Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02773368
Sponsor trial ID:	NN9068-4229
Official title of study:	A clinical trial comparing glycaemic control and safety of insulin degludec/liraglutide (IDegLira) versus insulin glargine (IGlar) as add-on therapy to SGLT2i in subjects with type 2 diabetes mellitus
Document date:	22-March-2018

16.1.1 Protocol and protocol amendments

List of contents

Protocol

Trial ID: NN9068-4229

DUAL™ IX - Add-on to SGLT2i

A clinical trial comparing glycaemic control and safety of insulin degludec/liraglutide (IDegLira) versus insulin glargine (IGlar) as add-on therapy to SGLT2i in subjects with type 2 diabetes mellitus

Redacted protocol
Includes redaction of personal identifiable information only.

Trial phase: 3b

Protocol originator

[redacted], [redacted]

Insulin & Diabetes Outcomes

Table of Contents

Appendices and attachments to the protocol

- Appendix A: Titration Guideline
- Appendix B: Events with additional data collection and events requiring adjudication
- Appendix C: Monitoring of calcitonin
- Attachment I – Global list of key staff and relevant departments and suppliers

Table of Figures

Page

Table of Tables

Page

List of abbreviations

ADA	American Diabetes Association	FSFV	first subject first visit
AE	adverse event	FU	follow-up
ALT	alanine aminotransferase	GCP	Good Clinical Practice
AST	aspartate aminotransferase	GLP-1	glucagon-like peptide-1
BG	blood glucose	HbA_{1c}	glycosylated haemoglobin
BMI	body mass index	hCG	human Chorionic Gonadotropin
CCDS	company core data sheet	HDL	high density lipoprotein
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration	IB	Investigator's Brochure
CR	copy reference	ICH GCP	International Conference on Harmonisation. Guideline for Good Clinical Practice
CRF	case report form	IDeg	insulin degludec
CTR	clinical trial report	IDegLira	insulin degludec/liraglutide
DPP4i	dipeptidyl peptidase-4 inhibitors	IDMS	isotope-dilution mass spectrometry
DUN	dispensing unit number	IGlar	insulin glargine
EAC	Event Adjudication Committee	IMPs	investigational medicinal products
EASD	European Association for the Study of Diabetes	IRB/IEC	Institutional Review Board/Independent Ethics Committee
ECG	electrocardiogram	IWRS	interactive web response system
eCRF	electronic case report form	J2R	jump to reference
eGFR	estimated Glomerular Filtration Rate	LDL	low-density lipoprotein
EoT	end of treatment	LLOQ	lower limit of quantification
EMA	European Medicines Agency	LSFV	last subjects first visit
FAS	full analysis set	MACE	major adverse cardiovascular events
FDA	U.S. Food and Drug Administration	MI	myocardial infarction
FPG	fasting plasma glucose	NIMPs	non-investigational medicinal products

NYHA	New York Heart Association
OAD	oral antidiabetic drugs
OD	once daily
PG	plasma glucose
Pre-disc	premature discontinued from trial product
PRO	patient reported outcome
Px	phone contacts for subjects premature discontinued from trial product
SAE	serious adverse event
SAS	safety analysis set
s.c.	subcutaneous
SF-36v2	Medical outcomes study 36-item short form version 2
SGLT2i	sodium-glucose co-transporter 2 inhibitors
SIF	safety information form
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TMM	trial materials manual
TRIM-D	Treatment related impact measure
TSH	thyroid stimulating hormone
TTT	treat to target
UTN	Universal Trial Number
VLDL	very-low-density lipoprotein

1 Summary

Objectives and endpoints:

Primary objective

To confirm the effect of insulin degludec/liraglutide (IDegLira) in terms of glycaemic control in subjects with type 2 diabetes mellitus (T2DM) on previous treatment with sodium-glucose co-transporter 2 inhibitors (SGLT2i) ± oral anti-diabetic drug (OAD) therapy. This is done by comparing the difference in change from baseline in HbA_{1c} after 26 weeks to a non-inferiority margin of 0.3% for IDegLira versus insulin glargine (IGlar), both in combination with SGLT2i ± OAD.

Primary endpoint

Change from baseline in HbA_{1c} after 26 weeks.

Key secondary objectives

To confirm superiority of IDegLira versus IGlar after 26 weeks in subjects with T2DM on previous treatment with SGLT2i ± OAD therapy in terms of one or more of the following:

- Weight change
- Treatment-emergent hypoglycaemic episodes (severe or blood glucose [BG] confirmed symptomatic)
- Glycaemic control
- Insulin dose

To compare the effect and safety of IDegLira versus IGlar after 26 weeks.

Key secondary endpoints

The key secondary endpoints are:

- Change from baseline in body weight after 26 weeks
- Number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks
- Insulin dose, total daily dose (U) after 26 weeks
- Responder after 26 weeks (Yes/No) for $HbA_{1c} < 7.0\%$
- Change from baseline after 26 weeks in fasting plasma glucose (FPG)
- Number of treatment-emergent adverse events during 26 weeks

Trial design:

This is a 26-week randomised, active-controlled, multicentre, multinational, two-arm parallel, open-label, treat-to-target trial (TTT) in subjects with T2DM. Subjects inadequately controlled on OAD

treatment with SGLT2i will be eligible for the trial. Pre-trial OAD treatments must include SGLT2i either as monotherapy, or in combinations with metformin ± dipeptidyl peptidase-4 inhibitor (DPP4i) ± pioglitazone. If a subject is treated with DPP4i these have to be discontinued at randomisation. Subjects on fixed dose combinations of SGLT2i and DPP4i should be shifted to the corresponding SGLT2i, whereas fixed dose combinations of SGLT2i and metformin should be continued. Pioglitazone is allowed in all subjects, except those treated with dapagliflozin. The trial will compare IDegLira to IGlar as an add-on to treatment with SGLT2i ± OAD. Inadequately controlled T2DM is defined as an HbA_{1c} level of 7.0-11.0%, both inclusive.

Trial population:

Planned number of subjects to be randomised and started on trial products is 416.

Key inclusion criteria

- Male or female, age ≥ 18 years at the time of signing informed consent
- Subjects diagnosed (clinically) with type 2 diabetes mellitus
- HbA_{1c} 7.0-11.0% [53-97 mmol/mol] (both inclusive) by central laboratory analysis
- Body mass index (BMI) ≥ 20 kg/m^2 and < 40 kg/m^2
- Insulin naïve subjects; however short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed, as well as prior insulin treatment for gestational diabetes
- A stable daily dose for at least 90 days prior to the day of screening of any SGLT2i in monotherapy or in combination with metformin ± DPP4i ± pioglitazone. Use of pioglitazone is not allowed in subjects treated with dapagliflozin

Key exclusion criteria

- Receipt of any investigational medicinal product within 90 days prior to screening
- Use of any OADs (other than SGLT2i in monotherapy or in combination with metformin or DPP4i or pioglitazone as described in the inclusion criteria) within 90 days prior to the day of screening
- Use of glucagon-like peptide-1 (GLP-1) receptor agonist (e.g., exenatide or liraglutide) within 90 days prior to the day of screening
- Acute decompensation of glycaemic control requiring immediate intensification of treatment to prevent severe metabolic dysregulation (e.g., diabetes ketoacidosis) in the previous 90 days prior to the day of the screening
- Subjects presently classified as being in NYHA Class III or IV[1]
- Renal impairment estimated Glomerular Filtration Rate < 60 mL/min/1.73 m^2 as per CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)

- Impaired liver function, defined as ALT ≥ 2.5 times upper normal limit at screening
- Known or suspected hypersensitivity to trial product(s) or related products

Key efficacy assessments:

- HbA_{1c}
- Body weight

Key safety assessments:

- Hypoglycaemic episodes
- Adverse events (AEs)

Trial products:

- IDegLira 100 units/mL + 3.6 mg/mL, a fixed ratio of IDeg (100 units/mL) and liraglutide (3.6 mg/mL) solution provided in a 3 mL pre-filled PDS290 pen-injector for subcutaneous (s.c.) injection
- IGlar (Lantus®) 100 units/mL solution for injection in a pre-filled pen (SoloStar®) for s.c. injection

The subject's de-facto cost of SGLT2i and metformin (mono- or fixed dose combination products) will be reimbursed in accordance with local legislation and Ethics Committee approval.

2 Flow chart

Trial Periods	Screen	Rand	Treatment																	EoT	Follow-up		Pre-disc[1]	
Trial site visit (V) Phone contact (P)[2]	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11 P12 P13	V14	P15 P16 P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29 P30 P31	V32	FU1 V33	FU2 P34	PX	V32A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	0.5[3]	1	1.5[3]	2	2.5[3]	3	3.5[3]	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 -25	26	7 days after last trial product	30 days after last trial product	Every 4 weeks	26
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
SUBJECT RELATED INFO/ASSESSMENTS																								
Informed consent	X																							
In/exclusion criteria	X	X																						
Randomisation		X																						
Pre-discontinuation of trial product			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Rescue criteria				X		X		X		X	X	X	X	X	X	X	X	X	X	X				
Withdrawal of consent			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[4]	X	
Demography[5]	X																							
Concomitant illness	X																							
Medical history	X																							
Diagnosis of diabetes	X																							
Diabetes complications	X																							

[1] Subjects discontinuing trial product prematurely will be asked to attend the end of treatment (EoT) visit and the two follow up visits after discontinuation corresponding to V32, V33 and P34. After the follow-up period the subject should have phone contacts scheduled every 4 weeks (PX) until the additional premature discontinuation follow-up visit (V32A) performed at week 26. See section 8.1.7 for further details.
[2] A phone contact may be converted to a trial site visit e.g. if further titration is needed.
[3] Corresponding to previous visit date plus 3 days.
[4] Only applicable for subjects discontinuing trial product prematurely.
[5] Collection of sex and date of birth, race and ethnicity only if applicable by local law.

Trial Periods	Screen	Rand	Treatment																	EoT	Follow-up		Pre-disc[1]	
Trial site visit (V) Phone contact (P)[2]	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11 P12 P13	V14	P15 P16 P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29 P30 P31	V32	FU1 V33	FU2 P34	PX	V32A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	0.5[3]	1	1.5[3]	2	2.5[3]	3	3.5[3]	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 -25	26	7 days after last trial product	30 days after last trial product	Every 4 weeks	26
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Diabetes treatment history	X																							
Family history of diabetes	X																							
Hypoglycaemia unawareness	X																							
Concomitant medication	X	X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X[6]	X[6]	X[6]	X[6]
Insulin dose																								X[7]
Tobacco use	X																							
EFFICACY																								
Body measurements																								
Body weight[8]	X	X								X		X		X		X		X		X				X
BMI	X																			X				
Height	X																							
Waist circumference		X												X						X				
Glucose metabolism																								
HbA1c	X	X								X		X		X		X		X		X				X
Fasting plasma glucose[9]		X								X		X		X		X		X		X				
Lipids		X												X						X				

[6] Only anti-diabetic medication will be collected.
[7] If no insulin is taken by the subject, please enter "0" in the eCRF
[8] Body weight should be measured fasting except at V1, see section 8.1.1
[9] The subjects must attend visits fasting, see section 8.1.1

Trial Periods	Screen	Rand	Treatment																	EoT	Follow-up		Pre-disc[1]	
Trial site visit (V) Phone contact (P)[2]	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11 P12 P13	V14	P15 P16 P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29 P30 P31	V32	FU1 V33	FU2 P34	PX	V32A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	0.5[3]	1	1.5[3]	2	2.5[3]	3	3.5[3]	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 -25	26	7 days after last trial product	30 days after last trial product	Every 4 weeks	26
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Self measured plasma glucose (SMPG)																								
Once daily[10]				X		X		X		X	X	X	X	X	X	X	X	X	X	X				
9-point profile[11]		X												X						X				
SAFETY																								
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[12]	X[12]
Hypoglycaemic episodes				X		X		X		X	X	X	X	X	X	X	X	X	X	X	X			
Technical complaints		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X				
ECG	X																			X[13]				
Eye examination	X[14]																			X[15]				
Physical examination	X																			X				
Vital signs	X	X												X						X				
Biochemistry	X	X								X				X		X				X				
Haematology	X	X												X						X				
Hormones (calcitonin)	X	X												X						X				
Urinalysis (albumin:creatinine ratio)	X													X						X				

[10] Subjects should measure "self measured plasma glucose" prior to breakfast. Diabetes medication should be withheld until after the SMPG measurement.
[11] 9-point profile should be measured within one week prior to the site visit (on a day where unusual strenuous exercises is not anticipated).
[12] Only AE information for potential major adverse cardiovascular events (MACE) and SAE information will be collected
[13] ECG obtained within 2 weeks prior to V32 is acceptable if results are available for evaluation at V32.
[14] Eye examination performed within 12 weeks prior to V2 as part of routine practice may replace the screening assessment if results are available for evaluation at V2.
[15] Eye examination performed within 2 weeks prior to V32 is acceptable if results are available for evaluation at V32.

Trial Periods	**Screen**	**Rand**	**Treatment**																	**EoT**	**Follow-up**		**Pre-disc[1]**	
Trial site visit (V) **Phone contact (P)[2]**	**V1**	**V2**	**P3**	**V4**	**P5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11** **P12** **P13**	**V14**	**P15** **P16** **P17**	**V18**	**P19** **P20** **P21**	**V22**	**P23** **P24** **P25**	**V26**	**P27** **P28** **P29** **P30** **P31**	**V32**	**FU1** **V33**	**FU2** **P34**	**PX**	**V32A**
Timing of visit (weeks)	**≤ 2 weeks prior to V2**	**0**	**0.5[3]**	**1**	**1.5[3]**	**2**	**2.5[3]**	**3**	**3.5[3]**	**4**	**5** **6** **7**	**8**	**9** **10** **11**	**12**	**13** **14** **15**	**16**	**17** **18** **19**	**20**	**21 -25**	**26**	**7 days after last trial product**	**30 days after last trial product**	**Every 4 weeks**	**26**
Visit window (days)			**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**+3**	**±3**	**±3**
Urine dipstick		X												X						X				
Pregnancy test[16]	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X				
OTHER ASSESSMENTS																								
Barriers in Diabetes Treatment questionnaire		X																						
PRO questionnaires																								
TRIM-D		X										X								X				
SF-36v2		X										X								X				
TRIAL MATERIAL																								
Dispensing trial product		X						X		X		X		X		X		X						
IWRS call	X	X						X		X		X		X		X		X		X				
Dosing dates[17]				X																X				
Drug accountability		X						X		X		X		X		X		X		X				
REMINDERS																								
Hand-out ID card	X																							
Discontinue DPP4i		X																						
Training in trial product and pen handling.		X						X		X		X		X		X		X						

[16] For women of childbearing potential a blood sample pregnancy test must be performed at V1 and V32. Additionally, a urine pregnancy test should be performed at site if pregnancy is suspected or if a menstrual period is missed. If the subject reports missing menstrual period at a phone contact, the subject will have to attend the site for an unscheduled visit as soon as possible to have an urine pregnancy test performed. If positive a confirmatory serum hCG test should be sent to the central laboratory. If required by local law, pregnancy test may be performed regularly.

[17] First and last dates and doses as recorded in patient diaries.

Trial Periods	**Screen**	**Rand**	**Treatment**																	**EoT**	**Follow-up**		**Pre-disc**[1]	
Trial site visit (V) **Phone contact (P)**[2]	**V1**	**V2**	**P3**	**V4**	**P5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11** **P12** **P13**	**V14**	**P15** **P16** **P17**	**V18**	**P19** **P20** **P21**	**V22**	**P23** **P24** **P25**	**V26**	**P27** **P28** **P29** **P30** **P31**	**V32**	**FU1** **V33**	**FU2** **P34**	**PX**	**V32A**
Timing of visit (weeks)	**≤ 2 weeks prior to V2**	**0**	**0.5**[3]	**1**	**1.5**[3]	**2**	**2.5**[3]	**3**	**3.5**[3]	**4**	**5** **6** **7**	**8**	**9** **10** **11**	**12**	**13** **14** **15**	**16**	**17** **18** **19**	**20**	**21 -25**	**26**	**7 days after last trial product**	**30 days after last trial product**	**Every 4 weeks**	**26**
Visit window (days)			**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**+3**	**±3**	**±3**
Dispense directions for use		X						X		X		X		X		X		X						
Hand-out and instruct in diary	X	X		X		X		X		X		X		X		X		X		X	X			
Collect and review diary		X		X		X		X		X		X		X		X		X		X	X			
Hand-out and instruct in BG meter	X																							
Attend visit fasting		X								X		X		X		X		X		X				
Make appointment for eye examination																			X					
Sign off Casebook																						X[18]		X
End of trial (subject completion)																						X[18]		X

[18] Not applicable for subjects that have prematurely discontinued trial product.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[2] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[3].

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

3.1 Background information

The progressive deterioration of glucose control in T2DM increases the need for multiple additive therapies in order to attain recommended glycaemic targets in the majority of subjects[4]. Landmark studies have demonstrated the importance of maintaining good glycaemic control to reduce the risk of long-term complications associated with diabetes[5,6]. The initial step in management of T2DM includes lifestyle intervention and treatment with OADs, often with metformin as a first choice. Given the progressive nature of T2DM, anti-diabetic therapies with mono-treatment may need intensification over time, and more anti-diabetic therapies may be combined, often two OADs. If the glycaemic target is not achieved or sustained with this treatment, several treatment options exist such as intensifying with insulin treatment, GLP-1 receptor agonist treatment or a combination of these. The successful outcome of recent global trials combining basal insulin and GLP-1 receptor agonist treatment as separate injections has led to the inclusion of this treatment combination in the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) position statement on management of hyperglycaemia in T2DM[4,7,8].

IDeg is a long-acting basal insulin and the active ingredient used in Tresiba®, which has been approved for use in amongst others the USA, European Union (EU) and Japan. For more details on IDeg see current Investigator's Brochure (IB)[9] and any updates hereof and locally approved labelling in countries where this is available.

Liraglutide is an analogue native (human) GLP-1 receptor agonist and the active ingredient used in Victoza®, which is approved amongst others in Australia, Canada, China, EU, Japan and the US for the treatment of adults with T2DM to achieve glycaemic control. For more details on liraglutide, please see the local approved labelling for Victoza®.

IDegLira (the combination of IDeg and Liraglutide) is a solution for s.c. injection for treatment of T2DM with once daily (OD) use. It is to be initiated and titrated to achieve adequate glycaemic control in a similar way as basal insulin therapy. The basal insulin and GLP-1 analogue combination provides complimentary effects of the two compounds on fasting and postprandial glycaemic control in a single injection. IDegLira is on the market as Xultophy® and has been approved for use amongst others in EU. Efficacy and safety of IDegLira has been demonstrated in previous randomised clinical trials (NN9068-3697, NN9068-3912, NN9068-3951, NN9068-3851 and NN9068-3952) and is currently being evaluated in the randomised clinical trials NN9068-4056

and NN9068-4185. In all finalised clinical trials, IDegLira has shown to effectively improve the glycaemic control of the subjects, and no unexpected safety issues were identified. For more information, see the IDegLira NN9068 IB[10] current version or any updates hereof.

The basal insulin and GLP-1 analogue combination brings complementary effects of the two compounds on fasting (IDeg and liraglutide) and postprandial (liraglutide) glycaemic control. The addition of liraglutide to IDeg reduces the requirement of exogenous insulin (i.e. insulin sparing effect) hence minimising the risk of hypoglycaemia and weight gain often associated with insulin treatment. The inherent weight reducing effect of liraglutide further contributes to the favourable weight profile of the combination drug compared to basal insulin treatment. Furthermore, given the glucose dependent effect of liraglutide, liraglutide reduces postprandial glucose excursions while reducing the risk of unwanted lowering of inter-prandial or fasting glucose.

IGlar (Lantus®) is a long-acting insulin analogue, indicated for treatment of diabetes mellitus in combination with oral antidiabetic agents. For further details, please refer to the Summary of Product Characteristics (SmPC)[11] for IGlar and the United States (U.S.) Label Information[12].

For an assessment of benefits and risks of the trial, see section 18.1.

3.2 Rationale for the trial

Recently, a new OAD class has been introduced on the market, the SGLT2i. The mode of action of SGLT2i is to inhibit renal re-absorption of glucose in the renal cortex, thereby increasing urinary glucose secretion and lowering blood glucose[13]. Treatment with SGLT2i is also associated with a lowering of systolic blood pressure of ~5 mmHg and a weight reduction in the range of 1–3 kg[14,15]. SGLT2i act independently of other diabetes treatment modalities, and combination therapy with most of the current therapies is expected. In line with this, SGLT2i in fixed dose combinations with various OADs, e.g., metformin and DPP4i are approved for use. However, as with current OAD regimens, it must be expected that a number of patients with T2DM treated with SGLT2i will need intensification of glycaemic control after a certain period of treatment.

This protocol describes a clinical trial aiming to demonstrate effect and safety of IDegLira versus IGlar as an add-on to SGLT2i ± OAD treatment in subjects with T2DM uncontrolled on this OAD treatment. IGlar has been chosen as a comparator as it is currently a widely used basal insulin.

4 Objectives and endpoints

4.1 Objectives

Primary objective

To confirm the effect of IDegLira in terms of glycaemic control in subjects with T2DM on previous treatment with SGLT2i ± OAD therapy. This is done by comparing the difference in change from baseline in HbA_{1c} after 26 weeks to a non-inferiority margin of 0.3% for IDegLira versus IGlar, both in combination with SGLT2i ± OAD.

