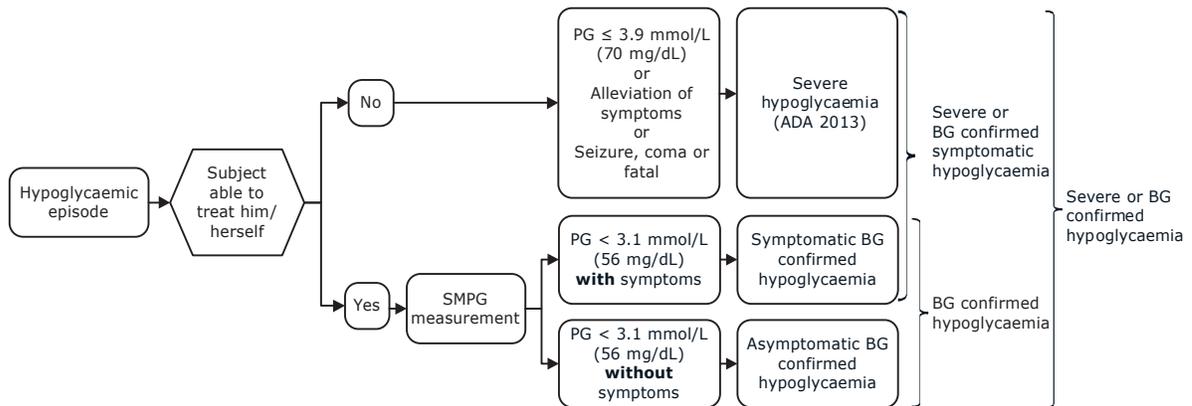
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see [Figure 17-1](#)) and the ADA classification of hypoglycaemia (see [Figure 17-2](#)).

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)³⁸. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see [Figure 17-1](#)) in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification²⁹.
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification²⁹ or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia.



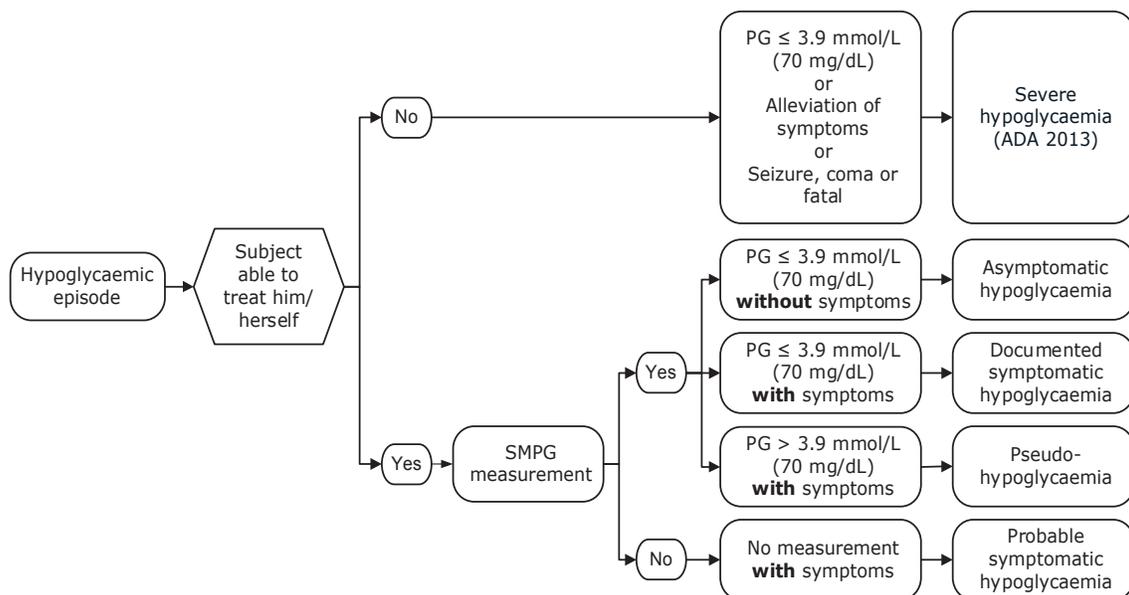
Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

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

Figure 17-1 Novo Nordisk classification of hypoglycaemia

ADA classification²⁹ of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).