Secondary objectives

To confirm superiority of IDegLira versus IGlar after 26 weeks in subjects with T2DM on previous treatment with SGLT2i ± OAD therapy in terms of one or more of the following:

- Weight change
- Treatment-emergent hypoglycaemic episodes (severe or blood glucose [BG] confirmed symptomatic)
- Glycaemic control
- Insulin dose

To compare the effect and safety of IDegLira versus IGlar after 26 weeks.

4.2 Endpoints

4.2.1 Primary endpoint

Change from baseline in HbA_{1c} after 26 weeks.

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

The confirmatory secondary endpoints are:

- Change from baseline in body weight after 26 weeks
- Number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks
- Insulin dose, total daily dose (U), after 26 weeks

4.2.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints:

- Responder after 26 weeks (Yes/No) for:
  - $HbA_{1c} < 7.0\%$ *

- $HbA_{1c} < 7.0\%$ without weight gain
- $HbA_{1c} < 7.0\%$ without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment
- $HbA_{1c} < 7.0\%$ without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment and without weight gain
- $HbA_{1c} \leq 6.5\%$
- $HbA_{1c} \leq 6.5\%$ without weight gain
- $HbA_{1c} \leq 6.5\%$ without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment
- $HbA_{1c} \leq 6.5\%$ without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment and without weight gain

- Change from baseline after 26 weeks in:
  - Waist circumference
  - Fasting plasma glucose (FPG)*
- Fasting lipid profile
  - Cholesterol
  - Low-density lipoprotein cholesterol (LDL cholesterol)
  - High-density lipoprotein cholesterol (HDL cholesterol)
  - Very-low-density lipoprotein cholesterol (VLDL cholesterol)
  - Triglycerides
  - Free fatty acids
- Self-measured plasma glucose (SMPG) 9-point profile
  - 9-point profile
  - Mean of the 9-point profile
  - Prandial plasma glucose increments (from before meal to 90 min after breakfast, lunch and dinner). The mean increment over all meals will be derived as the mean of all available meal increments
- Vital signs
  - Systolic and diastolic blood pressure

Supportive secondary safety endpoints:

- Number of treatment-emergent adverse events during 26 weeks*
- Number of treatment-emergent nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks
- Number of treatment-emergent hypoglycaemic episodes according to ADA definition during 26 weeks
- Change from baseline in clinical evaluation after 26 weeks:
  - Electrocardiogram (ECG)

- Eye examination
- Physical examination
- Pulse rate

- Change from baseline in laboratory assessments after 26 weeks:
  - Biochemistry
  - Haematology
  - Calcitonin
  - Urine albumin/creatinine ratio

Supportive secondary health economics endpoints:

- Change from baseline in patient reported outcomes (PROs) after 26 weeks:
  - Summary scores of medical outcomes study 36-item short form (SF-36v2)[16]
  - Summary scores of treatment related impact measure for diabetes (TRIM-D)[17]

* Key supportive secondary endpoint prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT)

5 Trial design

5.1 Type of trial

This is a 26-week randomised, active-controlled, multicentre, multinational, two-arm parallel, open-label, TTT trial in subjects with T2DM. Subjects inadequately controlled on treatment with SGLT2i ± OAD will be eligible for the trial. The trial will compare IDegLira to IGlar as an add-on to treatment with SGLT2i ± OAD. Inadequately controlled T2DM is defined as an HbA_{1c} level of 7.0-11.0 % (53-97 mmol/mol) (both inclusive).

A total of 416 subjects will be randomized using IWRS in a 1:1 manner to either of the two trial arms, IDegLira (OD) or IGlar (OD).

Figure 5–1 Trial Design

The total trial duration will be approximately 32 weeks, consisting of a 2 week screening period, a 26-week treatment period, and two follow-up contacts (FU1 and FU2). FU1 is scheduled 7 days (+3 days) after last dose of trial product, and FU2 is scheduled 30 days (+3 days) after last dose of trial product. The purpose of FU1 and FU2 are to collect all treatment-emergent adverse events (AEs).

5.2 Rationale for trial design

Based on experience from previous insulin titration trials a duration of 26 weeks is sufficient to reach a stable HbA_{1c} level, i.e. minimum of 12 weeks in maintenance period and to obtain sufficient data for efficacy and safety evaluation.

The multinational approach is chosen to ensure that the results are applicable for subjects with different race and ethnicity, and to ensure that local regulatory requirements are fulfilled for a marketing approval.

The TTT approach and thereby the very high frequency of visits has been chosen in order to ensure optimal titration of IDegLira or IGlar based on pre-breakfast SMPG values and thereby to obtain improved HbA_{1c} results.

The primary endpoint, HbA_{1c}, is being assessed at a central laboratory, thus avoiding assessment bias.

The trial is open-label, as blinding the trial and including placebo would require a double dummy design with two s.c. injections, which is deemed to pose an unacceptable burden to the subjects and increase the trial design complexity, thereby increasing the risk of subjects withdrawing from the trial, discontinuing treatment prematurely or being non-compliant.

5.3 Treatment of subjects

Subjects with T2DM treated with SGLT2i and OAD(s) in accordance with the inclusion and exclusion criteria are eligible for the trial. When randomised the subjects will get one of the investigational medicinal products (IMPs) described below in combinations with previous SGTL2i ± OAD. Pre-trial OAD treatments must include SGLT2i according to current local label, either as monotherapy, or in combination with metformin ± DPP4i ± pioglitazone. If a subject is treated with DPP4i these have to be discontinued at randomisation. Subjects on fixed dose combinations of SGLT2i and DPP4i should be shifted to the corresponding SGLT2i included in the original fixed dose combinations of SGLT2i and DPP4i. Pre-trial SGLT2i and metformin treatment should be continued at unchanged pre-trial doses throughout the trial, unless there is a safety concern. Pioglitazone is allowed in all subjects, except those treated with dapagliflozin, and pre-trial doses should be unchanged during the trial, unless there is a safety concern.

- IDegLira added to OAD therapy (SGLT2i ± OAD): IDegLira will be given s.c. once daily. The recommended starting dose of IDegLira is 10 dose steps (10 units insulin degludec/0.36 mg liraglutide). IDegLira will be titrated twice weekly according to a predefined titration algorithm, see appendix A, with a maximum dose of 50 dose steps (50 units insulin degludec/1.8 mg liraglutide) aiming to reach a pre-breakfast SMPG target between 4.0 – 5.0 mmol/L (72 – 90 mg/dL).

- IGlar added to OAD therapy (SGLT2i ± OAD): IGlar will be given s.c. once daily. IGlar should be administered according to the approved label. The recommended starting dose of IGlar is 10 units and will be titrated twice weekly according to a predefined titration algorithm, see appendix A, with no maximum dose aiming to reach a pre-breakfast SMPG target between 4.0 – 5.0 mmol/L (72 – 90 mg/dL).

The IMPs used in this trial are described in section 9.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products, either prematurely or at V32 the subject should be switched to a suitable marketed product at the discretion of the investigator.

5.5 Rationale for treatment

IDegLira will be investigated in this trial to demonstrate efficacy and safety, when added to SGTL2i ± OAD in T2DM subjects, inadequately controlled on SGTL2i ± OAD. If a subject is treated with DPP4i these have to be discontinued at randomisation, as IDegLira cannot be combined with DPP4i.

IGlar has been chosen as comparator as it is currently a widely used basal insulin.

The TTT approach will be applied after randomisation in order to optimise glycaemic control throughout the trial.

All subjects in both arms will continue with SGTL2i ± OAD at pre-trial doses. In case of a safety concern the dose(s) may be reduced or temporarily interrupted at the discretion of the investigator. SGTL2i ± OAD treatment must follow the current locally approved label and any local recommendations present at the time of conducting the trial.

The duration of 26 weeks has been chosen to obtain a stabilised HbA_{1c} ensuring an adequate length of time of trial product at steady state.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be randomised and started on trial products: 416

Number of subjects expected to complete the trial (on trial product): 354

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age ≥ 18 years at the time of signing informed consent.
3. Subjects diagnosed (clinically) with type 2 diabetes mellitus.
4. HbA_{1c} 7.0-11.0% (53-97 mmol/mol) (both inclusive) by central laboratory analysis.
5. BMI ≥ 20 kg/m^2 and < 40 kg/m^2.
6. Insulin naïve subjects; however short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed, as well as prior insulin treatment for gestational diabetes.
7. Oral antidiabetic treatment:
    a. <u>SGLT2i:</u> Subjects must have been on a stable daily dose of any SGLT2i (≥ half of the maximum approved dose according to current local label or maximum tolerated dose as documented in subject medical record, or minimum recommended maintenance* dose according to current local label) for at least 90 days prior to the day of screening.

    b. <u>Combination therapy:</u> Stable daily dose of SGLT2i as outlined above in combination with stable daily dose(s) of metformin ± DPP4i is allowed:

        i. Metformin (≥ 1500 mg or maximum tolerated dose as documented in the subject medical record) for at least 90 days prior to the day of screening.

        ii. DPP4i (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record) for at least 90 days prior to the day of screening.

        iii. Stable daily doses, as outlined above, of fixed dose combination products combining either SGLT2i and metformin or SGLT2i and DPP4i, according to locally approved label for at least 90 days prior to the day of screening are also allowed.

c. Pioglitazone: Stable daily dose (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record) for at least 90 days prior to the day of screening is allowed if a subject is treated with SGLT2i as outlined above, except in subjects treated with dapagliflozin.

* E.g. 100 mg Invokana® (canagliflozin) is recommended, but 300 mg is maximum approved dose.

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Receipt of any investigational medicinal product within 90 days prior to screening.
4. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).
5. Use of any OADs (other than SGLT2i in monotherapy or in combination with metformin or DPP4i or pioglitazone as described in the inclusion criteria) within 90 days prior to the day of screening.
6. Use of GLP-1 receptor agonist (e.g., exenatide or liraglutide) within 90 days prior to the day of screening.
7. Acute decompensation of glycaemic control requiring immediate intensification of treatment to prevent severe metabolic dysregulation (e.g., diabetes ketoacidosis) in the previous 90 days prior to the day of the screening.
8. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroids carcinoma.
9. Screening calcitonin ≥ 50 ng/L.
10. History of pancreatitis (acute or chronic).
11. Any of the following: myocardial infarction, stroke or hospitalisation for unstable angina and/or transient ischaemic attack within the past 180 days prior to the day of screening.
12. Subjects presently classified as being in NYHA Class III or IV.
13. Planned coronary, carotid or peripheral artery revascularisation at the day of screening.
14. Renal impairment eGFR < 60 mL/min/1.73 m^2 as per CKD-EPI.
15. Impaired liver function, defined as ALT ≥ 2.5 times upper normal limit at screening.
16. Inadequately treated blood pressure as defined as Class 2 hypertension or higher (systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg) at screening.
17. Anticipated initiation or change in concomitant medications for more than 14 consecutive days or on a frequent basis known to affect weight or glucose metabolism (e.g., orlistat, thyroid hormones, corticosteroids).

18. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomisation.
19. History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas).
20. History of diabetic ketoacidosis.
21. Any disorder, except for conditions associated with diabetes, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

6.4 Premature discontinuation of trial product

All efforts should be made to keep the subject on trial product. Trial product must be discontinued if the subject meets rescue criteria or if the following applies:

- If the investigator suspects acute pancreatitis, all drugs suspected to relate to this condition must be discontinued until confirmatory tests have been conducted and appropriate treatment should be initiated

Trial product must be permanently discontinued if the following applies:

- Included in the trial in violation of the inclusion and/or exclusion criteria
- Pregnancy or intention to become pregnant
- Participation in other clinical trials throughout the trial
- In case the calcitonin value is ≥ 50 ng/L. Please see Appendix C
- Initiation or significant change in concomitant medications (in excess of 14 days) which in the investigator's opinion could affect weight or glucose metabolism
- Subjects that are diagnosed with acute pancreatitis (as a minimum 2 of 3: characteristic abdominal pain, amylase and/or lipase > 3x upper normal range or characteristic findings on ultrasound, computerised axial tomography /magnetic resonance imaging)

Permanent premature discontinuation of treatment with trial product will not lead to subject withdrawal from the trial. Trial product may be permanently discontinued at the discretion of the investigator due to a safety concern, unacceptable tolerability, or if a subject is judged to be non-compliant with trial procedures.

6.5 Rescue criteria

If the pre-breakfast SMPG values taken on three consecutive days or if any of the FPG samples analysed by the central laboratory exceeds the limit of:

- 15.0 mmol/L (270 mg/dL) from baseline to week 6
- 13.3 mmol/L (240 mg/dL) from week 7 to week 12
- 11.1 mmol/L (200 mg/dL) from week 13 to week 26

and if no treatable intercurrent cause for the hyperglycaemia has been identified, the subject should be called for a confirmatory FPG measurement as soon as possible. The FPG sample should be

analysed by the central laboratory and if it exceeds the limits described above, the subject must discontinue treatment with trial product.

See procedures for premature discontinuation further described in section 8.1.7.

6.6 Withdrawal criteria

The subject may withdraw at will at any time.

A subject randomised in the trial in violation of the inclusion and/or exclusion criteria but not exposed to trial product must be withdrawn from the trial, and should not attend further visits.

A subject randomised in the trial in violation of the inclusion and/or exclusion criteria and exposed to trial product must discontinue treatment with trial product, but will not be withdrawn from the trial and will be followed as "premature discontinued of trial product" described in section 8.1.7.

Only subjects who decline any further contact with the site in relation to the trial, and hence do not agree to report information which is relevant for the assessments of trial end-points at the end of trial should be considered as withdrawn from the trial.

Subjects who consider withdrawing informed consent should be encouraged to have procedures performed according to the EoT visit and the two follow-up contacts (see section 2).

Please see section 8.1.7 for procedures to be performed in case of subject withdrawal.

6.7 Subject replacement

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

6.8 Rationale for trial population

The target population for this trial is insulin naïve subjects with T2DM inadequately controlled on SGLT2i treatment ± OAD treatment. The following types of anti-diabetic pre-trial therapy are allowed: SGLT2i monotherapy or SGLT2i in combination with metformin ± DPP4i ± pioglitazone for a period of at least 90 days prior to screening (inclusion criteria 7). Since pioglitazone should not be combined with dapagliflozin this is specified in the inclusion criteria. Subjects on DPP4i should discontinue this OAD treatment at randomisation. Thus the randomised subjects will be on either SGLT2i monotherapy or SGLT2i ± metformin ± pioglitazone, this treatment should be unchanged throughout the trial, unless there is a safety concern.

To ensure a homogeneous SGLT2i-treated population, subjects may not be treated with other anti-diabetic treatment (e.g., other OADs [such as sulfonylureas], or GLP-1 receptor agonists) within 90 days of screening (exclusion criteria 4 and 5). Stable OAD treatment for at least 90 days prior to enrolment is furthermore chosen to minimize carry over effect of OAD treatment on trial endpoints,

including weight loss secondary to initiation of SGLT2i treatment, and to ensure a population tolerating SGLT2i treatment.

To ensure the safety of the subjects, subjects that are particularly vulnerable due to various illnesses are excluded from participation.

Eligible subjects are presenting with an HbA_{1c} in the range of 7.0-11.0% (both inclusive), while maintaining antidiabetic treatment with SGLT2i as described above. This HbA_{1c} range is chosen to include a representative T2DM population in need of further intensification without imposing an increased risk of hypoglycaemia for the subject.

BMI limits of ≥ 20 kg/m^2 and < 40 kg/m^2 are chosen to include as broad a population as possible while excluding under-weight individuals in risk of unsafe weight loss, and excluding morbidly obese individuals who may be extremely insulin resistant.

7 Milestones

Planned duration of the recruitment period i.e. First Subject First Visit (FSFV) – Last Subject First Visit (LSFV): 42 weeks.

End of trial is defined as Last Subject Last Visit (LSLV).

Recruitment:
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.

The screening and randomisation rate will be followed closely via 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 included in the screening period and eligible for randomisation can be randomised.

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[18], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[19], the Food and Drug Administration Amendment Act (FDAAA)[20], European Commission Requirements[21,22] 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

The following sections describe the assessments and procedures as well as how to record the results. Timing of the site visits, telephone contacts, visit windows and the assessments to be performed are specified in the flow chart (see section 2).

Investigator assessments

Review of diaries, patient reported outcomes (PROs), laboratory reports, ECGs, eye examinations, physical examinations must be documented with the investigator´s dated signature either on the front page of the document and/or in the subject´s medical records. The signed documents must be retained at the trial site as source documentation.

Visit schedule

It is the responsibility of the investigator to ensure that all site visits and phone contacts occur according to the flow chart (section 2). A phone contact may be converted to a site visit, if needed.

Date of visit and corresponding visit windows are always calculated in relation to V2 (randomisation) except for V33 which should take place at least 7 days (+3 days) after last dose of trial product and phone contact 34 which should take place at least 30 days (+3 days) after last dose of trial product.

Diaries

At each site visit the subjects will be provided with a new diary. The diary must be collected at the next site visit, and retained at the site as source data in accordance with section 14. However, after V32 the diary will only be collected at the first FU visit (V33), whereas diary data at the second FU contact (P34) will be collected per phone. Consequently, source data will be the notes written by the investigator in the subject's medical record, and be based on an interview performed by phone at the second FU contact (P34).

The investigator is only allowed to record the following data in the diary:

- Subject ID number
- Site contact details
- Time and date of next visit or phone contact
- Prescribed dose of trial product
- Doses and values from SMPG measurements from previous diary, if required to complete next dose adjustment
- Review signature

The subject must record the following information in the diary:

- Date, time and value of the daily pre-breakfast SMPG measurement(s)
- Date, time and value of the 9-point profile SMPG prior to V2, V18 and V32
- Date, time and dose of trial product each day
- Hypoglycaemic episodes (see section 8.5.2)
- Any medical issues
- Any changes to concomitant medication (see section 8.3.5)

If the subject is not able to complete the diary themselves (taking exclusion criterion no. 21 into account) and need assistance from a third party to complete the diary, this must be stated in the subject's medical records.

Based on the values from the SMPG measurements, the investigator/subject will assess whether trial product dose needs adjustment according to the titration guideline (Appendix A).

The diary must be reviewed by the investigator to ensure that AEs, including medical issues and concomitant medication, are reported (see section 8.3.2 and 12). In addition, the investigator must consider whether the reported values from the SMPG measurements must be reported as hypoglycaemic episodes (see section 8.5.2).

The investigator or delegated staff should transcribe the diary data to the eCRF as soon as possible, preferable within 24 hours after each site visit/phone contact. Safety data from the diaries must be handled according to the timelines described in Figure 12–1. If data is obtained via phone and a discrepancy is later detected, the values in the eCRF should be corrected according to the diary.

Review of the diary must be documented either on the document and/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.

8.1.1 Fasting requirements

The subjects should be fasting when attending some of the visits, see flowchart, section 2. Fasting is defined as at least 8 hours without food and drink intake, except for water and other prescribed medication. Trial product and other glucose lowering agents should be withheld on the day of the visit until blood sampling and body weight (if applicable) have been performed. Any other prescribed medication should be taken as usual. If the subject attends a fasting visit in a non-fasting state the blood sampling and body weight procedures should be re-scheduled within the visit window.

8.1.2 Screening (V1)

Screening visit and all screening assessments must take place within 14 calendar days prior to randomisation (V2).

Informed consent process
Prior to screening, the investigator must provide the subject with verbal and written information about the trial. Informed consent must be obtained before any trial related activity, see section 18.2. The date of informed consent must be transcribed to the eCRF for all screened subjects.

Screening
Screening of subjects will be registered by using IWRS (see section 10). Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. The first three digits in the subject ID number will consist of the site number and the last three digits of the subject ID number will indicate the individual subject number.

All inclusion and exclusion criteria must be reviewed and if any criteria cannot be assessed e.g. criteria related to results from blood sampling performed at screening or if a valid eye examination is missing, the investigator must ensure these are obtained for assessment of eligibility prior to the randomisation of the subject.

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 instructed to destroy the card after the last phone contact.

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

8.1.3 Screening failures

If a screened subject for any reason is not eligible or are not randomised within 14 calendar days after the screening visit (V1), the subject will be considered a screening failure. For screening failures the screening failure form in the eCRF must be completed with the reason for not continuing in the trial. Serious and non-serious AEs from screening failures must be transcribed by the investigator into the eCRF. Follow-up of SAEs must be carried out according to section 12.3. Screening failures experiencing an AE that would otherwise qualify for adjudication (see section 12.7) will not be adjudicated as no trial product has been administered.

A screening failure session must be made in the IWRS. The case book must be signed.

Re-sampling or re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria. The only exception where re-sampling of the screening samples is allowed is if the blood samples are lost or haemolysed and analysis is not possible at the central laboratory.

8.1.4 Randomisation (V2)

Randomisation must NOT take place more than 14 calendar days after V1 (screening). All results from screening assessments, including laboratory results, ECG and eye examination must be available and reviewed by the investigator and the inclusion/exclusion criteria must be carefully reviewed to ensure the subject is eligible prior to the randomisation.

Randomisation of subjects will be done using the IWRS (see sections 10 and 11).