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

PG: plasma glucose SMPG: Self-measured plasma glucose

Figure 17–2 ADA classification of hypoglycaemia

Protocol
Trial ID: NN1250-4252
UTN: U1111-1184-8175
EudraCT no.: 2016-002801-20

~~CONFIDENTIAL~~

Date: 23 February 2018
Version: 3.0
Status: Final
Page: 92 of 108

Novo Nordisk

17.8 Health economics and/or patient reported outcomes

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

18 Ethics

18.1 Benefit-risk assessment of the trial

The trial population will consist of insulin-treated subjects with T2DM presenting with an HbA_{1c} equal to or below 9.5% while treated continuously with basal insulin with or without OADs for at least 90 days and who recently have experienced hypoglycaemia or have increased risk of severe hypoglycaemia. For all subjects participating in this trial, the anticipated benefits include improved glycaemic control. Titration algorithms, specifying recommended adjustments of the basal 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.

Trial products will be provided by Novo Nordisk free of charge. Subjects will receive IDeg or IGlax 300 U/mL in prefilled pens and NPH during 7 days follow-up. For a description of risks and benefits please refer to current versions and any updates of the following:

- IDeg IB²
- IGlax 300 U/mL SmPC¹⁴ or local labelling^{15,16}
- NPH SmPC³⁴ or local labelling^{35,36}

The subjects will be provided with a glucose meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use.

The trial products may be associated with side effects, but relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participating in the trial. These precautions include thorough information regarding the correct administration of the trial product and in handling of low BG measurement. Furthermore, subjects will be fully informed about possible AEs and inconveniences.

Clinical benefits and risk considerations for the trial

For the individual subjects, the personal health-related benefits are related to the medical examination and the benefit from a treatment regimen anticipated being equal to or better than the treatment they receive at the time they enter the trial. However, subjects will have to spend some extra time monitoring and recording data and on additional visits to the clinic and phone contacts. The maximum trial duration for each subject is up to 94 weeks and the treatment duration for a subject is planned to be up to 88 weeks. Subjects will be asked to perform SMPG recording every day.

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

For the individual subjects, the anticipated side effects associated with the trial products are not different from what is seen with other insulins and include hypoglycaemia, hypersensitivity

reactions, injection site reactions, lipodystrophy and antibody development (for more detailed description, please refer to the local labelling for each product). The side effects will be mitigated by the close supervision of the subjects and the frequent measurements of BG levels.

All treatments are contraindicated in case of hypersensitivity to the active substances or any of the excipients. The risk of hypersensitivity is partly mitigated by excluding subject with known hypersensitivity towards any trials products or related products.

Injection site reactions can occur. The nature of the injection site reactions is expected to be mild, transient, and more of a visual character and is not expected to be of concern to the subject's safety. Lipodystrophy (including lipohypertrophy, lipoatrophy) at the injection site can occur. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

Conclusion

Subjects in this trial will benefit from a basal insulin treatment in a treat-to-target setting under close supervision.

The safety profiles of the trial products are well established.

It is concluded that the clinical benefits from the trial outweigh the potential risks of participating in this trial.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP¹ and the requirements in the Declaration of Helsinki².

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 investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

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

18.3 Data handling

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

- Data already collected and any data collected at the end-of-trial visit including follow up visits will be retained by Novo Nordisk, entered into the database and used for the clinical 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.

18.4 Information to subjects during trial

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

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

18.5 Premature termination of the trial and/or trial site

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

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

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

19 Protocol compliance

19.1 Protocol deviations

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

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

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

19.2 Prevention of missing data

A significant proportion of missing data is a potential source of bias when analysing data in clinical trials leading to a risk of misinterpretation of the trial results. Missing data may affect both estimation of treatment effect and the confidence interval that surrounds it as well as the representativeness of the sample size in relation to the target population.

Only absolutely necessary criteria to discontinue trial drug have been stated, see Section [6.4](#), and a process has been set up to follow-up on subjects discontinuing trial drug prematurely, see section [8.1.9](#).

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

The subjects will be carefully informed about the trial procedures before signing informed consent, so that they know the implications of participating in the trial. In addition, only absolutely necessary criteria for premature discontinuation of trial products primarily focusing on subjects safety are included and thereby reducing the number of discontinuations and limiting the amount of missing data.