At V2, the subject will be supplied with trial product, receive training in trial product and pen handling, and given directions for use verbally and in writing. For further information on trial product please see section 9. The subject should take the first dose of trial product at V2 after the randomisation is done if possible, or on the day after randomisation. The date and dose of the first dose of trial product should be recorded in the diary and the eCRF.

DPP4i must be discontinued at randomisation and subjects on fixed dose combinations of SGLT2i and DPP4i should be shifted to a corresponding dose of SGLT2i.

8.1.5 Follow-up contacts (FU1 and FU2)

FU1 should be scheduled 7 days (+ 3 days) after last dose of trial product and FU2 should be scheduled 30 days (+ 3 days) after last dose of trial product. At FU1 information on antidiabetic treatment, any AEs and hypoglycaemic episodes occurring since visitV32 must be collected and recorded in the eCRF. At FU2 information on antidiabetic treatment and any AEs occurring since V32 must be collected and recorded in the eCRF.

8.1.6 Unscheduled visits

Unscheduled visits can be performed at any time at the discretion of the investigator. An unscheduled visit should be performed if:

- An AE occurs that needs further attention
- Additional laboratory samples are needed due to an AE requiring special forms in the eCRF (see section 8.5.1.1)
- A confirmatory pregnancy test is needed
- A blood re-sampling related to a specific visit (if not possible to schedule the re-sampling within the visit window). Only if initial blood sample for some reason was not able to be analysed
- Confirmatory FPG test for rescue criteria evaluation

For the above an unscheduled visit form must be completed in the eCRF, indicating the reason for the visit.

An unscheduled visit form should not be completed if the subject attends the trial site for a blood re-sampling within the visit window. Instead a requisition form must be completed with the visit number the re-sampling refers to and the data must be entered to the eCRF for the corresponding visit. Also, additional trial product dispensing or auxiliary supply does not require the use of the unscheduled visit form. Additional dispensing session should be made in the IWRS prior to additional trial product dispensing.

8.1.7 Premature discontinuation of trial product

Subjects discontinuing trial product prematurely due to any of the rescue criteria (see section 6.5), criteria for premature discontinuation of trial product (see section 6.4) or at subjects own will, should be called in for an EoT visit corresponding to V32 as soon as possible after discontinuation of trial product, FU1 must be scheduled 7 days (+3 days) after discontinuation of trial product and FU2 must be scheduled 30 days (+3 days) after discontinuation of trial product.

Once the two follow-up contacts after discontinuation of trial product are completed the subject should be contacted by phone every 4 weeks. Information on antidiabetic medication and information on potential major cardiovascular events (MACE) and any SAEs occurring since last contact must be collected and recorded in the eCRF. Phone contacts must be documented in the medical record and in the eCRF. The subject should finally come in for a V32A at week 26 to report MACE, SAEs, total daily insulin dose, use of other antidiabetic medication, and have body weight measured and a blood sample taken to measure HbA_{1c}, see flow chart (section 2).

Final drug accountability must be done once the subject has discontinued the trial product and the premature discontinuation must be recorded in the IWRS through a treatment discontinuation session.

The reason for the premature discontinuation of trial product must be recorded in the eCRF.

8.1.8 Withdrawal of consent

If a subject decides to withdraw from the trial, the investigator must aim to undertake procedures similar to those for V32, FU1 and FU2 (see section 8.1.5) as soon as possible after the last dose of trial product.

The end-of-trial form must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be made in the IWRS and the subject should be registered as withdrawn in the eCRF. The case book must be signed.

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

8.2 Laboratory assessments

The laboratory analyses will be handled by a central laboratory. Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling, transportation and storage of biological samples and information regarding who will perform the assessments, will be described in a trial specific laboratory manual, provided by the central laboratory (for central laboratory details, see Attachment I).

Laboratory samples not drawn on the day of the actual visit should preferably be drawn on another day within the visit window, see flow chart (section 2). For some of the samples drawn during the trial the subject must be fasting, see the flow chart (section 2) and fasting requirements in section 8.1.1.

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.

Laboratory results will be provided by the central laboratory to the investigator on an ongoing basis. For laboratory results outside the normal range the investigator must specify an evaluation on the laboratory report. The evaluation of the results must follow the categories:

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

The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol (see section 8.3.2 and section 12). The review of laboratory reports must be documented either on the documents and/or in the subject's medical record. The laboratory report must be signed and dated by the investigator on the day of evaluation and the signed report must be retained at the site as source documentation.

The investigator should ensure that all laboratory samples for the subject are shipped to the laboratory immediately after the samples from V1 and V32 (or V32A for prematurely discontinued subjects) have been collected.

All samples will be destroyed on an ongoing basis after the analysis or at the latest at the completion of the clinical trial report (CTR).

8.3 Subject related information

8.3.1 Demography

Demography consists of:

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

8.3.2 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at V1) or found as a result of a screening procedure. Concomitant illness includes any pre-planned procedures, surgery and any intermittent illness (e.g. allergies) that may not be apparent at the time of screening. T2DM should not be recorded as concomitant illness.

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.

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

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

8.3.3 Diabetes history and diabetes complications:

Diabetes history and diabetes complications will be recorded at screening and consists of:

- Date of diagnosis of type 2 diabetes
- Information regarding diabetes complications including date of onset
  - Diabetic retinopathy
  - Diabetic neuropathy
  - Diabetic nephropathy
  - Macroangiopathy (including peripheral vascular disease).

Current diabetes treatment is an account in the eCRF where information about current diabetes treatment, dose of current diabetes treatment and start date of current diabetes treatment is collected.

Family history of diabetes is an account in the eCRF where information about the family history of diabetes is collected.

8.3.4 Hypoglycaemia unawareness

Information on hypoglycaemia unawareness will be recorded at screening according to Clarke's questionnaire, question 8[23].

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.

8.3.5 Concomitant medication

A **concomitant medication** is any medication, other than the trial product, which is taken during the trial.

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.

8.3.6 Smoking status (tobacco use)

Details of smoking status must be recorded at V1. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked. If the subject smokes or has smoked, record approximate number of years of smoking.

8.4 Assessments for efficacy

8.4.1 Body measurements

Height
Height is measured without shoes in centimetres (cm) or inches and rounded to the nearest cm or inch.

Body weight
Body weight should be measured without shoes and only wearing light clothing in kilograms (kg) or pounds (lb) with one decimal. The measurements are to be performed in a fasting state, except for the measurement at V1. Body weight should be assessed with the same equipment throughout the trial, if possible.

Body Mass Index (BMI)
BMI will be calculated automatically in the eCRF once height and weight are entered.

Waist circumference
The waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest.

Three consecutive measurements of waist circumference must be performed and entered into the eCRF. The waist circumference will be measured to the nearest 0.5 cm or 0.2 inch using a non-stretchable measuring tape (measuring tapes will be provided to the sites by Novo Nordisk).

The subject should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject should be standing with arms down their side and feet together. The tape should touch the skin but not compress soft tissue. The subject should be asked to breathe normally and the measurement should be when the subject is breathing out gently.

8.4.2 Blood samples for efficacy

Blood samples will be drawn in accordance with the flow chart (section 2) and analysed at the central laboratory to determine levels of the laboratory parameters listed below.

Glucose metabolism: HbA_{1c} and FPG.

HbA_{1c} and FPG results out of range do not need to be reported as an AE unless the result is unexpected by the investigator.

Fasting lipid profile: Cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides and free fatty acids.

8.4.3 Fasting plasma glucose (FPG)

FPG is measured in order to evaluate metabolic control. The subject must attend these visits fasting. For definition of fasting, refer to section 8.1.1.

FPG results ≤ 3.9 mmol/L (70 mg/dL) should not be reported as hypoglycaemic episodes but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator (see section 12.1.).

8.4.4 Self-measured plasma glucose (SMPG)

At V1 subjects will be provided with a BG meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use. The subjects will be instructed in how to use the device, the instruction will be repeated as necessary during the trial.

The BG meters use test strips calibrated to plasma values (SMPG values). Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display of the BG meter.

Subjects should be instructed in how to record the results of the SMPG measurements in the diaries.

Once daily
Subjects should perform OD SMPG measurement in a fasting state prior to breakfast. Diabetes medication (including trial products) should be withheld until after the measurement.

9-point profile
Subjects should perform SMPG measurements and record the obtained values for a 9-point profile within a week prior to V2, V18 and V32 on a day where the subject does not anticipate unusual strenuous exercise.
Diabetes medication (including trial products) should be withheld until after the pre-breakfast SMPG measurement has been performed.

The SMPG values obtained should be recorded in the diary (including actual clock time and date of the measurement) at the following time points, always starting with the pre-breakfast measurement:

- Before breakfast
- 90 min after the start of breakfast
- Before lunch
- 90 min after the start of lunch
- Before dinner
- 90 min after the start of dinner
- At bedtime
- At 4 am
- Before breakfast the following day

8.5 Assessments for safety

8.5.1 Adverse events (AEs)

All AEs must be collected and reported according the procedures described in section 12.

8.5.1.1 Adverse Events requiring additional data collection in the eCRF

For some AEs the investigator must fill in additional forms in the eCRF. AEs requiring additional data collection in the eCRF are:

- Cardiovascular events
- Pancreatitis
- Thyroid disease
- Neoplasms
- Renal failure
- Medication errors

In case any of these events fulfil the criteria for a SAE, please report accordingly. See section 12.2.

Further details of AEs requiring additional data collection in the eCRF can be found in appendix B.

8.5.2 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 V2 to V33.

Upon onset of a hypoglycaemic episode the subject is recommended to measure plasma glucose every 15 minutes until the SMPG value is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance to current guidelines[24].

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 will per 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. One hypoglycaemic episode form is to cover these measurements and/or symptoms. However, each hypoglycaemic episode form will cover a period of maximum 60 minutes after onset of a hypoglycaemic episode.

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.

If a new low SMPG value is measured or the subject still has symptoms more than 60 minutes after the first reported low SMPG value and/or symptoms it is considered as a new hypoglycaemic episode and a new hypoglycaemic episode form is to be filled in.

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.
- Whether the episode was symptomatic (Yes/No)
  A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the subject experience 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 (and other anti-diabetic treatment) 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
- Change in any concomitant illness
- Any sign of fever 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 concentration[24].

Oral carbohydrates should 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 other 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 changed, medication error (i.e. overdose, mix-up between products), miscalculation of insulin dose, other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[25] (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 at each contact 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 on a hypoglycaemic episode form.

Low SMPG values for non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement should be reported on a hypoglycaemic episode form with as much information as possible. Novo Nordisk will not query

for additional data except for the start date, SMPG value and whether the subject was able to self-treat due to decreased validity of such data[26,27].

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 and a SIF must also be filled in, see section 12.

8.5.3 Physical examination

A physical examination must include:

- General appearance
- Head, ears, eyes, nose, throat, neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- Abdomen
- Lymph node palpation
- Thyroid gland

8.5.4 Vital Signs

Diastolic blood pressure, systolic blood pressure and pulse rate should be measured while the subject is in a sitting position and after 5 minutes of rest.

At V1 the blood pressure must be measured three times and all three values must be entered in the eCRF. The mean value will be calculated by the system and must be in accordance with the relevant exclusion criteria (see section 6.3). At the following visits, the blood pressure should only be measured once.

8.5.5 Electrocardiogram (ECG)

A 12-lead ECG must be performed by the investigator or delegated staff. The ECG must be interpreted, signed and dated by the investigator to verify that the data has been reviewed. The ECG at screening must be done at the latest at V2 and the results interpreted by the investigator prior to determine the eligibility of the subject.

The evaluation transcribed to the eCRF must follow the categories:

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

8.5.6 Eye examination

An eye examination (dilated fundoscopy/fundus photography) must be performed by the investigator, a local ophthalmologist or an optometrist according to local practise. Results of the eye examination must be interpreted, signed and dated by the investigator to verify that the data has been reviewed before randomisation and in order to determine the eligibility of the subject.

The evaluation of the results must follow the categories:

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

If an eye examination has been performed within 12 weeks prior to V2 the procedure does not need to be repeated, if the results are available for evaluation at V2. If the eye examination is performed before the subject consented to participate in the trial, it must be stated in the subject´s medical records that the procedure was not performed in relation to this trial.

If an eye examination has been performed within 2 weeks prior to V32 the procedure does not need to be repeated, if the results are available for evaluation at V32.

8.5.7 Blood samples for safety

Blood samples will be drawn in accordance with the flow chart (section 2) and analysed by the central laboratory to determine levels of the following laboratory parameters:

Haematology: Erythrocytes, haematocrit, haemoglobin, leucocytes, thrombocytes, differential count (eosinophils, neutrophils, basophils, monocytes and lymphocytes).

Biochemistry: Amylase, lipase, ALT, AST, alkaline phosphatase, albumin, bilirubin (total), creatinine, potassium, sodium, calcium (ionized), urea, GFR (estimated).

Hormones: Blood samples for the measurement of calcitonin concentration will be drawn as per flow chart (see section 2). In case any calcitonin value at any time of the trial is ≥ 10 ng/L the algorithm in appendix C Monitoring of calcitonin must be followed.

Pregnancy test: Females of childbearing potential will have a human chorionic gonadotropin (hCG) serum pregnancy test performed according to the flow chart (section 2).

8.5.8 Urine test for safety

A urine sample must be collected at V1, V18 and V32 to determine the **albumin/creatinine ratio**, see flow chart (section 2). The analysis will be performed by the central laboratory.

Urine dipstick test must be performed at the site according to the flow chart, section 2. The following parameters will be tested; glucose, ketone, nitrite, pH, protein, leucocyte, and erythrocyte.

Urine pregnancy test using urine dipsticks will be performed at site during the trial for females of childbearing potential if a menstrual period is missed or pregnancy is suspected. If a urine test is positive, a confirmatory serum-hCG test must be taken and sent to the central laboratory for analysis. It should be documented in the eCRF in an unscheduled visit, describing "pregnancy test" under "other".

8.6 Other assessments

8.6.1 Questionnaires

The investigator is only allowed to fill in the headings of the questionnaires.

The investigator should check for empty fields in the questionnaires when returned by the subject. Review of the questionnaires must be documented either on the documents and/or in the subject's medical record.

If clarification of entries or discrepancies in the questionnaires 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.

All responses to the questionnaires must be transcribed to the eCRF.

Novo Nordisk baseline questionnaire
The Novo Nordisk baseline questionnaire; Barriers in Diabetes Treatment must be completed at V2, see flowchart, section 2

Patient reported outcomes
The following PRO questionnaires must be completed at V2, V14 and V32, see flowchart, section 2:

- SF-36v2, standard[16]
- TRIM-D[17]

The PRO questionnaires should be completed at the same time point of the visit for both visits, e.g. prior to any other trial related activities.

8.7 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. The investigator should assess the compliance of the subject at each visit based on a review of glycaemic control, adherence of the visit schedule, completion of the subject diary including SMPG measurements. In addition, subject compliance will be assessed by monitoring of drug accountability. The unused amount of trial product will be assessed against the dispensed amount and, in case of discrepancies, the subject must be asked to clarify. 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.

9 Trial supplies

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

Trial products must not be dispensed to any person not included in the trial.

Trial product must not be used:
- If it does not appear clear and colourless
- If it is dropped, damaged or crushed as there is a risk of leakage
- If it has not been stored correctly according to the storage condition on the label

9.1 Trial products

The following trial products are considered as Investigational Medicinal Products (IMPs) and will be provided by Novo Nordisk A/S, Denmark:

Table 9–1 Investigational medicinal products

IMPs	Strength	Dosage form	Route of administration	Container/delivery device
Insulin degludec/liraglutide	100 units/mL + 3.6 mg/mL	Solution for injection	Subcutaneous (s.c.)	3 mL pre-filled PDS290 pen injector
Insulin glargine	100 units/mL			3 mL pre-filled SoloStar®

OADs are considered as non-investigational medicinal products (NIMPs) and hence will not be provided by Novo Nordisk, unless required by local law.
Argentina: All NIMPs, including pioglitazone, will be reimbursed by Novo Nordisk Pharma Argentina S.A. NIMPs should be purchased or otherwise delivered to the subjects in accordance with local health plans.
Slovakia: Pre-trial OADs and/or rescue medication used during the trial will not be supplied by Novo Nordisk, however these medications will be reimbursed by Novo Nordisk Slovakia s.r.o.

During the 26-weeks treatment period and the 4 weeks follow-up period; the patients de-facto cost (actual patient cost, not covered by the Health Authorities/any insurance) of SGLT2i and metformin

(mono- or fixed dose combination products) will be reimbursed in accordance with local legislation and Ethics Committee approval. Pioglitazone will not be reimbursed.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[28], 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. Dispensing unit numbers (DUNs) 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 verbally and in writing at the first dispensing visit (V2). On all other visits the direction for use must be given in writing.

9.3 Storage

Storage and in-use conditions of the trial products are outlined in Table 9–2

Table 9–2 Storage conditions for investigational medicinal products

IMPs	Storage conditions (not-in-use)	In-use conditions	In-use time*
Insulin degludec/liraglutide	Store in refrigerator (2°C-8°C/36°F-46°F) Do not freeze Protect from light	Store below 30°C (86°F) Do not freeze Protect from light	Use within 3 weeks
Insulin glargine		Do not store above 30°C US: Do not store above 30°C (86°F) Do not refrigerate Protect from light	Use within 4 weeks

* In-use time starts when the product is taken out of the refrigerator at the subject's home

The investigator must ensure the availability of proper storage conditions, and also record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range).

Trial product that has been stored improperly must not be dispensed to any subject before it has been 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 is the responsibility of the investigator.

Subjects must be instructed to return all used, partly used and unused trial products including empty packaging material at each dispensing visit.

Returned trial product (used/partly used or unused) ,expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product. Non-allocated trial products including expired or damaged products must be accounted as unused at the latest at closure of the trial site.

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

9.5 Auxiliary supplies

The following will be provided by Novo Nordisk in accordance with the TMM:

- Directions for Use (DFU) for pen devices
- Needles for pen devices
- BG meters and BG meter auxiliaries

10 Interactive web response system (IWRS)

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

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

It is important that the trial site dispenses the trial products allocated by IWRS in order to:

- Provide the correct trial product (correct DUN) according to randomisation and dispensing visits
- Secure available stock at site to cover the drug supply need for all enrolled subjects
- Ensure that no subjects receive trial product that will expire in between dispensing visits
- Secure that drug accountability is possible

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure

Subjects randomised at V2 will in a 1:1 manner (208 in each arm) get one of the treatments described below in combination with previous SGTL2i ± OAD:

- IDegLira added to OAD therapy (SGLT2i ± OAD)
- IGlar added to OAD therapy (SGLT2i ± OAD)

Pre-trial OAD treatments must include SGLT2i either as monotherapy, or in combination with metformin ± DPP4i ± pioglitazone. If a subject is treated with DPP4i these have to be discontinued at randomisation. There will not be applied any stratification on baseline characteristics.

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

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

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

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness)
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see section 8.5.2

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

Serious adverse event

A SAE is an experience that at any dose results in any of the following:

- Death
- A life-threatening[a] experience
- In-patient hospitalisation[b] or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity[c]
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life threatening[a] or require hospitalisation[b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE[d]
  Suspicion of transmission of infectious agents via the trial product must always be considered an SAE

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

[b] The term "hospitalisation" is used when a subject:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
- Stays at the hospital for treatment or observation for more than 24 hours

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

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

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

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

Adverse events with additional data collection
AEs with additional data collection are AEs defined as critical for the evaluation of product safety. For these AEs the investigator must fill in additional forms in the eCRF. AEs requiring additional data collection in the eCRF are:

- Cardiovascular events:
  - Acute coronary syndrome (MI or hospitalisation for unstable angina)
  - Cerebrovascular event (stroke or TIA)
  - Heart failure requiring hospital admission
- Pancreatitis
- Thyroid disease
- Neoplasms
- Renal failure
- Medication errors

For detailed information on AEs with additional data collection and definition of medication errors, see Appendix B.

Along with fatal events, certain events will be adjudicated by an external independent Event Adjudication Committee (EAC) as described in section 12.7.2. For further information regarding definitions, rationales, and events that will be adjudicated, see Appendix B.

Major adverse cardiovascular event
A major adverse cardiovascular event (MACE) is any AE which can be categorised into the following groups:

- Cardiovascular Death
- Myocardial Infarction
- Hospitalisation for Unstable Angina
- Transient Ischemic Attack and Stroke
- Heart Failure Event (requiring hospitalisation)
- Cardiac procedures
  - Interventional Cardiology
  - Peripheral Vascular Intervention
  - Stent Thrombosis

Technical complaint

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

Examples of technical complaints:

- The physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- The packaging material (e.g. leakage, cracks, rubber membrane issues or errors in labelling text)
- Problems related to devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen and the needle)

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the two post-treatment follow-up periods. Please be aware that hypoglycaemic episodes should not be reported before any trial drug is given e.g. hypoglycaemic episodes should be reported from the randomisation visit (V2). Subjects discontinuing trial product prematurely (see section 6.4) will be contacted every 4th week and asked for information about antidiabetic medication, MACE and SAEs. These subjects should finally come in for a V32A at week 26, only to assess antidiabetic medication, MACE, SAEs and a blood sample to measure HbA_{1c}.