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

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

20 Audits and inspections

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

21 Critical documents

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

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

- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For US sites:

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

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

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

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP¹ applicable regulatory requirements and the Declaration of Helsinki².

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

22 Responsibilities

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

A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator will follow instructions from Novo Nordisk when processing data.

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

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator

must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

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

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

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

23 Reports and publications

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

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

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

One investigator will be appointed by Novo Nordisk to review and sign the 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 publications³⁹.

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 Disclosure²³.

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

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

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

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

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 Editors³⁹ (sometimes referred to as the Vancouver Criteria).

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

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

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

Protocol
Trial ID: NN1250-4252
UTN: U1111-1184-8175
EudraCT no.: 2016-002801-20

~~CONFIDENTIAL~~

Date:	23 February 2018	Novo Nordisk
Version:	3.0	
Status:	Final	
Page:	101 of 108	

23.2 Investigator access to data and review of results

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

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

24 Retention of clinical trial documentation and human bio samples

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 provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

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

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

24.2 Retention of human bio samples

Antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug if required by health authorities, for safety reasons or in relation to exploratory analysis.

Remaining anti-insulin antibody samples may be used for exploratory investigation of antibodies. The analyses will be performed by Immunogenicity Assessment, Novo Nordisk A/S or a laboratory assigned by Novo Nordisk A/S. Results will be reported under a separate study and the data documented independently from the clinical trial report.

The samples will be stored at a central bio-repository after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.

Protocol
Trial ID: NN1250-4252
UTN: U1111-1184-8175
EudraCT no.: 2016-002801-20

~~CONFIDENTIAL~~

Date:	23 February 2018	Novo Nordisk
Version:	3.0	
Status:	Final	
Page:	103 of 108	

The subject's identity will remain confidential and the antibody samples will be identified only by subject number, visit number and trial identification number. No direct identification of the subject will be stored together with the samples.

Only Novo Nordisk staff and bio-repository personnel will have access to the stored antibody samples.

Subjects can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

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

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to 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 benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the clinical trial report synopsis to the 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 trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

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

26 Indemnity statement

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

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

For Poland only: Novo Nordisk carries liability for the trial exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal of Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the trial, Novo Nordisk and the investigators are covered by the insurance policy issued according to applicable Polish law.

27 References

1. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1), Step 4. 10 June 1996.
2. World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.
3. Leahy JL. Pathogenesis of type 2 diabetes mellitus. *Arch Med Res.* 2005;36(3):197-209.
4. Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal TP, Hemmingsen C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2013(11):CD008143.
5. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia.* 2015;58(3):429-42.
6. Garber AJ, King AB, Del Prato S, Sreenan S, Balci MK, Munoz-Torres M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet.* 2012;379(9825):1498-507.
7. Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care.* 2012;35(12):2464-71.
8. Wysham H, Carol, Bhargava A, Chaykin BL, Rosa RDL, Handelsman Y, Troelsen NL, et al. SWITCH 2: Reduced Hypoglycemia with Insulin Degludec (IDeg) vs. Insulin Glargine (IGlar), Both U100, in Patients with T2D at High Risk of Hypoglycemia: A Randomized, Double-Blind, Crossover Trial. *Diabetes.* 2016;65 (Supplement 1):90-LB.
9. Novo Nordisk A/S. Investigator's Brochure, insulin degludec (11th edition). December 2015.
10. Novo Nordisk A/S. Tresiba[®] (insulin degludec) EU Summary of Product Characteristics (SmPC). 2015.
11. Novo Nordisk A/S. Tresiba[®] U.S. Label information. 2015.
12. Ritzel R, Roussel R, Bolli GB, Vinet L, Brulle-Wohlhueter C, Glezer S, et al. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. *Diabetes Obes Metab.* 2015;17(9):859-67.
13. Yki-Järvinen H, Bergenstal R, Ziemien M, Wardecki M, Muehlen-Bartmer I, Boelle E, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care.* 2014;37(12):3235-43.
14. European Medicines Agency. Toujeo[®] - Summary of Product Characteristics. 4/24/ 2015.
15. Food and Drug Administration. Toujeo[®] - U.S. Label information. 2015.
16. Health Canada. Toujeo[™] SoloSTAR[®], CA Prescribing Information (PI). 15-July-2015 2015.

17. Yki-Järvinen H, Bergenstal RM, Bolli GB, Ziemer M, Wardecki M, Muehlen-Bartmer I, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus insulin glargine 100 U/ml in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension. *Diabetes Obes Metab.* 2015;17(12):1142-9.
18. Home PD, Bergenstal RM, Bolli GB, Ziemer M, Rojas M, Espinasse M, et al. New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 1 Diabetes: A Randomized, Phase 3a, Open-Label Clinical Trial (EDITION 4). *Diabetes Care.* 2015.
19. Vora J, Christensen T, Rana A, Bain SC. Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: a meta-analysis of endpoints in phase 3a trials. *Diabetes Ther.* 2014;5(2):435-46.
20. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-12.
21. Stevens LA, Schmid CH, Zhang YL, Coresh J, Manzi J, Landis R, et al. Development and validation of GFR-estimating equations using diabetes, transplant and weight. *Nephrol Dial Transplant.* 2010;25(2):449-57.
22. Lamb EJ, Levey AS, Stevens PE. The Kidney Disease Improving Global Outcomes (KDIGO) guideline update for chronic kidney disease: evolution not revolution. *Clin Chem.* 2013;59(3):462-5.
23. Novo Nordisk A/S. <http://www.novonordisk-trials.com/website/content/how-we-disclose-trial-information.aspx>.
24. De Angelis 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. *N Engl J Med.* 2004;351(12):1250-1.
25. U.S. Department of Health and Human Services, Food and Drug Administration. Food and Drug Administration Amendments Act of 2007. 27 September 2007.
26. The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, article 11. *Official Journal of the European Communities.* 1 May 2001.
27. The European Parliament and the Council of the European Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. *Official Journal of the European Communities.* 2004.
28. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care.* 1995;18(4):517-22.
29. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care.* 2013;36(5):1384-95.

30. McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. *Diabet Med.* 2001;18(9):690-705.
31. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009.
32. Stull DE, Leidy NK, Parasuraman B, Chassany O. Optimal recall periods for patient-reported outcomes: challenges and potential solutions. *Curr Med Res Opin.* 2009;25(4):929-42.
33. Rewers MJ, Pillay K, de Beaufort C, Craig ME, Hanas R, Acerini CL, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and monitoring of glycemic control in children and adolescents with diabetes. *Pediatr Diabetes.* 2014;15 Suppl 20:102-14.
34. Novo Nordisk A/S. Insulatard[®] (human isophan insulin), EU Summary of Product Characteristics. SEP 2015.
35. Novo Nordisk A/S. NOVOLIN[®] N, US Prescribing Information (PI). 01-August-2016 2016.
36. Novo Nordisk A/S. Novolin[®] ge, CA prescribing Information (PI). 11-March-2016 2016.
37. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1). 2 Jul 2010.
38. Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. *J Clin Invest.* 1987;79(3):777-81.
39. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals; current version available at www.icmje.org.

Appendix A: Insulin Titration Guideline

Trial ID: NN1250-4252

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

Table of Contents

	Page
Table of Contents	2
Table of tables	2
1 Introduction	3
2 Treatment regimens	4
2.1 Injection area	4
2.2 Time of injection	4
3 Initiation and titration	5
3.1 Initiation	5
3.2 Titration	5
3.3 Deviations from the algorithm	6
4 Data collection	7
5 Review procedure	8
6 References	9

Table of tables

	Page
Table 1 IDeg 200 U/mL or IGlax 300 U/mL dose increase	5
Table 2 IDeg 200 U/mL or IGlax 300 U/mL reduction	6

1 Introduction

The goal of insulin therapy is to achieve near normoglycaemia, i.e. to reach a pre-defined HbA_{1c} level with a low rate of hypoglycaemic episodes and as little weight gain as possible. Several trials have shown that this is difficult to achieve, unless plasma glucose (PG) values are intensively monitored and the insulin dose(s) frequently adjusted¹⁻⁶.