The events must be recorded in the applicable CRF 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. Novo Nordisk assessment of expectedness is performed according to the following reference documents:

- IDegLira: Current version of the Company Core Data Sheet (CCDS) or any updates hereof
- IGlar: European Summary of Product Characteristics (SmPC) current version or any updates hereof[11]

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

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

For AEs requiring additional data collection and for AEs requiring adjudication, a specific event form in addition to the AE form must be completed.

The AE form for a non-serious AE not fulfilling the additional data collection criteria should be signed when the event is resolved or at the end of the trial.

Timelines for initial reporting of AEs:

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

- **SAEs**: The AE form **within 24 hours** and the SIF **within 5 calendar** days of the investigator's first knowledge of the SAE. Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF
- **SAEs with additional data collection:** in addition to above, also the specific event form **within 14 calendar days** of the investigator's first knowledge of the AE
- **Non –serious AEs with additional data collection**: The AE form, and specific event form within **14 calendar days** of the investigator's first knowledge of the event
- **Events for adjudication**: Event Adjudication Document Collection Form must be completed **within 14 calendar days**. The investigator must provide the applicable medical documentation **within 4 weeks** of event identification

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

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

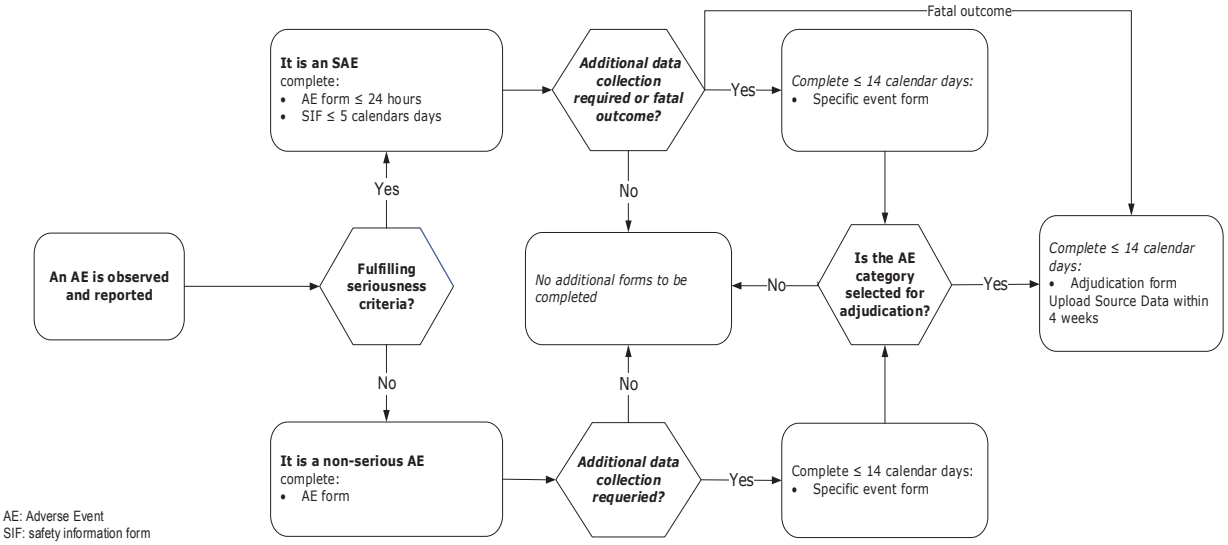


Figure 12–1 Initial reporting of AEs

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 GCP[2]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and GCP[2], unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication:

If a SAE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the SIF. 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 worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

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

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- IDegLira (100 units/mL + 3.6 mg/mL), 3 mL pre-filled PDS290 pen
- Novo Nordisk needles for prefilled pen
- IGlar (100 units/mL), 3 mL pre-filled Solostar®,

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 or SAEs.

Technical complaints must be reported on a separate technical complaint form. A technical complaint form for each batch or lot number or for each DUN must be completed.

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

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

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. 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 print or copy of the technical complaint form must be sent with the sample.

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

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

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

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

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

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

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

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 newborn 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 newborn 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.

<u>Forms and timelines for reporting AEs:</u>
Non-serious AEs:

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

SAEs:

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

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

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

12.5.2 Pregnancies in female partners of male subjects (only applicable for US)

Male subjects must be instructed to notify the investigator if their female partner becomes pregnant during the trial, except in the screening period. At the last scheduled visit, male subjects must be asked if their female partner has become pregnant.

If a female partner has become pregnant during the trial, the investigator must follow-up on the pregnancy outcome and until the new-born infant is one month of age, irrespective of whether the trial is completed or not. The investigator must ask the male subject and assess, if the pregnancy outcome is normal or abnormal.

When the pregnancy outcome is **normal** this information is recorded in the subject's medical record only, no further information is collected and reported to Novo Nordisk. 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), the following must be reported by the investigator to Novo Nordisk electronically (e.g. in PDF format) or by fax:

1. **Reporting of pregnancy information**

   Information from the male subject has to be reported on the Paternal Form. Furthermore, information from the female partner (including information about the pregnancy outcome and health status of the infant until the age of one month) has to be reported on the Maternal Forms 1A, 1B and 2, after an informed consent has been obtained from the female 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 following AEs in the foetus and newborn infant have to be reported:
   - Non-serious AEs evaluated as possible/probably related to the father's treatment with the trial product(s)
   - SAEs in the foetus and newborn infant - whether or not related to the father's treatment with the trial product(s). This includes an abnormal outcome - such as foetal death (including spontaneous abortion) and congenital anomalies (including those observed at gross examination or during autopsy of the foetus)

Forms and timelines for reporting AEs:
Please see section 12.5.1, point 2, "Forms and timelines for reporting AEs".

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.

Symptoms of hypoglycaemia usually occur suddenly and may include cold sweat, nervousness or tremor, anxious feelings, unusual tiredness, confusion, difficulty in concentrating, excessive hunger, temporary vision changes, headache, nausea and palpitation. Severe hypoglycaemia may lead to unconsciousness.

Hypoglycaemic episodes should be treated according to best practise at the discretion of the investigator. Attention should be given to the fact that the action profile of the insulin component in IDegLira is flat and of somewhat longer duration than currently marketed long-acting insulin preparations. It may therefore take several hours longer before stable normal blood glucose is achieved after a hypoglycaemic episode when comparing to existing long acting insulin analogues.

Symptoms of minor hypoglycaemia should be treated with ingestion of carbohydrates. Severe hypoglycaemia resulting in loss of consciousness must be treated according to best medical practice (e.g. 25 mL of 50% dextrose solution given intravenously, or 0.5-1 mg of glucagon given s.c. or intramuscularly).

From clinical trials and marketed use of Victoza® overdoses up to 40 times the recommended maintenance dose (72 mg) have been reported. Events reported included severe nausea and severe vomiting. None of the reports included severe hypoglycaemia. All subjects recovered without complications.

When initiating treatment with IDegLira, the subject may in some cases experience loss of fluids/dehydration, due to vomiting, nausea or diarrhoea. It is important to avoid dehydration by drinking plenty of fluids.

For further information see the IDegLira IB[10] or any update hereof.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

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

12.7.2 Event adjudication committee (EAC)

An independent external EAC is established to perform qualitative 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 EAC in a blinded manner.

The following AEs will be adjudicated in this trial:

- Fatal events
- Acute coronary syndrome (MI or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or TIA)
- Heart failure requiring hospital admission
- Pancreatitis
- Thyroid disease requiring thyroidectomy and thyroid neoplasms
- Neoplasms (all kinds of abnormal growth) – excluding thyroid neoplasms

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

The EAC will review translated copies in English of source documentation received in the adjudication packages (for example X-ray, ECGs, ultrasound images, discharge summaries, pathology reports, and death certificates). The EAC can evaluate an event not initially reported as an AE for adjudication, to be adjudicated. The investigator must provide source documentation as soon as possible, once the request from Novo Nordisk or the event adjudication vendor is received.

All AEs will be screened by Novo Nordisk for being potential missed events for adjudication. If needed, the investigator will be asked to provide additional information such as an alternative aetiology.

Based on the information provided, the event adjudication vendor or EAC can decide to have an AE adjudicated even if not initially reported as an event for adjudication by the investigator. If so, the investigator must provide source documentation as soon as possible, once the request from Novo Nordisk or the event adjudication vendor is received.

AEs for adjudication must be reported according to section 12.2. 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 in accordance with the event adjudication site manual.

13 Case report forms

Novo Nordisk will provide a system for the 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), the investigator must indicate this according to the data entry instructions.

The following will be provided as paper CRFs :

- Pregnancy forms
- AE forms (These must be used when access to the eCRF is revoked or if the eCRF is unavailable)
- SIFs (only to be used if eCRF is unavailable)
- Technical complaint forms (only to be used if eCRF is unavailable or the TC concerns a product not allocated to a subject)

On the paper CRF forms the investigator must print legibly, using a ballpoint pen. The investigator must ensure that all questions are answered, and that no empty data blocks exist. It must be ensured that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, the investigator must 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) the investigator must indicate this by writing “NA” (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

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

13.1 Corrections to case report forms

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

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

13.2 Case report form flow

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

The SMPG measurements and corresponding trial drug doses for titration purpose must be entered within **24 hours** after the site visit/phone contact throughout the trial.

The PRO questionnaires and the baseline questionnaire will be completed by the subjects on paper and data must be transcribed into the eCRF by the trial site staff.

At the end of trial the investigator must ensure that all remaining data have been entered into the eCRF no later than **24 hours** after the subject's last visit at the site. In addition, queries must be resolved immediately in order to ensure the planned lock of the database.

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 FSFV 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 CRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks.

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

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

The investigator is required to make a reasonable effort to obtain necessary additional information from external sources e.g. primary physician and other hospitals/departments to document the subjects' eligibility.

For SMPG measurements; only the values entered in the diary should be monitored as source data, although the BG meter can log a number of SMPG readings.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction. The original diaries and PROs must be collected by the trial site and not be removed from the trial site.

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

- Date for obtaining informed consent
- Screen failure reason

Monitors must review the subject's medical records and other source data (e.g. the diaries and PROs) to ensure consistency and/or identify omissions compared to the CRF. If discrepancies are found, the investigator must be questioned about these. A follow-up letter (paper or electronic) will

be sent to the investigator following each monitoring visit. This should address any action to be taken.

15 Data management

Novo Nordisk is responsible for data management.

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.

17 Statistical considerations

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

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

All statistical analyses of efficacy and safety endpoints will be based on the full analysis set (FAS) unless otherwise specified. Confirmatory analyses will include on-treatment data and available retrieved (V32A) data.

Unless otherwise specified, all continuous measurements will be summarised descriptively at each visit by treatment using on-treatment observed data. Endpoints are summarised by arithmetic mean, standard deviation (SD), median, and minimum and maximum value. Selected endpoints, e.g. endpoints that are analysed log-transformed, will be reported with geometric mean and coefficient of variation in place of mean and SD. For measurements over time, mean values will be plotted to explore the trajectory over time. Observed data will be used as the basis for plotting data if not otherwise specified. For endpoints that are summarised with geometric mean, the geometric mean values will be plotted. Mean profiles for the primary and continuous confirmatory secondary endpoints by time of treatment discontinuation and treatment will be plotted in order to investigate discontinuation patterns. In addition, selected endpoints will be summarised by empirical distribution, box and mean change from baseline over time plots.

The primary objective is to confirm the effect of IDegLira in terms of glycaemic control in subjects with T2DM on previous treatment with SGLT2i ± OAD therapy. The primary estimand for the primary objective will be the difference in change from baseline in HbA_{1c} after 26 weeks between T2DM subjects randomised to IDegLira and IGlar, both in combination with SGLT2i ± OAD, regardless of whether subjects remained on initially assigned treatment or not until week 26. This estimand is a de facto estimand addressing effectiveness. With the aim of comparing treatment strategies this estimand is considered clinically relevant. It resembles the ITT principle. For the confirmatory secondary endpoints de facto estimands addressing effectiveness are chosen as primary estimand too.

The secondary estimand for the primary objective will be the difference in change from baseline in HbA_{1c} after 26 weeks between T2DM subjects randomised to IDegLira and IGlar, both in combination with SGLT2i ± OAD, attributable to randomised treatment, if all randomised subjects had tolerated and adhered to treatment until week 26. This estimand is a de jure estimand addressing efficacy. In the non-inferiority setting this estimand has higher assay sensitivity than an effectiveness estimand. The estimand is considered clinically relevant since it provides information to treating clinicians about the glycaemic efficacy attributable to IDegLira for the purpose of

treating individual subjects with T2DM. For the confirmatory secondary endpoints de jure estimands addressing efficacy are chosen as secondary estimand too.

Only endpoints derived after 26 weeks will be analysed statistically. The expected percentage of missing data is around 15%. In accordance with guidance[29] endpoints will be assessed at frequent visits and also on subjects who prematurely discontinue treatment. If an assessment has been made both at screening and randomisation, and if not otherwise specified, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment also has been made at screening, then the screening value will be used as the baseline value.

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

The test strategy is hierarchical testing in order to control the familywise Type I error. Inferences will be based on the primary analyses of the primary estimands. The trial will be powered with respect to the primary objective and endpoint.

Presentation of results from a statistical analysis will include the estimated mean treatment effects using LSMean for absolute values, and change from baseline where applicable. The LSMean is either obtained by Rubin's rule weighing together LSMeans from multiple imputation estimations or obtained directly from estimation of a parameterized statistical model. In addition, estimated mean treatment difference (or ratio) will be presented together with the two-sided 95% confidence interval and corresponding two-sided *p*-value.

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

- Treatment: IDegLira, IGlar
- Pre-trial OAD: SGLT2i ± pioglitazone(pio), SGLT2i + metformin(met) ± pio, SGLT2i + DPP4i ± pio, SGLT2i + met + DPP4i ± pio
- Region: Europe (Finland, Hungary, Russia, Slovakia, Slovenia, Spain, Switzerland), North America (CA, USA), South America (Argentina), Asia (India)
- Visit: Planned visits for actual endpoint according flow-chart

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

17.1 Sample size calculation

The sample size is based on the primary objective and primary endpoint of the trial.

The primary objective of this trial is to confirm the effect of IDegLira in terms of glycaemic control in subjects with T2DM on previous treatment with SGLT2i ± OAD therapy. This will be done by

comparing the difference in change from baseline in HbA_{1c} after 26 weeks to a non-inferiority margin of 0.3% for IDegLira versus IGlar, both arms on continued SGLT2i ± OAD therapy.

The non-inferiority margin of 0.3% is due to guidance[30,31], a treatment effect −0.85% $[-1.04; -0.66]_{95\%\ CI}$ of IGlar versus placebo reported in a placebo controlled clinical trial[32] in T2DM subjects, and the effect of IGlar stated to be clinically equal to NPH[33]. With the superiority of IGlar to placebo and IGlar established as being as efficacious as NPH, a non-inferiority margin of 0.3% is considered to give sufficient assay sensitivity in this trial.

Formally, let D be the mean treatment difference (IDegLira – IGlar) in change from baseline in HbA_{1c}. The null-hypothesis of IDegLira inferior by 0.3% or more will be tested against the alternative hypothesis of non-inferiority (IDegLira inferior by less than 0.3%) as given by

$$H_0: D \geq 0.3\% \quad \text{against} \quad H_A: D < 0.3\%.$$

Non-inferiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval for D (mean treatment difference in change from baseline in HbA_{1c}) is strictly below 0.3%. This is equivalent to using a one-sided test of size 2.5%, i.e. the Type I error rate is controlled at 2.5% one-sided.

Accordingly, the sample size is calculated using a *t*-statistic under the assumptions of a one-sided test of size 2.5%, a mean treatment difference of 0.0%, a standard deviation of 1.0%, a non-inferiority margin of 0.3%, and that 15% of the randomised subjects will be excluded from the PP analysis set. These assumptions are based on experience from the phase 3a development programs for IDegLira and insulin degludec. With the 1:1 randomisation scheme the sample size is set to 208 subjects per treatment arm; in total 416 subjects will be randomised. This will ensure a nominal power of 80% for confirming the primary objective based on PP.

Considering inferior efficacy retention for IDegLira as opposed to IGlar amongst the anticipated 15% of subjects discontinuing randomised treatment, the expected treatment difference may be adjusted by the NI margin for discontinued subjects leading to an adjusted treatment difference of $0.85\times0.0\% + 0.15\times0.3\% = 0.045\%$. A total of 208 subjects per treatment arm will then yield a power of at least 74% (see Table 17–1)

Table 17–1 Power for various rates of discontinuation

	Adjusted treatment difference (% discontinued)			
SD	0.000 (0%)	0.045 (15%)	0.060 (20%)	0.075 (25%)
0.9	0.924	0.822	0.774	0.720
1.0	0.863	0.737	0.685	0.629
1.1	0.792	0.655	0.603	0.548
1.2	0.720	0.580	0.530	0.479

Power is computed under the assumption of 208 subjects in either arm, 1:1 randomization, and a penalty of the NI margin 0.3% in treatment difference for discontinuing subjects. SD: standard deviation.

For the confirmatory secondary endpoints body weight and hypoglycaemic episodes the marginal powers are in the order of 75% and 60% respectively under assumptions of moderate treatment effects: a treatment difference of 1 kg in weight change in favour of IDegLira, and a hypoglycaemic episode event rate of 1.8 event/PYE and rate ratio of 0.66 versus comparator. Such treatment differences have been observed for IDegLira in the phase 3a development programme. The order of hypotheses in the hierarchical testing procedure reflects this.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 guidance[34].

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. The statistical evaluation of the full analysis set will follow the ITT principle and subjects will contribute to the evaluation "as randomised".

Per-protocol (PP) analysis set: includes all subjects in the full analysis set who fulfils the following criteria:

- Have not violated any inclusion criteria
- Have not fulfilled any exclusion criteria
- Have a non-missing HbA_{1c} at screening or randomisation
- Have at least one non-missing HbA_{1c} after 12 weeks of exposure
- Have at least 12 weeks of exposure

Subjects will contribute to the evaluation "as treated".

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".

Completer analysis set (**CAS**): includes all randomised subjects who have completed the trial without discontinuation from randomised treatment. Subjects in the completer analysis set will contribute to the evaluation "as randomised".

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. Any decision to exclude any subject or observation from the statistical analysis 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 and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

17.3 Primary endpoint

17.3.1 Primary statistical analysis primary estimand

Multiple imputation – jump to reference – retrieved data – NI penalty

The primary objective of this trial is to confirm the effect of IDegLira in terms of glycaemic control in subjects with T2DM on previous treatment with SGLT2i ± OAD therapy.

The primary estimand for the primary objective will be the difference in change from baseline in HbA_{1c} after 26 weeks between T2DM subjects randomised to IDegLira and IGlar, both in combination with SGLT2i ± OAD, regardless of whether subjects remained on initially assigned treatment or not until week 26.The treatment difference is to be compared to a non-inferiority margin of 0.3%.

Formally, let D be the mean treatment difference (IDegLira – IGlar) in change from baseline in HbA_{1c}. The null-hypothesis of IDegLira inferior by 0.3% or more will be tested against the alternative hypothesis of non-inferiority (IDegLira inferior by less than 0.3%) as given by

$$H_0: D \geq 0.3\% \quad \text{against} \quad H_A: D < 0.3\%.$$

Non-inferiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval for D (mean treatment difference in change from baseline in HbA_{1c}) is strictly below 0.3%. This is equivalent to using a one-sided test of size 2.5%, i.e. the Type I error rate is controlled at 2.5% one-sided.

The primary estimand will be estimated based on the FAS using all post baseline HbA_{1c} measurements obtained at planned visits up to and including week 26, and data retrieved at week 26

(V32A) from subjects prematurely discontinued from randomised treatment. To estimate this estimand for evaluation of non-inferiority of HbA_{1c}, a pattern mixture model approach[35] will be adopted. It mimics an ITT scenario where withdrawn and prematurely discontinued subjects from the investigational treatment (IDegLira) arm not having a week 26 measurement are assumed to be switched to a treatment inferior to comparator (IGlar) or any other treatment received after premature treatment discontinuation. This corresponds to a jump to reference (J2R) principle where a penalty in terms of the NI margin is added to withdrawn or prematurely discontinued subjects in the IDegLira arm. Observe that the J2R principle and use of retrieved (V32A) data in analyses will equalise treatment effects and in turn assay sensitivity in the non-inferiority setting may be jeopardized. The penalty of the non-inferiority margin[36] is to remedy this. Multiple copies (1000 copies) of the full dataset will be generated by imputing missing values based on estimated parameters for a subgroup of subjects in the trial. This will be done as follows:

- As a first step, all post-randomisation HbA_{1c} values for prematurely discontinued subjects in the investigational treatment group (IDegLira) not having retrieved (V32A) data are set to missing
- In the second step, intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each treatment group separately and 1000 copies of the dataset will be generated. Subjects from either group with retrieved (V32A) data will now have a non-missing data pattern
- In the third step, for each of the 1000 copies of the dataset, an ANOVA model with pre-trial OAD and region as factors, and baseline HbA_{1c} as covariate is fitted to the change in HbA_{1c} from baseline to first planned HbA_{1c} measurement visit after randomisation (V10) based on the control group (IGlar) and subjects with retrieved (V32A) data in the investigational group (IDegLira). The estimated parameters, and their variances, from this model are used to impute missing values at the first planned HbA_{1c} measurement visit after randomisation (V10) for subjects in both treatment groups, based on their pre-trial OAD, region and HbA_{1c} at baseline
- In the fourth step, for each of the 1000 copies of the dataset, missing HbA_{1c} values at the second planned HbA_{1c} measurement visit after randomisation (V14) are imputed in the same way as in the previous step, now based on an ANOVA model with pre-trial OAD and region as factors, and the HbA_{1c} values at baseline and at previous planned HbA_{1c} measurement visits as covariates, fitted to the control group (IGlar) and subjects with retrieved (V32A) data in the investigational group (IDegLira)
- This fourth step is then repeated sequentially over visits where HbA_{1c} measurement is planned, adding one visit in each step until the last planned visit (V32)
- In the sixth step a penalty equal to the non-inferiority margin 0.3% is added to the EOT HbA_{1c} value for any prematurely discontinued subject in the investigational group (IDegLira), irrespective of the EOT value being retrieved (V32A) data or an imputed value from the sequential imputation steps (step 3 to 5)

- In the seventh step, for each of the 1000 complete data sets, the change from baseline to the EOT visit (V32) is analysed using an ANOVA model with treatment, pre-trial OAD and region as factors and baseline HbA_{1c} value as a covariate
- In the eighth step, the estimates and standard errors for the 1000 data sets are pooled to one estimate and associated standard error using Rubin's rule[37]. From these pooled estimates the confidence interval for the treatment difference and the associated *p*-value are calculated

17.3.2 Sensitivity analyses primary estimand

Any marked difference between the primary statistical analysis and sensitivity analyses will be commented upon in the CTR.