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

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

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

2 Treatment regimens

At Visit 2 (randomisation), pre-trial insulin treatment must be discontinued. Eligible subjects are randomised 1:1 into one of the two treatment arms:

- Insulin degludec (IDeg 200 U/mL) either morning or evening OD \pm OAD
- Insulin glargine (IGlar 300 U/mL) either morning or evening OD \pm OAD

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

There are no maximum or minimum doses.

2.1 Injection area

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

2.2 Time of injection

According to the randomisation the daily dose of basal insulin should be taken either in the morning between waking up and breakfast or in the evening from main evening meal to bedtime.

3 Initiation and titration

3.1 Initiation

For patients randomised to IDeg 200 U/mL OD, the daily basal insulin dose should be reduced by 20% from pre-trial dose.

Patients randomised to IGLar 300 U/mL should switch unit-to-unit, if they prior to randomisation received basal insulin once daily. For patients that prior to randomisation received a BID basal insulin regimen, the following applies:

- US patients that prior to randomisation received a BID basal regimen with NPH insulin should have their total daily insulin dose reduced by 20% and injected once daily
- US patients that prior to randomisation received a BID basal regimen with other basal insulin types than NPH should have a unit to unit conversion of their total daily basal insulin dose and injected once daily
- EU patients that prior to randomisation received a BID basal regimen with any basal insulin type should have their total daily basal insulin dose reduced by 20% and injected once daily

3.2 Titration

After randomisation the insulin dose will be adjusted once weekly by the investigator in connection with the scheduled visits/phone contacts.

The dose adjustment will be based on the mean of three fasting SMPG values measured on two days prior to titration and on the day of the visit. Adjustments will be in accordance with [Table 1](#) and [Table 2](#).

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

Table 1 IDeg 200 U/mL or IGLar 300 U/mL dose increase

Mean pre-breakfast SMPG		Dose adjustment
mmol/L	mg/dL	U
4.0 – 5.0	71 – 90	No adjustment
5.1 – 7.0	91 – 126	+ 2
7.1 – 8.0	127 – 144	+ 4
8.1 – 9.0	145 – 162	+ 6
> 9.0	> 162	+ 8

Table 2 IDeg 200 U/mL or IGLar 300 U/mL reduction

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

3.3 Deviations from the algorithm

It is recommended that the algorithm is followed. However, it is also important that the decision to adjust the IDeg 200 U/mL or IGLar 300 U/mL doses are based on all relevant information as described in [Section 1](#). A reason for deviating from the algorithm should be entered into the eCRF .

4 Data collection

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

- Per protocol pre-breakfast SMPG values measured since last visit/telephone contact as described in section [3.2](#)
- IDeg 200 U/mL/IGlar 300 U/mL doses taken day -2 and day -1 prior to the visit/phone contact

- New IDeg 200 U/mL/IGlar 300 U/mL dose prescribed at this contact.
- Reasons for deviation from the titration algorithms, if applicable
- Hypoglycaemic episodes

5 Review procedure

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

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

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

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

6 References

1. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia*. 2008;51(3):408-16.
2. Hermansen K, Davies M, Derezinski T, Ravn GM, Clauson P, Home P, et al. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care*. 2006;29(6):1269-74.
3. Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther*. 2006;28(10):1569-81.
4. Riddle MC, Rosenstock J, Gerich J, Insulin Glargine Study I. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003;26(11):3080-6.
5. Garber AJ, King AB, Del Prato S, Sreenan S, Balci MK, Munoz-Torres M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet*. 2012;379(9825):1498-507.
6. 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):1489-97.

insulin degludec
Trial ID: NN1250-4252
Clinical Trial Report
Appendix 16.1.1

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29 May 2019
1.0
Final

Novo Nordisk

Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Protocol Amendment
Trial ID: NN1250-4252
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1 of 9

Novo Nordisk

Protocol Amendment
no 1
to Protocol, final version 2.0
dated 11 November 2016

Trial ID: NN1250-4252

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

Trial phase: 3b

Applicable to Serbia

Amendment originator:

[REDACTED]

[REDACTED]

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Table of Contents

	Page
Table of Contents	2
1 Introduction including rationale for the protocol amendment	3
1.1 Rationale for amendment	3
2 Changes	3
2.1 Section 8.1.6. Follow up visits.....	3
2.2 Section 8.1.8 Premature discontinuation of trial product	4
2.3 Section 8.1.9 Withdrawal from trial.....	6
2.4 Section 9.5 Auxiliary supplies	6
2.5 Section 12.4.1 Reporting of technical complaints.....	7
2.6 Section 13.3 eDiary.....	7

1 Introduction including rationale for the protocol amendment

In this protocol amendment:

- Any new text is written *in italics*.
- Any text deleted from the protocol is written using ~~strike through~~.