MMRM – retrieved data

A mixed model for repeated measurement (MMRM) with an unstructured covariance matrix will be applied for the statistical analysis. The MMRM model accounts for missing data by an assumption of missingness at random. That is, the trajectory of treatment discontinued subjects is assumed to be as for those subjects on similar treatment that complete treatment. All observed and retrieved (V32A) data will be included in the analysis. Thus this model operates under a different assumption on missingness and includes more observed data. The latter implies that any treatment effect up until premature discontinuation is taken into account.

The MMRM model will include treatment, pre-trial OAD, region and visit as fixed factors and the corresponding baseline value as a covariate. Interactions between visit and all factors and the covariate are also to be included in the model. This model will be referred to as the standard MMRM model.

Multiple imputation – copy reference– retrieved data – NI penalty

In this analysis withdrawn and prematurely discontinued subjects from the investigational treatment (IDegLira) arm not having a week 26 measurement are assumed to respond as if treated with a treatment inferior to comparator (IGlar) or any other treatment received after premature treatment discontinuation from the time of treatment discontinuation.

The analysis is similar to the primary analysis except that observed values for prematurely discontinued IDegLira subjects are not set missing (step 1 is left out). Observe that for IDegLira now only missing data after premature discontinuation are imputed by the sequential ANOVAs (step 3 to 5) and this principle is named copy reference (CR); intermittent missing data are imputed by MCMC (step 2). Thus this analysis is to include more observed values and applying the sequential ANOVAs at a later point in the visit structure. The latter implies that any treatment effect up until premature discontinuation is taken into account.

Multiple imputation – jump to reference – retrieved data – NI penalty – tipping point

A tipping point analysis will be performed based on the model of the primary analysis. Subjects who prematurely discontinue from the IDegLira arm are assumed to have received a treatment inferior to IGlar or any other treatment received after premature treatment discontinuation. The extent of the inferiority (also termed the 'penalty') will be gradually increased to evaluate at which point (penalty) IDegLira is no longer non-inferior to IGlar.

Multiple imputation – jump to reference – retrieved data – NI penalty – CAS

This is a repeat of the primary analysis restricted to the CAS.

Multiple imputation – jump to reference – retrieved data – NI penalty – PP

This is a repeat of the primary analysis restricted to the PP analysis set.

17.3.3 Primary statistical analysis secondary estimand

MMRM

The secondary estimand for the primary objective is difference in change from baseline in HbA_{1c} after 26 weeks between T2DM subjects randomised to IDegLira and IGlar, both in combination with SGLT2i ± OAD, attributable to randomised treatment, if all randomised subjects had tolerated and adhered to treatment until week 26.

This analysis is a repeat of the standard MMRM this time leaving out retrieved (V32A) data.

17.3.4 Sensitivity analyses secondary estimand

ANOVA – LOCF imputation

This analysis is an ANOVA with treatment, pre-trial OAD and region as factors and baseline value as covariate based on the FAS and with missing data imputed by LOCF.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoints

The confirmatory secondary endpoints of the trial are tested for superiority of IDegLira to IGlar.

In order to control the overall Type I error, a hierarchical testing procedure will be used. If non-inferiority in glycaemic control (change from baseline in HbA_{1c}) is concluded in the primary statistical analysis of the primary estimand, testing proceeds down the following hierarchy as long as superiority at a given stage is confirmed based on the primary statistical analysis of the primary estimand:

1. Superiority in weight change
2. Superiority in number of treatment-emergent (severe or BG confirmed symptomatic) hypoglycaemic episodes
3. Superiority in glycaemic control (change from baseline in HbA_{1c})
4. Superiority in insulin dose (total daily dose [U])

The following paragraphs detail the hypotheses and statistical analyses of the confirmatory secondary endpoints.

17.4.1.1 Primary statistical analyses primary estimand

Body weight

Let D_W be the mean treatment difference (IDegLira – IGlar) in change from baseline in body weight. The null-hypothesis of IDegLira not superior will be tested against the alternative hypothesis of superiority as given by

$$H_0: D_W \geq 0 \text{ kg} \quad \text{against} \quad H_A: D_W < 0 \text{ kg}.$$

Superiority will be considered confirmed if the test procedure was not stopped and if the upper bound of the two-sided 95% confidence interval for D_W (mean treatment difference in change from baseline in weight) is strictly below 0 kg. This is equivalent to using a one-sided test of size 2.5%, i.e. the Type I error rate is controlled at 2.5% one-sided. The change from baseline in body weight after 26 weeks will be analysed with the J2R pattern mixture model for HbA_{1c}, substituting body weight for HbA_{1c} and leaving out the non-inferiority penalty (step 6).

Treatment-emergent hypoglycaemic episodes

Let RR be the rate ratio (IDegLira/IGlar) of the rate of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks. The null-hypothesis of IDegLira not superior will be tested against the alternative hypothesis of superiority as given by

$$H_0: RR \geq 1 \quad \text{against} \quad H_A: RR < 1.$$

Superiority will be considered confirmed if the test procedure was not stopped and if the upper bound of the two-sided 95% confidence interval for RR (rate ratio of rate of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during-treatment) is strictly below 1. This is equivalent to using a one-sided test of size 2.5%, i.e. the Type I error rate is controlled at

2.5% one-sided. The number of hypoglycaemic episodes will be analysed using a multiple imputation technique for count data under the J2R principle as follows.

For prematurely discontinued subjects the number of events in the missing period (time of premature discontinuation to planned TE period [max of 27 weeks and longest TE exposure time observed in the trial]) will be imputed using a multiple imputation technique[38], and assuming that all subjects have an event rate in the period before and after premature discontinuation corresponding to the event rate in the control group (IGlar). This will be done as follows:

- As a first step, a Bayes negative binomial model is fitted to the event rate data to obtain the posterior distribution of model parameters
- In the second step, based on the estimated parameters for comparator (IGlar) in this model, the number of events in the missing period is imputed for all prematurely discontinued subjects. I.e. pre and post discontinuation event rates in the conditional distribution used for imputation are as for comparator (IGlar). Multiple copies (1000 copies) of a complete data set are generated by sampling from the estimated distribution
- In the third step, for each of the complete data sets, the number of events is analysed using a negative binomial model
- In the fourth step, the estimates and standard deviations for the 1000 data sets are pooled to one estimate and associated standard deviation using Rubin's rule[37]. From these pooled estimates the confidence interval for the treatment ratio and the associated *p*-value are calculated

The negative binomial model will have a log-link function, and the logarithm of the time period, in which a hypoglycaemic episode is considered treatment-emergent, will be used as offset. The model will include treatment, pre-trial OAD and region as factors.

Glycaemic control

As above, let D be the mean treatment difference (IDegLira – IGlar) in change from baseline in HbA_{1c}. The null-hypothesis of IDegLira not superior will be tested against the alternative hypothesis of superiority as given by

$$H_0: D \geq 0\% \quad \text{against} \quad H_A: D < 0\%.$$

Superiority will be considered confirmed if the test procedure was not stopped and if the upper bound of the two-sided 95% confidence interval for D (mean treatment difference in change from baseline in HbA_{1c}) is strictly below 0%. This is equivalent to using a one-sided test of size 2.5%, i.e. the Type I error rate is controlled at 2.5% one-sided. The change from baseline in HbA_{1c} after 26 weeks will be analysed with the J2R pattern mixture model for HbA_{1c} but leaving out the non-inferiority penalty (step 6).

Insulin dose

Let D_D be the mean treatment difference (IDegLira – IGlar) in insulin dose after 26 weeks. The null-hypothesis of IDegLira not superior will be tested against the alternative hypothesis of superiority as given by

$$H_0: D_D \geq 0 \text{ U} \quad \text{against} \quad H_A: D_D < 0 \text{ U}.$$

Superiority will be considered confirmed if the test procedure was not stopped and if the upper bound of the two-sided 95% confidence interval for D_D (mean treatment difference in insulin dose after 26 weeks) is strictly below 0 U. This is equivalent to using a one-sided test of size 2.5%, i.e. the Type I error rate is controlled at 2.5% one-sided. The insulin dose after 26 weeks will be analysed with the J2R pattern mixture model for HbA_{1c}, substituting insulin dose for HbA_{1c}, leaving out the non-inferiority penalty (step 6) and using baseline HbA_{1c} as covariate as there is no baseline dose. That is, in the sequential ANOVAs (step 3 to 5) both insulin dose at previous visits and baseline HbA_{1c} will be included as covariates whilst in the EOT ANOVA (step 7) only baseline HbA_{1c} will be included as covariate.

17.4.1.2 Sensitivity analyses primary estimand

Continuous endpoints, body weight, HbA_{1c} and insulin dose – multiple imputation – copy reference– retrieved data

These analyses are repeats of the primary analyses using the CR principle in place of the J2R principle, just as for the CR sensitivity analysis of the primary estimand of the primary objective.

Continuous endpoints body weight, HbA_{1c} and insulin dose – multiple imputation – jump to reference – retrieved data – tipping point

These analyses are repeats of primary analyses where subjects who prematurely discontinue from the IDegLira arm are assumed to have received a treatment inferior to IGlar or any other treatment received after premature treatment discontinuation. The extent of the inferiority will be gradually increased to evaluate at which point (penalty) IDegLira is no longer superior to IGlar.

Count endpoint hypoglycaemic episodes – multiple imputation – copy reference

This is a repeat of the primary analysis using the CR principle in place of the J2R principle. More specifically, in this analysis IDegLira subjects are assumed to have the event rate of the IDegLira arm prior to premature discontinuation and the event rate of IGlar after premature discontinuation. The method follows the multiple imputation J2R for count data above, but in the second step pre discontinuation rates are the respective groups rates whilst post discontinuation rate is the rate of comparator (IGlar).

Count endpoint hypoglycaemic episodes – multiple imputation – jump to reference – tipping point

This is a repeat of the multiple imputation J2R above, now varying a penalty on the post discontinuation event rate until IDegLira is no longer superior to IGlar.

17.4.1.3 Primary statistical analyses secondary estimand

Continuous endpoints body weight, HbA_{1c} and insulin dose – MMRM

This is the same analysis as for the primary objective. For insulin dose baseline HbA_{1c} will be used as covariate.

Count endpoint hypoglycaemic episodes

Here the negative binomial model described above is simply applied to data as is.

17.4.1.4 Sensitivity analyses secondary estimand

Continuous endpoints body weight, HbA1c and insulin dose – multiple imputation – jump to reference – retrieved data

These analyses are identical to the primary analyses of the primary estimand and serve to evaluate the MAR assumption.

17.4.2 Supportive secondary endpoints

The supportive secondary endpoints will be addressed in terms of the primary estimand only.

17.4.2.1 Efficacy endpoints

HbA_{1c} responder after 26 weeks (yes/no)

Two dichotomous endpoints (responder=yes/non-responder=no) will be defined based on whether a subject has met a specific target level after 26 weeks:

- $HbA_{1c} < 7.0$ %
- $HbA_{1c} \leq 6.5$ %

Analysis of each the two responder endpoints will be based on a logistic regression model with treatment, pre-trial OAD and region as fixed factors and baseline HbA_{1c} value as a covariate, hereafter referred to as the standard logistic regression model.

For each of the multiple copies (1000) of the full dataset of the primary analysis of the primary estimand (multiple imputation J2R with retrieved data, NI penalty section 17.3.1) the responder endpoints are derived without using the non-inferiority penalty (step 6) and analysed with the standard logistic regression model. Estimates are pooled using Rubin's rule.

HbA_{1c} responder endpoints without weight gain after 26 weeks

Responder for HbA_{1c} without weight gain after 26 weeks will be defined as

- $HbA_{1c} < 7.0\%$ and change in body weight from baseline ≤ 0 kg
- $HbA_{1c} \leq 6.5\%$ and change in body weight from baseline ≤ 0 kg

Theses endpoint will be analysed as the HbA_{1c} responder endpoints, now using also the multiple copies of the full dataset for weight (section 17.4.1), and including baseline weight too as covariate in the standard logistic regression model.

HbA_{1c} responder endpoints without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes after 26 weeks

Responder for HbA_{1c} without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes after 26 weeks will be defined as

- $HbA_{1c} < 7.0\%$ and without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment
- $HbA_{1c} \leq 6.5\%$ and without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment

Theses endpoints will be analysed as the HbA_{1c} responder endpoints, where subjects with less than 12 weeks of treatment conservatively will be set to being non-responder.

HbA_{1c} responder endpoints without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes and weight gain after 26 weeks

Responder for HbA_{1c} without treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes and weight gain after 26 weeks will be defined as

- $HbA_{1c} < 7.0\%$without treatment-emergent severe or BG confirmed symptomatic during the last 12 weeks of treatment, and change in body weight from baseline ≤ 0 kg
- $HbA_{1c} \leq 6.5\%$ without treatment-emergent severe or BG confirmed symptomatic during the last 12 weeks of treatment, and change in body weight from baseline ≤ 0 kg

Theses endpoints will be analysed as the composite HbA_{1c} and weight responder endpoints, where subjects with less than 12 weeks of treatment conservatively will be set to being non-responder.

Waist circumference change from baseline after 26 weeks

Change from baseline in waist circumference will be analysed by multiple imputation J2R.

Fasting plasma glucose change from baseline after 26 weeks

Change from baseline in FPG will be analysed by multiple imputation J2R.

Fasting lipid profile after 26 weeks

Cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, triglycerides and free fatty acids will be analysed separately by multiple imputation J2R. In these statistical analyses, the endpoint will be log-transformed and so will the corresponding baseline covariate.

Self-measured plasma glucose (SMPG) 9-point profile change from baseline after 26 weeks

The following six endpoints from the 9-point SMPG profile will be defined:

- 9-point profile (individual SMPG values). [One endpoint]
- Mean of the 9-point profile, defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time. [One endpoint]
- Prandial plasma glucose increments (from before meal to 90 min after meal for breakfast, lunch and dinner). The mean increment over all meals will be derived as the mean of all available meal increments. [Four endpoints]

A linear mixed effect model will be fitted to the 9-point SMPG profile data. The model will include treatment, pre-trial OAD, time (within 9-point profile), the interaction between treatment and time, the interaction between pre-trial OAD and time as fixed factors, and subject as random effect. From the model mean profile by treatment and relevant treatment differences will be estimated and explored.

Change from baseline in mean of the 9-point profile and prandial increment endpoints will be analysed separately by multiple imputation J2R.

Blood pressure (systolic and diastolic) change from baseline after 26 weeks

Change from baseline in systolic and diastolic blood pressure will be analysed separately by multiple imputation J2R.

17.4.2.2 Safety endpoints

Adverse events during 26 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. If the event 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, then this event should also be considered as a TEAE. Major adverse cardiovascular events (MACEs) 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 of special interest including 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 reported by safety areas of interest
- 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

A listing for non-TEAEs with onset date before the first day of exposure to randomised treatment will be presented. A listing will also be presented for non-TEAEs collected after the treatment-emergent period according to the definition of TEAE.

Additional summaries will be displayed for MACEs collected between the end of treatment (V32) and the last follow-up visit (V32A) for subjects who discontinue trial product prematurely.

Hypoglycaemic episodes during 26 weeks

For the definition and classification of hypoglycaemic episodes refer to section 17.4.2.3.

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 or BG confirmed hypoglycaemic episodes, and the ADA (American Diabetes Association) classification of hypoglycaemia. The summaries are made for all and nocturnal (between 00:01 and 05.59 both inclusive) episodes respectively.

Number of nocturnal treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks will be analysed using the same J2R multiple imputation model as used for the treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes.

Clinical evaluation (ECG, eye examination and physical examination) change from baseline after 26 weeks

Eye examination (fundoscopy/fundusphotography) and 12-lead ECG findings will be summarised descriptively, including:

- Summaries for each visit
- Shift tables from baseline to after 26 weeks

Pulse rate change from baseline after 26 weeks

Change from baseline in pulse rate will be analysed by multiple imputation J2R.

Laboratory assessments (Biochemistry, Haematology, Calcitonin and urine analysis)

All laboratory parameters will be summarised descriptively including

- Summaries by visit
- Shift tables from baseline to after 26 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)

For lipase and amylase the following rule applies in the evaluation of the result:

- If the amylase or lipase baseline (at screening) value is > 3×upper normal range (UNR) the information will be regarded as medical history for that subject

17.4.2.3 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 trial product administration, and no later than 7 calendar days after the last day on trial product.

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

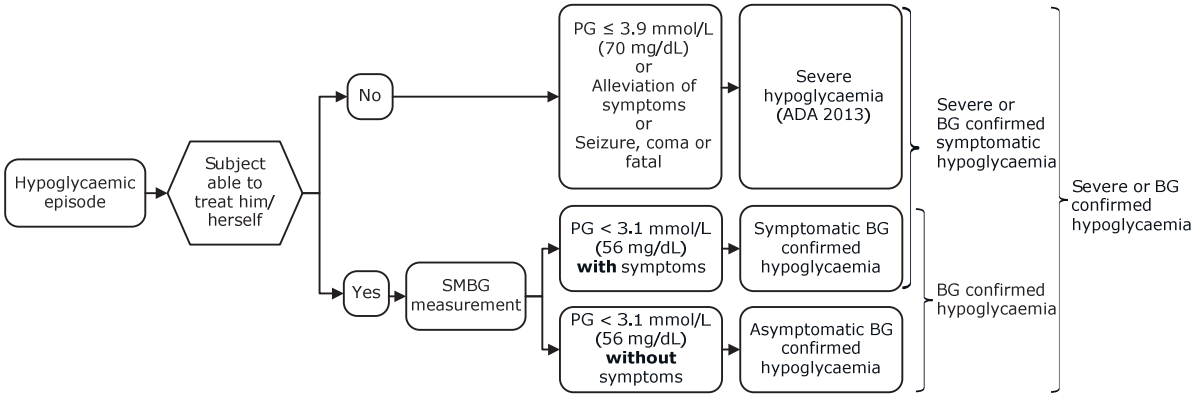
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–1) and the ADA classification of hypoglycaemia (see Figure 17–2).

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

Novo Nordisk uses the following classification (see Figure 17–1) in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[24] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia

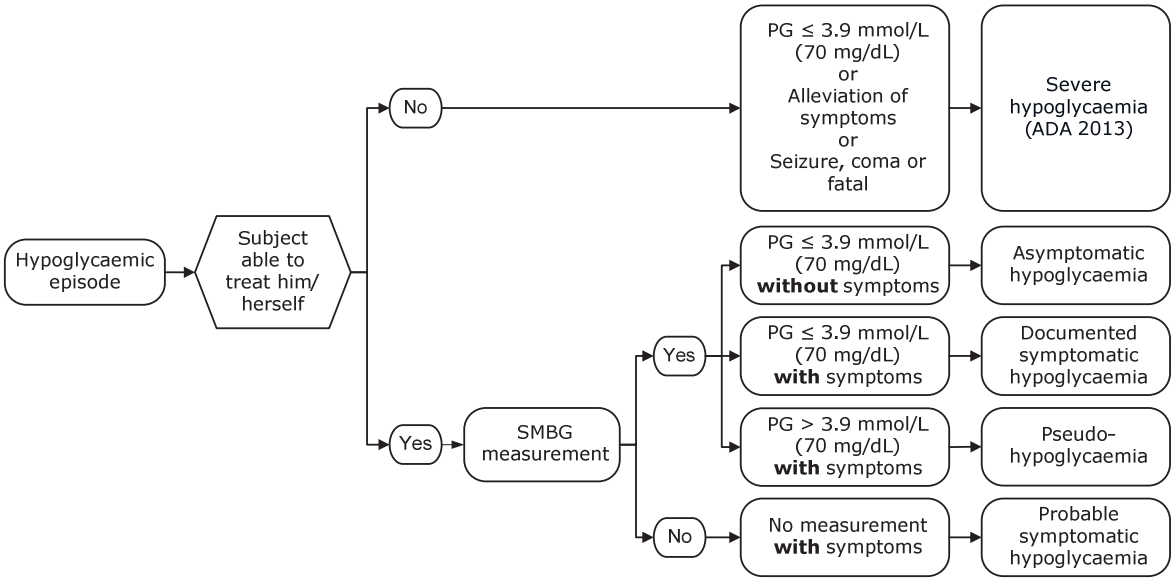


Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification[24] 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

Figure 17–2 ADA classification of hypoglycaemia

17.5 Health economics and/or patient reported outcomes

The following questionnaires will be used to compare PROs between treatments:

- Medical outcomes study 36-item short form (SF-36v2, standard)[16]
- Treatment related impact measure (TRIM-D)[17]

For each questionnaire, the summary scores will be summarised descriptively by visit and the change from baseline in score will be analysed separately by multiple imputation J2R.