1.1 Rationale for amendment

As stated in the protocol the MyGlucoHealth BG-meter used in NN1250-4252 is not marketed in Serbia and therefore regarded as an investigational device.

This protocol amendment has been created to reflect:

- The process for Technical Complaint handling on the MyGlucoHealth BG-meter, strips, lancets and control solution, including technical complaints related to adverse events and serious adverse events in Serbia
- The requirements to collect the MyGlucoHealth BG-meter at End of Trial for each subject in Serbia

2 Changes

2.1 Section 8.1.6. Follow up visits

The first follow up visit (V55) is a site visit and must take place 7-12 days after the end of treatment visit. Follow-up visit 2 (V56) is a site visit and must take place 30-35 days after end of treatment.

Follow-up visit 1 (V55)

At the first follow up visit (V55) treatment with insulin NPH must be stopped.

The following data will be collected:

- Date and dose of last injection of insulin NPH
- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)
- Technical complaints
- Antibody sample

~~The eDiary must be returned by the subject at this visit. Subjects who prematurely discontinue trial product should keep the eDiary and not return it until at V54A.~~

Please refer to the flow chart in section 2 for the full list of assessments and procedures to be performed at this visit.

Follow-up visit 2 (V56)

The following data will be collected:

- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)

The eDiary must be returned by the subject at this visit. Subjects who prematurely discontinue trial product should keep the eDiary and not return it until at V54A.

For Serbia: The BG meter must also be collected by the investigator. Subjects who prematurely discontinue trial product should keep the BG meter and not return it until at V54A.

2.2 Section 8.1.8 Premature discontinuation of trial product

If a subject prematurely discontinues trial product, the investigator must undertake procedures similar to those for the end of treatment visit (V54) as soon as possible including fasting blood sampling and dispensing of wash-out insulin NPH, see Section [8.1.5](#).

Treatment discontinuation must be performed in the eDiary web portal and in the IWRS.

Furthermore two follow up visits similar to V55 and V56 must be performed 7-12 and 30-35 days after discontinuation of trial product, respectively.

Follow-up visit 1 (V55)

At the first follow up visit (V55) the subject should be switched to treatment with a suitable marketed product at the discretion of the investigator.

The following data will be collected:

- Date and dose of last injection of insulin NPH prior to V55
- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)
- Technical complaints
- Antibody sample

Follow-up visit 2 (V56)

The following data will be collected:

- AEs
- Hypoglycaemic episodes

- Concomitant medication (diabetes)

In addition, subjects prematurely discontinued from trial product should come in for abbreviated site visits at week 16 (V18A), week 28 (V30A) and at week 40 (V42A) after randomisation depending on when the subject discontinues trial product. The abbreviated site visits can be converted to phone contacts if needed.

The following data will be collected:

- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)
- Blood sample to measure HbA_{1c} (only if site visit)

In between the abbreviated site visits listed above **monthly phone contacts (PX visits)** should be performed until the originally planned end of treatment.

The following data will be collected:

- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)

The earliest of the abbreviated site visits or monthly phone contacts (whichever comes first) should be scheduled at least 30 days after FU2. If the timing of a monthly phone contact (PX visit) is less than two weeks from a planned abbreviated site visit, the phone contact can be omitted.

Subjects prematurely discontinued from trial products should come in for a **final visit (V54A)** at the **originally planned end of treatment date** to collect:

- Date and dose of basal insulin
- AEs
- Hypoglycaemic episodes
- Concomitant medication (diabetes)
- Blood sample to measure HbA_{1c}

The eDiary must be returned by the subject at this visit.

For Serbia: The BG meter must also be collected by the investigator.

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

2.3 Section 8.1.9 Withdrawal from trial

If a subject withdraws consent, the investigator should aim to undertake procedures similar to those for the end of treatment visit (V54) as soon as possible. The eDiary must be returned by the subject at this visit.

For Serbia: The BG-meter must also be collected by the investigator.

If the subject agrees, the follow up visits (V55 and V56) must be performed 7-12 and 30-35 days after discontinuation of trial product.

The End-of-Treatment and End of Trial forms must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be made in the eDiary web portal and in the IWRS. The case book must be signed.

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

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

2.4 Section 9.5 Auxiliary supplies

The following will be provided by Novo Nordisk:

- Direction for use for the pen injectors
- Novo Nordisk needles for prefilled systems
- MyGlucoHealth Wireless Meter (CE approved) and strips, lancets and control solution for BG meters
- eDiary

Only needles provided by Novo Nordisk must be used for administration of trial product.

For Serbia: The BG-meter is regarded as an investigational device. Technical complaints regarding the BG-meter *including technical complaints related to AEs and SAEs* should be reported to the manufacturer of the device (Entra Health Systems). *Refer to Section [12.4.1](#) for details.* This device has been selected in order to have automatic transfer of SMPG data to the eDiary and thereby increase the accuracy of SMPG values. It is expected that the better accuracy in SMPG data will facilitate an improvement in the insulin titration efforts during the trial.

Please refer to the TMM for further auxiliary supplies' details.

2.5 Section 12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Insulin degludec 3ml PDS290 pen injector (FlexTouch[®])
- Insulin glargine (Toujeo[®]) 1.5ml prefilled pen (SoloStar[®])
- Insulin NPH (Insulatard[®]/Prothaphane[®]/Novolin NTM) 3ml prefilled pen (FlexPen[®])
- Novo Nordisk needles for pre-filled pen systems

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 and/or SAEs.

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

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

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

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

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

For Serbia: Technical complaints on the BG meter, strips, lancets and control solutions must be reported to ENTRA on a separate technical complaint paper form within the same timelines as for technical complaints specified above. AEs and SAEs related to the technical complaints on the BG meter must also be reported to Novo Nordisk, see Section [12.2](#) for details. Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

2.6 Section 13.3 eDiary

An eDiary will be used to capture patient reported data, see Sections [8.3.1](#), [8.3.2](#) and [8.4.2](#). The Investigator must carefully instruct the subject in how to use the eDiary. All data entered in the eDiary is considered source data. All data from the eDiary will be transferred electronically to the

electronic patient reported outcomes (ePRO) database. Data in the ePRO database will be viewable to investigator and Novo Nordisk personnel on a secure, password protected eDiary web portal.

The investigator must review all the data for the subjects belonging to the site through the eDiary web portal. The review of hypoglycaemic episode confirmation must be documented in the web portal, while review of remaining data must be documented in the subject's medical record. The review of data must be performed before or during each visit/phone contact.

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.

The Investigator should record the following administrative information in the eDiary/web portal:

- Subject ID
- Visit confirmation
- Hypoglycaemic episode confirmation
- Prescribed doses of trial products or confirm recommended dose
- Reason for deviation from the recommended dose, if needed
- Evaluate if a hypoglycaemic episode qualifies as an SAE

Data will be transferred to the Novo Nordisk trial database at defined intervals. For details on eDiary data flow, see [Figure 13-1](#).

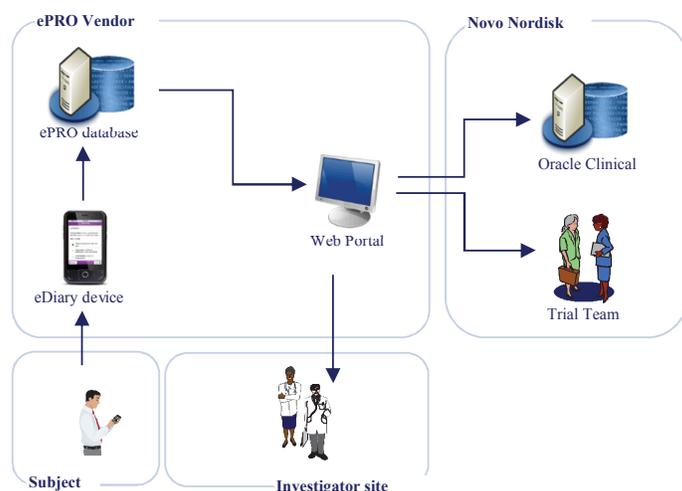


Figure 13-1 eDiary data flow

Selected titration data (e.g. certain SMPGs and dose data) will only be used during the trial for central titration surveillance, to ensure compliance with the titration guideline ([Appendix A](#)), and will not be reported in the clinical trial report (CTR). All data will be stored by Novo Nordisk (see Section [24](#)).