18 Ethics

The trial will be conducted in compliance with ICH GCP[2] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[3].

The subjects will have the right to withdraw from the trial at any time, without giving a specific reason.

18.1 Benefit-risk assessment of the trial

All subjects included in the trial will be treated with IDegLira or IGlar, both in combination with previous SGTL2i ± OAD, in order to improve their glycaemic control.

Subjects will be transferred to a treatment regimen (fixed ratio combination of IDegLira or IGlar) anticipated to be better than or equal to the treatment they received prior to entering the trial. All participating subjects will need to spend some extra time as additional visits to the clinic are required, and some of the required tests performed during the trial are outside the normal practice. When randomised the subjects will get one of the treatments described above in combination with previous SGTL2i ± OAD. By trial design pre-trial OAD treatments must include SGLT2i either as monotherapy, or in combination with metformin ± DPP4i ± pioglitazone. If a subject is treated with DPP4i these have to be discontinued at randomisation, since subjects may be randomised to an injectable treatment including a GLP-1 receptor agonist. It has previously been reported that subjects on DPP4i in need of improved glycaemic control have acquired this by being switched from DPP4i to a GLP-1 receptor agonist[40].

Inclusion and exclusion criteria have been defined in order to ensure that only subjects that are eligible for trial participation are enrolled in the trial. Furthermore, withdrawal criteria are defined to ensure that subjects are considered for withdrawal, if the level of glycaemic control exceeds acceptable limits during trial participation.

The trial product may be associated with AEs, 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 gradual dose adjustment. Furthermore, subjects are fully informed about possible AEs and inconveniences and will be instructed to contact the investigator in case of any concerns regarding trial participation.

18.1.1 Clinical risk profile of IDegLira and risk mitigations for this trial

18.1.1.1 Identified risks

Hypoglycaemia

Hypoglycaemia is a pharmacological effect from insulin administration. The addition of liraglutide to IDeg has shown to reduce the requirement of exogenous insulin and hence minimise the risk of hypoglycaemia.

Immunogenicity (allergic reactions)

All peptide/protein based drugs have an inherent risk of allergic reactions. Allergic reactions are well known class effects for insulins and GLP-1 receptor agonists. Subjects with previous allergic reactions to IDeg or liraglutide will be excluded from the trial.

Pancreatitis

An association between the use of GLP-1 receptor agonists and pancreatitis has been suggested based on case reports received in clinical trials and during marketed use of drugs from this class. Even though a final conclusion regarding a causal relationship has not been established[41] a causal relationship is possible, and acute pancreatitis is therefore considered an identified risk for all GLP-1 receptor agonists. Subjects with history of pancreatitis (acute or chronic) will be excluded from the trial as a precaution.

There have been few clinical reported events of acute pancreatitis (inflammation of the pancreas) presenting with persistent severe abdominal pain (usually accompanied by vomiting) with liraglutide treatment. As a consequence of the known events of acute pancreatitis, Novo Nordisk will analyse blood samples for amylase and lipase during the trial to monitor the subjects' safety. Furthermore, participating subjects should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, IDegLira and other potentially suspected medicinal products will be discontinued. All cases of pancreatitis will be evaluated by the external EAC.

Gastrointestinal adverse events

Gastrointestinal adverse events are considered class effects for GLP-1 receptor agonists and are among the most frequently reported events in patients treated with IDegLira. The titration of IDegLira is slow and has previously shown to result in a lower frequency of gastrointestinal adverse effects. The dose of the liraglutide component in the start dose of IDegLira in the present trial is 0.36 mg, which is less than the starting dose of liraglutide when administered as the mono-component (Victoza®).

18.1.1.2 Potential risks

Altered Renal Function

Dehydration due to known gastrointestinal effects associated with GLP-1 receptor agonists may in rare cases be associated with renal impairment in predisposed patients, and dehydration associated with treatment with SGLT2i could theoretically add to this risk. Patients treated with IDegLira should be advised of the risk of dehydration in relation side effects of GLP-1 receptor agonists and SGLT2i and take precautions to avoid fluid depletion. Furthermore, impaired renal function as defined in the protocol is an exclusion criterion in this trial. Monitoring of creatinine will be performed during the trial as part of standard safety laboratory surveillance.

Medullary Thyroid Cancer (C-Cell Carcinogenicity)

Thyroid C-cell carcinogenicity has been reported in rats and mice treated with GLP-1 receptor agonists in non-clinical studies. Based on these findings, monitoring of serum calcitonin will be performed approximately every 3 months in the present trial. Subjects with thyroid disease will be closely monitored and in case of elevated calcitonin a recommendation for follow-up is included in Appendix C in the protocol. Subjects with a personal or family history of medullary thyroid carcinoma and subjects with multiple endocrine neoplasia type 2 syndrome or/and subjects with a calcitonin value > 50 ng/L will be excluded from the trial.

Neoplasms

Epidemiologic evidence suggests that subjects with T2DM are at higher risk for many forms of cancer. Moreover, evidence from observational studies indicates that some medications used to treat hyperglycaemia are associated with either increased or reduced risk of cancer. It is thus important to demonstrate, that new antidiabetic therapies do not increase the inherent risk of neoplasms in the T2DM population.

Neoplasms will be followed closely. All neoplasms will be adjudicated externally by an EAC.

Pancreatic cancer

Pancreatic cancer is included as a potential risk, due to the focus on the potential association with GLP-1-based therapies. There is currently no support from non-clinical investigations or clinical trials that GLP-1 receptor agonists increase the risk of pancreatic cancer[42]. GLP-1 receptor agonists treatment shall be withdrawn in patients with suspicion of/diagnosed pancreatic cancer and appropriate treatment and monitoring shall be initiated.

Epidemiologic evidence suggests that subjects with T2DM are at significantly higher risk for many forms of cancer[43,44].

Cardiovascular Disorders

Subjects with T2DM have an increased risk of cardiovascular disorders, and it is a major comorbidity factor in this population.

The following cardiovascular events will be followed closely: acute coronary syndrome, cerebrovascular event, heart failure requiring hospital admission, revascularisation procedures and cardiac arrhythmia. In addition, selected cardiovascular events will be adjudicated by the EAC.

Lack of efficacy due to anti-IDeg or anti-liraglutide antibody formation

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-insulin degludec and anti-liraglutide antibodies following treatment with liraglutide and IDeg. Antibody formation seems to be of no consequence for the efficacy and the safety of liraglutide or current insulin preparations.

Medication errors, including errors with transfer from injectable diabetes therapy

Medication errors may occur due to the lack of training before initiating IDegLira therapy, patient's unawareness of difference between IDegLira and other injectable diabetes therapy (insulin or GLP-1 receptor agonists) or distraction during preparation for injection. Mixing up IDegLira with different types of insulin may result in hypo- and/or hyperglycaemia. Mixing up IDegLira with a GLP-1 agonist may result in gastrointestinal disorders. Investigators should mitigate this risk by providing clear instructions of use and importance of not mixing two injectable treatments by understanding their difference in function.

18.1.1.3 Other safety considerations

In reproduction and development toxicity studies liraglutide has been shown to be teratogenic in rats and rabbits including reduced growth and major abnormalities at systemic exposures below human exposure at the maximum recommended human dose (MRHD) of 1.8 mg/day. The US Victoza® Prescribing Information includes the Pregnancy Category C (US FDA Pharmaceutical Pregnancy Categories: "Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks"). Due to this pregnant women and women with the intention to become pregnant, are excluded from the trial.

Dorsal skin sarcomas at the injection site were significantly increased in male mice at the highest dose of 3 mg/kg/day. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/ml) is 10-times higher than the concentration in the formulation used in the carcinogenicity study (0.6 mg/ml). The observed increase in skin sarcomas in high-dose male mice is of unknown relevance for human safety.

Non-lethal thyroid C-cell tumours were seen in 2-year carcinogenicity studies in rats and mice. In rats, a no observed adverse effect level (NOAEL) was not observed. These tumours were not seen in monkeys treated for 20 months. These findings in rodents are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot be completely excluded. No other treatment-related tumours have been found.

GLP-1 receptor agonists may lead to dehydration due to gastrointestinal side-effects. Treatment with SGLT2i may be associated with dehydration in certain vulnerable patients, e.g. the elderly. By only including patients that have both been started on SGLT2i treatment independently of the trial, and have tolerated SGLT2i treatment for 90 days we minimize the risk of adverse events in this regards. Furthermore, IDegLira is titrated slowly and thus the risk of gastrointestinal side effect is minimal[45].

18.1.2 Summary of risk assessment

In conclusion, no safety or tolerability issues of concern have been observed so far in the nonclinical and clinical programme for IDegLira that would prohibit further clinical development of this product. This trial has been designed to mitigate potential risks, such as risk of dehydration, associated with SGLT2i treatment. The development programme has not identified any risks associated with the use of IDegLira that are not already known from IDeg or liraglutide; for further information please see section 3. The benefits are therefore concluded to outweigh the risks, and the proposed use of IDegLira in this trial is considered warranted.

Areas of special interest with regards to safety of trial products are described in detail in the IDeg NN1250 IB[9] current version or any updates hereof, the liraglutide local approved labelling current version or any updates hereof and/or the IDegLira NN9068 IB[10] current version or any updates hereof.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[2] and the requirements in the Declaration of Helsinki[3].

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.

In this trial additional informed consent must be obtained if:

- A female subject becomes pregnant during the trial, the male partner should be asked to sign a separate informed consent form (when abnormality is found in the foetus or new-born infant).
- A male subject report that his female partner becomes pregnant during the trial, the female partner should be asked to sign a separate informed consent form (only applicable for the US).

In addition, all subjects will be asked to sign a separate informed consent form in order to give permission to collect cardiovascular information in case the subject withdraws. The subject will be asked to sign this additional informed consent when entering the trial and the cardiovascular information will be collected at the time of the initial planned EOT.

18.3 Data handling

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

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

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

18.4 Information to subject during trial

The subject may receive information provided to the site by Novo Nordisk, an example of this may be 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 a trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the 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

Deviations from the protocol should be avoided.

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

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

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

20 Audits and inspections

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

21 Critical documents

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

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (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 or Summary of Product Characteristics
- 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)

Only applicable for US trial sites:

- 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, each investigator agrees to comply fully with ICH GCP[2], applicable regulatory requirements and the Declaration of Helsinki[3].

By signing the protocol, 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. 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 training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

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

The investigator must ensure adequate supervision of the conduct of the trial at the trial site.

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

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents including the subject identification code list should 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 CTR for this trial.

One investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications[46].

23.1 Communication of results

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

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[18].

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR 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 Editors[46] (sometimes referred to as the Vancouver Criteria).

The investigator(s) offered authorship will be asked to comment and approve the publication. No permission to publish will be granted to any clinical research organisation (CRO) involved in the trial described in this protocol.

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.

24 Retention of clinical trial documentation

24.1 Retention of clinical trial documentation

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

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

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

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for as long as the product is on the market plus 20 years.

The files from the trial site/institution must be retained for 15 years after the completion of the trial, 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.

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, according to local requirements.

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.

Novo Nordisk accepts liability in accordance with:

Russia: Federal Law of 12 April 2010 No. 61-FZ "On Medicinal Drugs' Cerculation
Switzerland: Federal Act on Medicinal Products and Medical Devices of (HMG/TPA) 15 December 2000 and Ordinance on Clinical Trials in Human Research (KlinV/ClinO) of 20 September 2013

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

Appendix A: Titration Guideline

Trial ID: NN9068-4229

DUAL™ IX - Add-on to SGLT2i

A clinical trial comparing glycaemic control and safety of insulin degludec/liraglutide (IDegLira) versus insulin glargine (IGlar) as add-on therapy to SGLT2i in subjects with type 2 diabetes mellitus

Trial phase: 3b

Table of Contents

List of in-text tables

1 Introduction

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

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

It is recognised that treatments differ between different regions and countries. Likewise, specific titration guidelines may not be applicable in certain clinical situations. It is important that other information, such as symptoms of hypo- or hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the subject's level of glycaemic control, is taken into consideration when decisions on dosing are made. The investigator should always use 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 trial product doses and to ensure the subject's welfare.

2 Treatment regimens

At randomisation the subjects will be randomised 1:1 into two parallel treatment arms:

- IDegLira OD + SGLT2i ± OAD
- IGlar OD + SGLT2i ± OAD

First dosing of IDegLira or IGlar should take place on day of randomisation or on the day following randomisation.

Maximum dose of IDegLira is 50 dose steps (50U of insulin degludec and 1.8 mg of liraglutide).

There is no maximum dose of IGlar.

Subjects should continue their SGLT2i ± metformin ± pioglitazone pre-trial doses.

2.1 Injection area

IDegLira should be injected subcutaneously into the thigh, upper arm (deltoid region) or the abdomen.

IGlar should be administered subcutaneously according to local labelling.

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

IDegLira should be injected once daily at any time of the day, but should approximately be the same time of the day throughout the trial.

IGlar should be injected once daily according to local labelling.

3 Initiation and titration

3.1 Initiation of IDegLira or IGlar

Subjects randomised to IDegLira will start on 10 dose steps, consisting of 10U insulin degludec/0.36 mg liraglutide once daily.

Subjects randomised to IGlar will start on 10U of insulin glargine once daily.

3.2 Titration of IDegLira or IGlar

The doses of IDegLira or IGlar should be adjusted twice weekly on fixed days (Mondays and Thursdays).

Dose adjustment will be based on the mean of three pre-breakfast SMPG values measured on the day of the titration and the two days prior to the titration in accordance with Table 1.

- Monday, Tuesday and Wednesday doses will be determined, based on the *mean* fasting glucose values, obtained on Saturday, Sunday and Monday
- Thursday, Friday, Saturday and Sunday doses will be determined, based on the *mean* fasting glucose values, obtained on Tuesday Wednesday and Thursday

Table 1 Adjustment of IDegLira or IGlar

Mean pre-breakfast SMPG		Dose adjustment
mmol/L	mg/dL	Dose steps/U
< 4.0	< 72	-2
4.0 – 5.0	72 – 90	0
> 5.0	> 90	+2

If one or more SMPG values are missing, the dose adjustment should be performed on the remaining SMPG value(s).

3.3 Deviation from the algorithm

It is recommended that the algorithm is followed. However, it is also important that the decision to adjust the IDegLira or IGlar 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 titration data from the diaries should be entered into the eCRF for all subjects within 24 hours on weekdays after each site visit/phone contact:

- Daily SMPG values
- Daily date, time and dose of IDegLira or IGlar
- Hypoglycaemic episodes
- Prescribed dose of IDegLira or IGlar
- Reasons for deviations from the titration guideline, if applicable.

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):408-416.

2 Hermansen K, Davies M, Derezinski T, Martinez RG, Clauson P, Home P. 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):1269-1274.

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. Clinical Therapeutics 2006; 28(10):1569-1581.

4 Riddle MC, Rosenstock J, Gerich J. 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):3080-3086.

5 Garber AJ, King AB, Del PS, 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):1498-1507.

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):1489-1497.

Appendix B: Events with additional data collection and events requiring adjudication

Trial ID: NN9068-4229

DUAL™ IX - Add-on to SGLT2i

A clinical trial comparing glycaemic control and safety of insulin degludec/liraglutide (IDegLira) versus insulin glargine (IGlar) as add-on therapy to SGLT2i in subjects with type 2 diabetes mellitus

Trial phase: 3b

1 Events with additional data collection and events requiring adjudication

Events with additional data collection and/or events requiring adjudication	Definitions	Rationale	Event Adjudication Committee
Fatal events	All fatal events must be reported including all-cause mortality: • Cardiovascular death • Non-cardiovascular death • Undetermined cause of death	An FDA guidance document[1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All events will be adjudicated
Acute coronary syndrome: • Myocardial infarction • Hospitalisation for unstable angina	All types of myocardial infarction (MI) must be reported: • Spontaneous MI (including re-infarction and MI associated with stent thrombosis) • Percutaneous coronary intervention (PCI) related MI • Coronary artery bypass graft surgery (CABG) related MI • Silent MI All events with symptoms of unstable angina requiring hospitalization must be reported.	An FDA guidance document[1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All events will be adjudicated
Cerebrovascular event (stroke or transient ischemic attack)	**Stroke** (ischaemic, haemorrhagic or undetermined) is defined as an acute episode of neurological dysfunction, caused by focal or global brain, spinal cord, or retinal vascular injury. **Transient Ischemic Attack** (TIA) is defined as a transient (<24 hours) episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.	An FDA guidance document[1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All events will be adjudicated

Events with additional data collection and/or events requiring adjudication	Definitions	Rationale	Event Adjudication Committee
Heart failure requiring hospital admission	Clinical manifestations of a new episode or worsening of existing heart failure requiring admission.	An FDA guidance document[1] requests that Sponsors demonstrate the cardiovascular safety profile of any new therapy for type 2 diabetes in order to ensure, that the new therapy does not increase the cardiovascular risk to an unacceptable extent.	All cases of heart failure requiring hospitalisation, defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour stay, will be adjudicated
Pancreatitis	Two of the following three diagnostic criteria fulfilling the diagnosis of acute pancreatitis: • Severe acute upper abdominal pain • Elevated blood levels of pancreatic enzymes (lipase and/or amylase) > 3xUNR • Characteristic imaging finding (ultrasound, computerised axial tomography (CT), magnetic resonance imaging (MRI) Chronic pancreatitis will be defined by characteristic imaging finding (ultrasound, CT, MRI) with abnormal pancreatic function tests or characteristic histological findings.	Treatment with GLP-1 agonists has been associated with acute pancreatitis. Pancreatitis (including necrotising pancreatitis) is an identified risk according to the Company Core Data Sheet (CCDS) for liraglutide, a component of IDegLira. Novo Nordisk therefore monitors these events closely.	All events will be adjudicated
Thyroid disease	All disorders of thyroid gland (incl. thyroid neoplasms) must be reported. Please refer to the protocol for further details on the	Thyroid C-cells carcinogenicity has been reported in rats and mice treated with GLP-1 receptor agonists in non-clinical studies.	All thyroid neoplasms will be adjudicated. Thyroid disorders

Events with additional data collection and/or events requiring adjudication	Definitions	Rationale	Event Adjudication Committee
	assessments.		which require thyroidectomy will be adjudicated
Neoplasm	All types of neoplasms (i.e. all new growth incl. polyps, warts etc.) must be reported including: • Malign neoplasm • In situ neoplasm • Benign neoplasm • Neoplasms of uncertain or unknown behaviour (Please note: for operational reasons thyroid neoplasms will be reported as a thyroid disease and should not be reported as a Neoplasm)	Neoplasm is an event we follow closely for GLP-1 analogues due to non-clinical findings in rats and mice treated with GLP-1 agonists.	All neoplasm events, irrespective of malignancy stage, will be adjudicated
Renal failure	• All events of renal failure should be reported, including events fulfilling one of the following three diagnostic criteria, fulfilling the diagnosis of acute renal failure: • Increase in serum creatinine ≥ 0.3 mg/dL within 48 hours • Increase in serum creatinine to ≥ 1.5 times baseline within 7 days • Urine volume < 0.5 mL/kg/h for 6 hours	Liraglutide (a component of IDegLira) and SGLT2i have been associated with dehydration/volume depletion. Severe dehydration/volume depletion per se can be associated with development of renal impairment and acute renal failure. Therefore renal impairment and acute renal failure are followed closely.	No adjudication

Events with additional data collection and/or events requiring adjudication	Definitions	Rationale	Event Adjudication Committee
Medication errors concerning trial products	1. Administration of wrong drug or use of wrong device. Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug. 2. Wrong route of administration, such as intramuscular instead of subcutaneous 3. Administration of an overdose with the intention to cause harm (e.g., suicide attempt) Accidental administration of a lower or higher dose than intended. That is a dose that deviates by more than ± 20% of the 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 are captured to collect information which may be used to improve the design, name or packaging of the product and/or information which may have an impact on product labelling (for example information about substantial overdoses).	No adjudication

2 Adverse Events Requiring Additional Data Collection in the eCRF

2.1 Cardiovascular events:

Cardiovascular events that are suspected as being related to one of the three categories below should be reported on the designated form in the eCRF:

2.1.1 Acute coronary syndrome

All types of myocardial infarction or hospitalisation for unstable angina. If an event of acute coronary syndrome is observed during the trial, this must be recorded as an AE and on a specific acute coronary syndrome form in the eCRF. The following information must be reported if available:

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

2.1.2 Cerebrovascular events, e.g. transient ischemic attack (TIA), stroke

If a cerebrovascular event is observed during the trial, this must be recorded as an AE and on a specific cerebrovascular event form in the eCRF. The following information must be reported if available:

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

2.1.3 Heart failure requiring hospitalisation

If an event of heart failure requiring hospitalisation (admission to an in-patient unit or a visit to an emergency department that results in at least a 24 hour stay) is observed during the trial, this must

be recorded as an SAE and in addition on a specific heart failure event form in the eCRF. The following information must be reported if available:

- Signs and symptoms of heart failure
- NYHA Class[2]
- Supportive imaging
- Supportive laboratory measurements
- Initiation or intensification of treatment for this condition

2.2 Pancreatitis

If an event of pancreatitis is observed during the trial, this must be recorded as an AE and on a specific pancreatitis event form in the eCRF. The following information must be reported **if available**:

- Signs and symptoms of pancreatitis
- Specific laboratory test supporting a diagnosis of pancreatitis:
  - Amylase
  - Lipase
  - ALT and AST
  - Bilirubin
  - Alkaline Phosphatase
- Imaging performed and consistency with pancreatic disease
- Complications to the event
- Relevant risk factors for pancreatic disease including:
  - History of gall-stones
  - History of pancreatitis
  - Family history of pancreatitis
  - Trauma

2.3 Thyroid disease

Non-lethal thyroid C-cell tumours were seen in 2-year carcinogenicity studies in rats and mice. In rats, a no observed adverse effect level (NOAEL) was not observed. These tumours were not seen in monkeys treated for 20 months. These findings in rodents are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot be completely excluded. No other treatment-related tumours have been found.