The eDiary should be collected by the Investigator at FU2 (V56).

For Serbia: The BG-meter must also be collected by the investigator at FU2 (V56).

Subjects who prematurely discontinue trial product should keep the eDiary and not return it until at V54A.

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23 February 2018
1.0
Final
1 of 4

Novo Nordisk

Protocol Amendment

no 2

**to Protocol, version 2.0
dated 11 Nov 2016**

Trial ID: NN1250-4252

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

**Trial phase: 3b
Applicable to all countries**

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Protocol Amendment no 2
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EudraCT no.: 2016-002801-20

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Date:	23 February 2018	Novo Nordisk
Version:	1.0	
Status:	Final	
Page:	2 of 4	

Table of Contents

1	Introduction including rationale for the protocol amendment.....	3
2	Changes	3

1 Introduction including rationale for the protocol amendment

Due to an unusual data reporting pattern of hypoglycaemia and glycaemic values in two ongoing randomised clinical trials (NN1250-4252 and NN1218-4113), Novo Nordisk has decided to discontinue the glycaemic data collection system (i.e. the combined use of a BG-meter and eDiary) in trials using this system to protect the safety of the trial participants. This affects the NN1250-4252, NN1218-4113 and NN1250-4300 trials.

This protocol amendment has been created in alignment with the above decision to replace the electronic glycaemic data collection system with a paper diary solution.

2 Changes

The discontinuation of the glycaemic data collection system necessitates update of many sections of the Protocol, Titration guideline and Protocol Metadata Document (PMD).

The changes are affecting the following sections of the protocol:

- 1 Summary
- 2 Flowchart
- 4 Objective(s) and endpoint(s)
- 5 Trial design
- 6.4 Criteria for premature discontinuation of trial product
- 8.1.5 Maintenance 2 initiation visit (57) New section
- 8.1.6 End of Treatment Visit
- 8.1.7 Follow up visits
- 8.1.9 Premature discontinuation of trial product
- 8.1.10 Withdrawal from trial
- 8.1.11 Review of results
- 8.2.5 Concomitant medication
- 8.2.6 Concomitant medication (Diabetes)
- 8.3.1 Self-measured plasma glucose
- 8.3.2 Insulin dose
- 8.4.2 Hypoglycaemic episodes
- 8.4.6 Eye examination
- 8.4.7 Electrocardiogram
- 8.5.2 Laboratory assessments for safety
- 8.6 Other assessments
- 8.7 Subject compliance
- 9.5 Auxiliary supplies
- 12.1.5 Adverse events requiring additional data collection
- 12.7.2 Event adjudication committee

- 13.3 eDiary – complete section deleted
- 14 Monitoring procedures
- 17 Statistical considerations
- 18 Ethics
- 19.2 Prevention of missing data

The changes are affecting the following sections of the Titration guideline:

- 3.3 Deviations from the algorithm
- 4 Data collection
- 5 Review procedure

The Protocol Metadata Document (PMD) will be updated after PRC approval of the updated flowchart.

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Memo

To:
TMF

Copy:

From:
[REDACTED]

11 January 2019

Ref.: PLLP

NN1250-4252 Handling of Anti-insulin antibodies

On 16 January 2018 it was decided by the Corporate Vice President not to analyse Anti-insulin antibodies collected in NN1250-4252 as the data are not required at present.

All collected antibody samples are being sent to the Central Laboratory and then transferred to the Novo Nordisk Laboratory in Måløv for storage until further notice.

The protocol states in section 17.6.2: "Anti-insulin antibodies will be summarised by visit".

This has been deleted from the Statistical Analysis Plan (SAP).