Subjects scheduled for thyroidectomy (partial or total) for any reason during the trial, must be instructed to inform the investigator prior to their operation. If an event of thyroid disease, including

any thyroid neoplasms is observed during the trial, this must be recorded as an AE and on a specific thyroid disease event form in the eCRF. The following information must be reported if available:

- History of thyroid disease
- Signs and symptoms leading to investigations of thyroid disease
- Specific laboratory tests describing thyroid function including:
  - Thyroid stimulating hormone (TSH)
  - Total and free T3 and T4 and Free Thyroid Index
  - Calcitonin
  - Thyroid Peroxidase antibodies
  - Thyroglobulin and Thyroglobulin antibody
  - TSH receptor antibody
- Diagnostic imaging performed and any prior imaging supporting the disease history
- Pathologic examinations
- Treatment given for the condition
- Risk factors identified
- Family history of thyroid disease

2.4 Neoplasms

All events of neoplasm (excluding thyroid neoplasm, but including malignant neoplasm, in situ neoplasm and benign neoplasm) must be recorded as an AE and on a specific neoplasm event form in the eCRF. The following information must be reported if available:

- Type of neoplasm
- Symptoms leading to identification of event
- Diagnostic imaging
- Pathological examination results
- Treatment for the event
- Participation in screening programs
- Risk factors associated to the event

2.5 Renal failure

If an event of renal failure is observed during the trial the following additional information should be reported if available:

- Signs and symptoms of renal failure
- Specific laboratory test supporting a diagnosis of renal failure
- Imaging performed supporting the diagnosis
- Kidney biopsy results

- Relevant risk factors associated to the event

2.6 Medication errors

If a medication error is observed during the trial the following additional information should be obtained:

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

3 References

1 Hicks KA, Hung HMJ, Mahaffey KW, Mehran R, Nissen SE, Strockbridge NL et al. *Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials (DRAFT)*. 20 Aug 2014.

2 The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria forDiagnosis of Diseases of the Heart and Great Vessels*. 9th ed., 253-256. 1994. Boston, Mass: Little, Brown & Co.

Appendix C: Monitoring of calcitonin

Trial ID: NN9068-4229

DUAL™ IX - Add-on to SGLT2i

A clinical trial comparing glycaemic control and safety of insulin degludec/liraglutide (IDegLira) versus insulin glargine (IGlar) as add-on therapy to SGLT2i in subjects with type 2 diabetes mellitus

Trial phase: 3b

1 Background

Treatment with GLP-1(glucagon-like peptide-1) receptor agonists has shown to be associated with thyroid C-cell changes in rodents but not in non-human primates. The human relevance of this finding is unknown. However, based on the findings in rodents, monitoring of serum calcitonin (a sensitive biomarker for C-cell activation) is currently being performed in clinical trials with insulin degludec/liraglutide (IDegLira).

While there is general agreement on the clinical interpretation of substantially elevated calcitonin levels (greater than 100 ng/L) as likely indicative of C-cell neoplasia, the interpretation of values between upper normal range (5.0 and 8.4 ng/L for women and men, respectively) and 100 ng/L is less clear with regards to indication of disease.

There are several known confounding factors affecting calcitonin levels, e.g.:

- renal dysfunction
- smoking
- autoimmune thyroiditis
- several drug classes (e.g. proton pump inhibitors, beta-blockers, H_2-blockers and glucocorticoids)

Physiology of C-cell activation in various clinical conditions and in different patient populations (i.e. with various co-morbidities) is poorly understood. There may be various clinical conditions not identified so far which mildly or moderately affect calcitonin secretion by C-cells.

2 Calcitonin monitoring

A blood sample will be drawn at pre-specified trial visits for measurement of calcitonin. Subjects with a calcitonin value ≥ 50 ng/L cannot be randomised according to protocol section 6.3. In case a subject has a calcitonin value ≥ 10 ng/L the algorithm outlined in Figure 1 and described below should be followed. The algorithm applies for all calcitonin values including screening values.

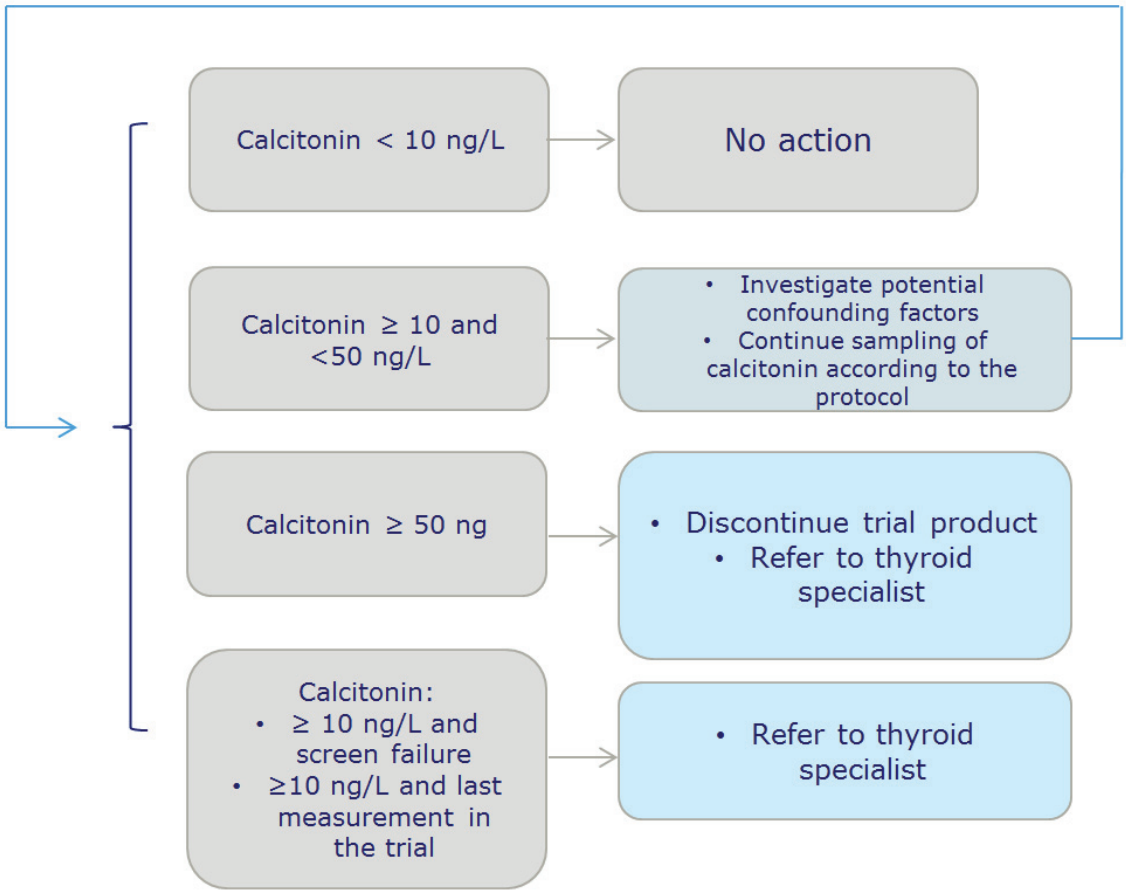

Figure 1 Flow of calcitonin monitoring

2.1 Calcitonin ≥ 100 ng/L

Action: The subject (even if a screen failure) must immediately be referred to a thyroid specialist for further evaluation and the trial product must be discontinued (see section 6.4 premature discontinuation of trial product). The subject can remain in the trial; however, all medications suspected to relate to this condition must be discontinued until diagnosis has been established.

Background: These values were found in 9 (0.15%) of a population of 5817 patients with thyroid nodular disease[1]. All of these patients were diagnosed with MTC (medullary thyroid cancer) resulting in a positive predictive value of 100 %.

Diagnostic evaluation should include:

- thyroid ultrasound
- fine needle aspiration of any nodules >1 cm
- potentially surgery with neck dissection

In case a subject is diagnosed with MTC, it is common clinical practice to explore the family history of MTC or MEN2 (multiple endocrine neoplasia type 2) and perform a genetic test for RET proto-oncogene mutation.

2.2 Calcitonin ≥ 50 and < 100 ng/L

Action: The subject (even if a screen failure) should be referred to a thyroid specialist for further evaluation and the trial product should be discontinued. The subject can remain in the trial however; all medications suspected to relate to this condition should be discontinued until appropriate treatment has been initiated.

Background: These values were found in 8 (0.14%) of the population of 5817 patients with thyroid nodular disease[1]. Two of these subjects were diagnosed with MTC and two were diagnosed with C-cell hyperplasia, resulting in a positive predictive value of a C-cell anomaly of 50%.

Diagnostic evaluation should include:

- thyroid ultrasound examination
- if available no contraindication, a pentagastrin stimulation test. Subjects with positive pentagastrin stimulation tests should be considered to undergo surgery
- if pentagastrin is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information informing the need for surgery

2.3 Calcitonin ≥ 10 and < 50 ng/L

Action: The subject can continue in the trial on trial product. Continue sampling of calcitonin according to the protocol. If the subject is a screen failure or if the value is from the last sample taken in the trial, the subject should be referred to a thyroid specialist for further evaluation.

Background: Calcitonin values from 20-50 ng/L were found in up to 1% of subjects of the population of 5817 patients with thyroid nodular disease[1]. The predictive value of a C-cell anomaly for this calcitonin level was 8.3%. However, the likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.

For calcitonin values 10-20 ng/L Costante et al[1] identified 216 (3.7%) patients. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin of 33 ng/L, and had C-cell hyperplasia at surgery. Two other studies used a cut-off of CT > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT >10 and <20 ng/L to allow conclusions[2,3].

3 References

1 Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab 2007; 92(2):450-455.

2 Scheuba C, Kaserer K, Moritz A, Drosten R, Vierhapper H, Bieglmayer C et al. Sporadic hypercalcitoninemia: clinical and therapeutic consequences. Endocr Relat Cancer 2009; 16(1):243-253.

3 Verga U, Ferrero S, Vicentini L, Brambilla T, Cirello V, Muzza M et al. Histopathological and molecular studies in patients with goiter and hypercalcitoninemia: reactive or neoplastic C-cell hyperplasia? Endocr Relat Cancer 2007; 14(2):393-403.

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

Substantial amendment nº 1 to protocol version 2.0 dated on 20-Nov-2015. .

Trial ID: NN9068-4229

DUAL™ IX - Add-on to SGLT2i

A clinical trial comparing glycaemic control and safety of insulin degludec/liraglutide (IDegLira) versus insulin glargine (IGlar) as add-on therapy to SGLT2i in subjects with type 2 diabetes mellitus.

Redacted protocol
Includes redaction of personal identifiable information only.

Trial phase: 3b

Applicable to Spain

Author

[redacted], [redacted]
Clinical Operations Spain
CMR Spain, CDC Europe

Table of contents

Page

1 Introduction including rationale for the substantial amendment

Based on the recommendation of Spanish HA (AEMPS) that the protocol should contain detailed information on the required level of contraception taking into account the possible toxicity of the investigational drug. And also we should consider recommendations on contraception in clinical trials by Clinical Trial Facilitation Group (CFTG[1]), the protocol has been revised with regards to the exclusion criteria nº 4 changing from "females of childbearing potential not using adequate contraceptive methods" to "females of childbearing potential not using highly effective contraceptive methods".

According to CFTG contraceptive methods defined as "highly effective" (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly) are:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

[1] http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

2 Changes

The protocol has been changed accordingly. Removed text is strikethrough and new text is shown in italics:

6.3 Exclusion criteria

4. Female who is pregnant, breast-feeding or intend to become pregnant or of childbearing potential not using ~~adequate~~ *highly effective* contraceptive methods (*highly effective* ~~adequate~~ contraceptive measures as required by local regulation or practice)

Spain*: Highly effective methods are defined as established use of:*

- *oral, injectable, transdermal, implantable or intravaginal hormonal methods of contraception associated with inhibition of ovulation*
- *placement of an intrauterine device*
- *female sterilisation*
- *male sterilisation (where partner is sole partner of subject)*
- *true abstinence (when in line with preferred and usual lifestyle)*

Protocol Amendment

No. 2
to Protocol, final version 2.0
dated 20 November 2015

Trial ID: NN9068-4229

DUAL™ IX - Add-on to SGLT2i
A clinical trial comparing glycaemic control and safety of insulin degludec/liraglutide (IDegLira) versus insulin glargine (IGlar) as add-on therapy to SGLT2i in subjects with type 2 diabetes mellitus

Trial phase: 3b

Applicable to all countries

Redacted protocol
Includes redaction of personal identifiable information only.

Amendment originator:

[redacted], [redacted]

Table of Contents

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 the amendment

This amendment has been prepared in order to:

1. Update List of abbreviations
2. Update the flowchart:
   - deletion of footnote 7 – as not applicable in final eCRF
   - update of flowchart and protocol section 8.17 to specify that subjects who premature discontinue trial product should attend V32A in a fasting state
3. Clarify the rescue criteria in section 6.5 in order to make it clear that they apply after baseline visit meaning after initiation of treatment
4. Update the wording relating to randomisation visit timeframe in section 8.1.3 in order to add an element of flexibility which may be required to accommodate scenarios where an eligible subject is not able to attend for randomisation on day 14 due to force majeure
5. Delete the wording relating to randomisation visit timeframe in section 8.1.4 as this is specified in Section 2 Flowchart
6. In section 8.2 add that in case of abnormal haematology analysis test results, part of the sample may be kept for up to 2 years
7. In section 8.4.1 - Height, deletion of text regarding rounding to nearest cm or inch as not applicable in final eCRF
8. In section 8.5.2 insert “>” in front of 3.9 mmol/L.
   In addition, in the 5th bullet in order to align with the diary, specify that date, time, and dose of last anti-diabetic treatment should not be collected in connection with a hypoglycaemic event between V32 and V33
9. In section 8.5.5 update text in order to specify that the ECG should be repeated in case the randomisation takes place more than 14 days after the ECG is obtained. In addition delete whom the ECG should be obtained by
10. In section 8.6.1, align with the PRO questionnaire that site staff can fill in the headings on the questionnaire forms and review the questionnaire for empty fields and potential adverse events
11. In Summary and section 9.1 specify that SGLT2i and metformin not necessarily “will be” but “can be” reimbursed in accordance with local legislation and Ethics Committee approval
12. In section 12.1 update serious adverse event with current protocol template text and definition of Major Adverse Cardiovascular Events (MACE)
13. In section 12.2 specify that “fasting body weight” should be measured at V32A

14. In section 12.5.1 specify forms to be completed
15. Update made to section 13.2 in order to align with other parts of the protocol
16. In section 17 statistical terminologies of “jump to reference” and “copy reference” have been abolished and updated with established terminologies “multiple imputation conditional” and “multiple imputation unconditional”
17. In section 18.1 align text with other parts of the protocol
18. Update section 18.1.1 with “acute gallstone disease” in accordance with update to IDegLira Minimum Mandatory Safety Text
19. Make typographical changes
20. In appendix A: align with section 5.3 the wording regarding starting dose of IDegLira and specification of dose adjustment

2 Changes

2.1 List of abbreviations

~~CR~~	~~copy reference~~
~~J2R~~	~~jump to reference~~
ANOVA	*analysis of variance*
CAS	*completer analysis set*
ITT	*intention to treat*
MCMC	*Markov Chain Monte Carlo*
NI	*non-inferiority*
PP	*per-protocol*

2.2 Section 1 Summary

Trial products:

The subject's de-facto cost of SGLT2i and metformin (mono- or fixed dose combination products) ~~will~~ *can* be reimbursed in accordance with local legislation and Ethics Committee approval.

2.3 Section 2 Flowchart

Trial Periods	Screen	Rand	Treatment																	EoT	Follow-up		Pre-disc[1]	
Trial site visit (V) Phone contact (P)[2]	V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11 P12 P13	V14	P15 P16 P17	V18	P19 P20 P21	V22	P23 P24 P25	V26	P27 P28 P29 P30 P31	V32	FU1 V33	FU2 P34	PX	V32A
Timing of visit (weeks)	≤ 2 weeks prior to V2	0	0.5[3]	1	1.5[3]	2	2.5[3]	3	3.5[3]	4	5 6 7	8	9 10 11	12	13 14 15	16	17 18 19	20	21 -25	26	7 days after last trial product	30 days after last trial product	Every 4 weeks	26
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
SUBJECT RELATED INFO/ASSESSMENTS																								
Informed consent	X																							
In/exclusion criteria	X	X																						
Randomisation		X																						
Pre-discontinuation of trial product			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Rescue criteria				X		X		X		X	X	X	X	X	X	X	X	X	X	X				
Withdrawal of consent			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[4]	X	
Demography[5]	X																							
Concomitant illness	X																							
Medical history	X																							
Diagnosis of diabetes	X																							
Diabetes complications	X																							

[1] Subjects discontinuing trial product prematurely will be asked to attend the end of treatment (EoT) visit and the two follow up visits after discontinuation corresponding to V32, V33 and P34. After the follow-up period the subject should have phone contacts scheduled every 4 weeks (PX) until the additional premature discontinuation follow-up visit (V32A) performed at week 26. See section 2.7 for further details.
[2] A phone contact may be converted to a trial site visit e.g. if further titration is needed.
[3] Corresponding to previous visit date plus 3 days.
[4] Only applicable for subjects discontinuing trial product prematurely.
[5] Collection of sex and date of birth, race and ethnicity only if applicable by local law.

Trial Periods	**Screen**	**Rand**	**Treatment**																	**EoT**	**Follow-up**		**Pre-disc**[1]	
Trial site visit (V) **Phone contact (P)**[2]	**V1**	**V2**	**P3**	**V4**	**P5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11** **P12** **P13**	**V14**	**P15** **P16** **P17**	**V18**	**P19** **P20** **P21**	**V22**	**P23** **P24** **P25**	**V26**	**P27** **P28** **P29** **P30** **P31**	**V32**	**FU1** **V33**	**FU2** **P34**	**PX**	**V32A**
Timing of visit (weeks)	**≤ 2 weeks prior to V2**	**0**	**0.5**[3]	**1**	**1.5**[3]	**2**	**2.5**[3]	**3**	**3.5**[3]	**4**	**5** **6** **7**	**8**	**9** **10** **11**	**12**	**13** **14** **15**	**16**	**17** **18** **19**	**20**	**21 -25**	**26**	**7 days after last trial product**	**30 days after last trial product**	**Every 4 weeks**	**26**
Visit window (days)			**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**+3**	**±3**	**±3**
Diabetes treatment history	X																							
Family history of diabetes	X																							
Hypoglycaemia unawareness	X																							
Concomitant medication	X	X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X[6]	X[6]	X[6]	X[6]
Insulin dose																								X
Tobacco use	X																							
EFFICACY																								
Body measurements																								
Body weight[7]	X	X								X		X		X		X		X		X				X
BMI	X																			X				
Height	X																							
Waist circumference		X												X						X				
Glucose metabolism																								
HbA1c	X	X								X		X		X		X		X		X				X
Fasting plasma glucose[8]		X								X		X		X		X		X		X				
Lipids		X												X						X				
Self measured plasma glucose (SMPG)																								

[6] Only anti-diabetic medication will be collected.
[7] ~~If no insulin is taken by the subject, please enter "0" in the eCRF~~
[7] Body weight should be measured fasting except at V1, see section 8.1.1
[8] The subjects must attend visits fasting, see section 8.1.1

Trial Periods	**Screen**	**Rand**	**Treatment**																**EoT**	**Follow-up**		**Pre-disc**[1]	
Trial site visit (V) **Phone contact (P)**[2]	**V1**	**V2**	**P3**	**V4**	**P5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11** **P12** **P13**	**V14**	**P15** **P16** **P17**	**V18**	**P19** **P20** **P21**	**V22**	**P23** **P24** **P25**	**V26**	**P27** **P28** **P29** **P30** **P31**	**V32**	**FU1** **V33**	**FU2** **P34**	**PX**	**V32A**
Timing of visit (weeks)	**≤ 2 weeks prior to V2**	**0**	**0.5**[3]	**1**	**1.5**[3]	**2**	**2.5**[3]	**3**	**3.5**[3]	**4**	**5** **6** **7**	**8**	**9** **10** **11**	**12**	**13** **14** **15**	**16**	**17** **18** **19**	**20**	**21 -25**	**26**	**7 days after last trial product**	**30 days after last trial product**	**Every 4 weeks**	**26**
Visit window (days)			**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**+3**	**±3**	**±3**
Once daily[9]				X		X		X		X	X	X	X	X	X	X	X	X	X	X				
9-point profile[10]		X												X						X				
SAFETY																								
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[11]	X[11]
Hypoglycaemic episodes				X		X		X		X	X	X	X	X	X	X	X	X	X	X	X			
Technical complaints		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X				
ECG	X																			X[12]				
Eye examination	X[13]																			X[14]				
Physical examination	X																			X				
Vital signs	X	X												X						X				
Biochemistry	X	X								X				X		X				X				
Haematology	X	X												X						X				
Hormones (calcitonin)	X	X												X						X				
Urinalysis (albumin:creatinine ratio)	X													X						X				
Urine dipstick		X												X						X				

[9] Subjects should measure "self measured plasma glucose" prior to breakfast. Diabetes medication should be withheld until after the SMPG measurement.
[10] 9-point profile should be measured within one week prior to the site visit (on a day where unusual strenuous exercises is not anticipated).
[11] Only AE information for potential major adverse cardiovascular events (MACE) and SAE information will be collected.
[12] ECG obtained within 2 weeks prior to V32 is acceptable if results are available for evaluation at V32.
[13] Eye examination performed within 12 weeks prior to V2 as part of routine practice may replace the screening assessment if results are available for evaluation at V2.
[14] Eye examination performed within 2 weeks prior to V32 is acceptable if results are available for evaluation at V32.

Trial Periods	**Screen**	**Rand**	**Treatment**																	**EoT**	**Follow-up**		**Pre-disc**[1]	
Trial site visit (V) **Phone contact (P)**[2]	**V1**	**V2**	**P3**	**V4**	**P5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11** **P12** **P13**	**V14**	**P15** **P16** **P17**	**V18**	**P19** **P20** **P21**	**V22**	**P23** **P24** **P25**	**V26**	**P27** **P28** **P29** **P30** **P31**	**V32**	**FU1** **V33**	**FU2** **P34**	**PX**	**V32A**
Timing of visit (weeks)	**≤ 2 weeks prior to V2**	**0**	**0.5**[3]	**1**	**1.5**[3]	**2**	**2.5**[3]	**3**	**3.5**[3]	**4**	**5** **6** **7**	**8**	**9** **10** **11**	**12**	**13** **14** **15**	**16**	**17** **18** **19**	**20**	**21 -25**	**26**	**7 days after last trial product**	**30 days after last trial product**	**Every 4 weeks**	**26**
Visit window (days)			**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**+3**	**±3**	**±3**
Pregnancy test[15]	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X				
OTHER ASSESSMENTS																								
Barriers in Diabetes Treatment questionnaire		X																						
PRO questionnaires																								
TRIM-D		X										X								X				
SF-36v2		X										X								X				
TRIAL MATERIAL																								
Dispensing trial product		X						X		X		X		X		X		X						
IWRS call	X	X						X		X		X		X		X		X		X				
Dosing dates[16]				X																X				
Drug accountability		X						X		X		X		X		X		X		X				
REMINDERS																								
Hand-out ID card	X																							
Discontinue DPP4i		X																						
Training in trial product and pen handling.		X						X		X		X		X		X		X						
Dispense directions for		X						X		X		X		X		X		X						

[15] For women of childbearing potential a blood sample pregnancy test must be performed at V1 and V32. Additionally, a urine pregnancy test should be performed at site if pregnancy is suspected or if a menstrual period is missed. If the subject reports missing menstrual period at a phone contact, the subject will have to attend the site for an unscheduled visit as soon as possible to have an urine pregnancy test performed. If positive a confirmatory serum hCG test should be sent to the central laboratory. If required by local law, pregnancy test may be performed regularly.

[16] First and last dates and doses as recorded in patient diaries.

Trial Periods	**Screen**	**Rand**	**Treatment**																	**EoT**	**Follow-up**		**Pre-disc**[1]	
Trial site visit (V) **Phone contact (P)**[2]	**V1**	**V2**	**P3**	**V4**	**P5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11** **P12** **P13**	**V14**	**P15** **P16** **P17**	**V18**	**P19** **P20** **P21**	**V22**	**P23** **P24** **P25**	**V26**	**P27** **P28** **P29** **P30** **P31**	**V32**	**FU1** **V33**	**FU2** **P34**	**PX**	**V32A**
Timing of visit (weeks)	**≤ 2 weeks prior to V2**	**0**	**0.5**[3]	**1**	**1.5**[3]	**2**	**2.5**[3]	**3**	**3.5**[3]	**4**	**5** **6** **7**	**8**	**9** **10** **11**	**12**	**13** **14** **15**	**16**	**17** **18** **19**	**20**	**21 -25**	**26**	**7 days after last trial product**	**30 days after last trial product**	**Every 4 weeks**	**26**
Visit window (days)			**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**+3**	**±3**	**±3**
use																								
Hand-out and instruct in diary	X	X		X		X		X		X		X		X		X		X		X	X			
Collect and review diary		X		X		X		X		X		X		X		X		X		X	X			
Hand-out and instruct in BG meter	X																							
Attend visit fasting		X								X		X		X		X		X		X				*X*
Make appointment for eye examination																			X					
Sign off Casebook																						X[17]		X
End of trial (subject completion)																						X[17]		X

[17] Not applicable for subjects that have prematurely discontinued trial product.

2.4 Section 6.5 Rescue criteria

If the pre-breakfast SMPG values taken on three consecutive days or if any of the FPG samples analysed by the central laboratory exceeds the limit of:

- 15.0 mmol/L (270 mg/dL) ~~from~~ *after* baseline to week 6
- 13.3 mmol/L (240 mg/dL) from week 7 to week 12
- 11.1 mmol/L (200 mg/dL) from week 13 to week 26

and if no treatable intercurrent cause for the hyperglycaemia has been identified, the subject should be called for a confirmatory FPG measurement as soon as possible. The FPG sample should be analysed by the central laboratory and if it exceeds the limits described above, the subject must discontinue treatment with trial product.

2.5 Section 8.1.3 Screening failures

If a screened subject for any reason is not eligible *for the trial* ~~or are not randomised within 14 calendar days after the screening visit (V1)~~, the subject will be considered a screening failure. For screening failures the screening failure form in the eCRF must be completed with the reason for not continuing in the trial. Serious and non-serious AEs from screening failures must be transcribed by the investigator into the eCRF. Follow-up of SAEs must be carried out according to section 12.3. Screening failures experiencing an AE that would otherwise qualify for adjudication (see section 12.7) will not be adjudicated as no trial product has been administered.

2.6 Section 8.1.4 Randomisation (V2)

~~Randomisation must NOT take place more than 14 calendar days after V1 (screening).~~ All results from screening assessments, including laboratory results, ECG and eye examination must be available and reviewed by the investigator and the inclusion/exclusion criteria must be carefully reviewed to ensure the subject is eligible prior to the randomisation.

2.7 Section 8.1.7 Premature discontinuation of trial product

Once the two follow-up contacts after discontinuation of trial product are completed the subject should be contacted by phone every 4 weeks. Information on antidiabetic medication and information on potential major cardiovascular events (MACE) and any SAEs occurring since last contact must be collected and recorded in the eCRF. Phone contacts must be documented in the medical record and in the eCRF. The subject should finally come in for a V32A at week 26 to report MACE, SAEs, total daily insulin dose, use of other antidiabetic medication, and have *fasting* body weight measured and a blood sample taken to measure HbA_{1c}, see flow chart (section 2).

2.8 Section 8.2 Laboratory assessments

All samples will be destroyed on an ongoing basis after the analysis or at the latest at the completion of the clinical trial report (CTR). *However in case of abnormal haematology analysis test results, part of the sample may be kept for up to 2 years.*

2.9 Section 8.4.1 Body measurements

Height is measured without shoes in centimetres (cm) or inches. ~~and rounded to the nearest cm or inch.~~

2.10 Section 8.5.2 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

5th bullet:

- Date, time, and dose of last trial product (and other anti-diabetic treatment, *except between V32 and V33*) administration prior to the episode

2.11 Section 8.5.5 Electrocardiogram (ECG)

A 12-lead ECG must be performed. ~~by the investigator or delegated staff.~~ The ECG must be interpreted, signed and dated by the investigator to verify that the data has been reviewed *prior to determining the eligibility of the subject.* The ECG at screening ~~must be done at the latest at V2 and the results interpreted by the investigator prior to determine the eligibility of the subject.~~ *can be obtained at the latest at V2. The result of the ECG must be available to the investigator prior to randomisation. The ECG must not be obtained more than 2 weeks prior to V2; in that case a re-assessment is necessary.*

2.12 Section 8.6.1 Questionnaires

The investigator *or site staff* are only allowed to fill in the headings of the questionnaires.

The investigator *or site staff* should ~~check~~ *review the questionnaire* for empty fields *and potential adverse events* ~~in the questionnaires~~ when returned by the subject. Review of the questionnaires must be documented either on the documents and/or in the subject's medical record.

2.13 Section 9.1 Trial products

During the 26-weeks treatment period and the 4 weeks follow-up period; the patients de-facto cost (actual patient cost, not covered by the Health Authorities/any insurance) of SGLT2i and metformin (mono- or fixed dose combination products) *can* ~~will~~ be reimbursed in accordance with local legislation and Ethics Committee approval. Pioglitazone will not be reimbursed.

2.14 Section 9.4 Drug accountability and destruction

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

2.15 Section 12.1 Definitions

Serious adverse event

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

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

Major adverse cardiovascular event

~~A major adverse~~ *Any* cardiovascular ~~event (MACE) is any~~ AE ~~which can be~~ categorised into the following groups *will be evaluated as a potential Major Adverse Cardiovascular Event (MACE)*:

- Cardiovascular Death
- Myocardial Infarction
- Hospitalisation for Unstable Angina
- Transient Ischemic Attack and Stroke
- Heart Failure Event (requiring hospitalisation)
- Cardiac procedures
  - Interventional Cardiology
  - Peripheral Vascular Intervention
  - Stent Thrombosis

A MACE is defined as:

- *Cardiovascular Death*
- *Non-fatal Myocardial Infarction*
- *Non-fatal Stroke*

2.16 Section 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 two post-treatment follow-up periods. Please be aware that hypoglycaemic episodes should not be reported before any trial drug is given e.g. hypoglycaemic episodes should be reported from the randomisation visit (V2). Subjects discontinuing trial product prematurely (see section 6.4) will be contacted every 4th week and asked for information about antidiabetic medication, MACE and SAEs. These subjects should finally come in for a V32A at week 26, only to assess antidiabetic medication, MACE, SAEs, *fasting body weight* and a blood sample to measure HbA_{1c}.

2.17 Section 12.5.1 Pregnancies in female subjects

Forms and timelines for reporting AEs:

Non-serious AEs:

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

SAEs:

- ~~Paper~~ AE form* **within 24 hours** of the investigator's first knowledge of the SAE
- ~~Paper~~ SIF **within 5 calendar days** of the investigator's first knowledge of the SAE
- **SAE follow-up information** to the AE form and/or SIF **within 24 hours** of the investigator's first knowledge of the follow-up information

* It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or newborn infant. *If the AE occurred in the foetus or newborn infant, the AE can only be reported on paper AE and SIF*.

2.18 Section 13.2 Case report form flow

The SMPG measurements and corresponding trial drug doses for titration purpose *should* ~~must~~ be entered within **24 hours** after the site visit/phone contact throughout the trial.

2.19 Section 17.3.1 Primary statistical analysis primary estimand

Multiple imputation – *unconditional* ~~jump to reference~~ – retrieved data – NI penalty

The primary estimand will be estimated based on the FAS using all post baseline HbA_{1c} measurements obtained at planned visits up to and including week 26, and data retrieved at week 26 (V32A) from subjects prematurely discontinued from randomised treatment. To estimate this estimand for evaluation of non-inferiority of HbA_{1c}, a pattern mixture model approach[35] will be

adopted *based on sequential modelling using the conditional approach described generally in section 7.3.1 and the conditional approach specifically in section 7.4.2 in the book by O'Kelly and Ratitch[35]. A penalty in terms of the NI margin is added to withdrawn or prematurely discontinued subjects in the IDegLira arm.* It mimics an ITT scenario where withdrawn and prematurely discontinued subjects from the investigational treatment (IDegLira) arm not having a week 26 measurement are assumed to be switched to a treatment inferior to comparator (IGlar) or any other treatment received after premature treatment discontinuation. ~~This corresponds to a jump to reference (J2R) principle where a penalty in terms of the NI margin is added to withdrawn or prematurely discontinued subjects in the IDegLira arm.~~ Observe that the *imputation method* ~~J2R principle~~ and use of retrieved (V32A) data in analyses will equalise treatment effects and in turn assay sensitivity in the non-inferiority setting may be jeopardized. The penalty of the non-inferiority margin[36] is to remedy this. Multiple copies (1000 copies) of the full dataset will be generated by imputing missing values based on estimated parameters for a subgroup of subjects in the trial.

2.20 Section 17.3.2 Sensitivity analyses primary estimand

Multiple imputation – *conditional* ~~jump to reference~~ – retrieved data – NI penalty

The analysis is similar to the primary analysis except that observed values for prematurely discontinued IDegLira subjects are not set missing (step 1 is left out). Observe that for IDegLira now only missing data after premature discontinuation are imputed by the sequential ANOVAs (step 3 to 5) and this *corresponds to the conditional sequential modelling approach described in section 7.4.3 in the book by O'Kelly and Ratitch[35]* ~~principle is named copy reference (CR)~~; intermittent missing data are imputed by MCMC (step 2).

Multiple imputation – *unconditional* ~~jump to reference~~ – retrieved data – NI penalty – tipping point

Multiple imputation – *unconditional* ~~jump to reference~~ – retrieved data – NI penalty – CAS

Multiple imputation – *unconditional* ~~jump to reference~~ – retrieved data – NI penalty – PP

2.21 Section 17.4.1.1 Primary statistical analyses primary estimand

Body weight – *multiple imputation – unconditional – retrieved data*

The change from baseline in body weight after 26 weeks will be analysed with the *multiple imputation unconditional sequential* ~~J2R~~ pattern mixture model for HbA_{1c}, substituting body weight for HbA_{1c} and leaving out the non-inferiority penalty (step 6).

Treatment-emergent hypoglycaemic episodes – *multiple imputation – method 1*

The number of hypoglycaemic episodes will be analysed using a multiple imputation technique ~~for count data under the J2R principle~~ as follows.

Glycaemic control – *multiple imputation – unconditional – retrieved data*

The change from baseline in HbA_{1c} after 26 weeks will be analysed with the *multiple imputation unconditional sequential* ~~J2R~~ pattern mixture model for HbA_{1c} but leaving out the non-inferiority penalty (step 6).

Insulin dose – *multiple imputation – unconditional – retrieved data*

The insulin dose after 26 weeks will be analysed with the *multiple imputation unconditional sequential* ~~J2R~~ pattern mixture model for HbA_{1c}, substituting insulin dose for HbA_{1c}, leaving out the non-inferiority penalty (step 6) and using baseline HbA_{1c} as covariate as there is no baseline dose.

2.22 Section 17.4.1.2 Sensitivity analyses primary estimand

Continuous endpoints, body weight, HbA_{1c} and insulin dose – multiple imputation – *conditional* ~~copy reference~~ retrieved data

These analyses are repeats of the primary analyses using the *conditional approach* ~~CR principle~~ in place of the *unconditional approach* ~~J2R principle~~, just as for the *conditional* ~~CR~~ sensitivity analysis of the primary estimand of the primary objective.

Continuous endpoints body weight, HbA_{1c} and insulin dose – multiple imputation – *unconditional* ~~jump to reference~~ retrieved data – tipping point

Count endpoint hypoglycaemic episodes – multiple imputation – *method 2* ~~copy reference~~

~~This is a repeat of the primary analysis using the CR principle in place of the J2R principle. More specifically, in~~ *In* this analysis IDegLira subjects are assumed to have the event rate of the IDegLira arm prior to premature discontinuation and the event rate of IGlar after premature discontinuation. The method follows *method 1* ~~the multiple imputation J2R~~ for count data above, but in the second step pre discontinuation rates are the respective groups rates whilst post discontinuation rate is the rate of comparator (IGlar).

Count endpoint hypoglycaemic episodes – multiple imputation – *method 1* ~~jump to reference~~ tipping point

This is a repeat of *method 1*~~the multiple imputation J2R~~ above, now varying a penalty on the post discontinuation event rate until IDegLira is no longer superior to IGlar.

2.23 Section 17.4.1.4 Sensitivity analyses secondary estimand

Continuous endpoints body weight, HbA1c and insulin dose – multiple imputation – *unconditional* ~~jump to reference~~ retrieved data

2.24 Section 17.4.2.1 Efficacy endpoints

For each of the multiple copies (1000) of the full dataset of the primary analysis of the primary estimand (*unconditional* multiple imputation ~~J2R~~ with retrieved data, NI penalty section 2.19) the responder endpoints are derived without using the non-inferiority penalty (step 6) and analysed with the standard logistic regression model. Estimates are pooled using Rubin's rule[37].

Waist circumference change from baseline after 26 weeks

Change from baseline in waist circumference will be analysed by *unconditional* multiple imputation~~J2R~~.

Fasting plasma glucose change from baseline after 26 weeks

Change from baseline in FPG will be analysed by *unconditional* multiple imputation~~J2R~~.

Fasting lipid profile after 26 weeks

Cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, triglycerides and free fatty acids will be analysed separately by *unconditional* multiple imputation ~~J2R~~. In these statistical analyses, the endpoint will be log-transformed and so will the corresponding baseline covariate.

Self-measured plasma glucose (SMPG) 9-point profile change from baseline after 26 weeks

A linear mixed effect model will be fitted to the 9-point SMPG profile data. The model will include treatment, pre-trial OAD, time (within 9-point profile), the interaction between treatment and time, the interaction between pre-trial OAD and time as fixed factors, and subject as random effect*, where measurements within subjects will be assumed correlated as specified by a compound symmetric covariance matrix*. From the model mean profile by treatment and relevant treatment differences will be estimated and explored.

Change from baseline in mean of the 9-point profile and prandial increment endpoints will be analysed separately by *unconditional* multiple imputation ~~J2R~~.

Blood pressure (systolic and diastolic) change from baseline after 26 weeks

Change from baseline in systolic and diastolic blood pressure will be analysed separately by *unconditional* multiple imputation ~~J2R~~.

2.25 Section 17.4.2.2 Safety endpoints

Hypoglycaemic episodes during 26 weeks

Number of nocturnal treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks will be analysed using the same *(method 1)* ~~J2R~~ multiple imputation model as used for the treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes.

Pulse rate change from baseline after 26 weeks

Change from baseline in pulse rate will be analysed by *unconditional* multiple imputation ~~J2R~~.

2.26 Section 17.5 Health economics and/or patient reported outcomes

For each questionnaire, the summary scores will be summarised descriptively by visit and the change from baseline in score will be analysed separately by *unconditional* multiple imputation ~~J2R~~.

2.27 Section 18.1 Benefit-risk assessment of the trial

Inclusion and exclusion criteria have been defined in order to ensure that only subjects that are eligible for trial participation are enrolled in the trial. Furthermore, ~~withdrawal~~ *rescue* criteria are defined to ensure that subjects are considered for ~~withdrawal~~ *premature discontinuation of trial product*, if the level of glycaemic control exceeds acceptable limits during trial participation.

2.28 Section 18.1.1.1 Identified risks

Acute gallstone disease

Cases of gallstones (cholelithiasis) and inflammation of the gallbladder (cholecystitis) have been reported from clinical trials with IDegLira. Both cholelithiasis and cholecystitis have possible clinical implications for the patients as the events might lead to hospitalisation and cholecystectomy. If cholelithiasis is suspected, treatment should be discontinued and gallbladder examination and appropriate clinical follow-up should be initiated. If acute gallstone disease is confirmed, the trial product must be permanently discontinued.

2.29 Appendix A: Titration Guideline

Section 3.1 Initiation of IDegLira or IGlar

For subjects randomised to IDegLira ~~will~~ *the recommended* start *dose is* ~~on~~ 10 dose steps, consisting of 10U insulin degludec/0.36 mg liraglutide once daily.

For subjects randomised to IGlar *the recommended* ~~will~~ start *dose is* ~~on~~ 10U of insulin glargine once daily.

Section 3.2 Titration of IDegLira or IGlar

The doses of IDegLira or IGlar ~~should~~ *must* be adjusted twice weekly on fixed days (Mondays and Thursdays).