Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03922750
Sponsor trial ID:	NN1436-4466
Official title of study:	A trial comparing NNC0148-0287 C (insulin 287) versus insulin glargine U100, both in combination with metformin, with or without DPP4 inhibitors and with or without SGLT2 inhibitors, in basal insulin treated subjects with type 2 diabetes mellitus
Document date:	28 May 2020

16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

Protocol title: A trial comparing NNC0148-0287 C (insulin 287) versus insulin glargine U100, both in combination with metformin, with or without DPP4 inhibitors, in basal insulin treated subjects with type 2 diabetes mellitus

Substance: NNC0148-0287 C (insulin 287)

Universal Trial Number: U1111-1219-5541

EUdraCT Number: 2018-003407-18

Trial phase: 2a

In the following, Novo Nordisk A/S and its affiliates will be stated as "Novo Nordisk".

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1 Synopsis

Rationale:

NNC0148-0287 formulation C (referred to as insulin 287) is a novel long-acting insulin analogue designed for subcutaneous (s.c.) administration, with the aim to develop a once weekly injectable basal insulin treatment with the potential of becoming a more convenient choice, and to improve treatment adherence, and quality of life, for subjects with type 2 diabetes mellitus.

The present trial, seeks to investigate the optimal switch algorithm for insulin 287 by examining the effect on glycaemic control and safety parameters of insulin 287 once weekly using either the 'unit to unit switch' (e.g. 30 U of once daily insulin glargine U100 switch to 210 U of once weekly insulin 287), or the 'unit to unit switch with additional 100% loading dose' (e.g. switch from 30 U of once daily insulin glargine U100 to 210 U of once weekly insulin 287 and additional 210 U of once weekly insulin 287 as 100% loading dose) compared to insulin glargine U100 once daily. Subjects with type 2 diabetes mellitus (T2DM) on a basal insulin analogue will be investigated during 16 weeks of treatment. The trial results will be used as guidance for the selection of the optimal switch approach of insulin 287 in the phase 3 development programme of insulin 287.

Objectives and endpoints

Primary objective

To compare the effect on glycaemic control of treatment with once weekly insulin 287 using 2 different switch approaches versus once daily insulin glargine U100 both in combination with metformin ± DPP4 inhibitors (DPP4i) in basal insulin analogue treated T2DM subjects.

Secondary objective

To compare the safety and tolerability of once weekly insulin 287 using 2 different switch approaches versus once daily insulin glargine U100 both in combination with metformin ± DPP4i in basal insulin analogue treated T2DM subjects

Overall design:

- This is a 16 weeks exploratory, multicentre, randomised, open label, active-controlled, parallel-group trial with 3 arms investigating the effect on glycaemic control and safety of treatment with once weekly insulin 287 using 2 different switch approaches (either 'unit to unit switch' approach, or 'unit to unit switch with an additional 100% loading dose' approach, versus once daily insulin glargine U100 in basal insulin analogue treated subjects with T2DM inadequately controlled on basal insulin analogue with metformin, with or without DPP4i.
- Subjects will be randomized at V2 and stratified to one of the three treatment arms (1:1:1).
- The trial will recruit subjects who are currently prescribed basal insulin along with metformin ±DDP4i for the treatment for type 2 diabetes mellitus.

The main inclusion criterions are:

1. Male or female, aged 18-75 years (both inclusive) at the time of signing informed consent.
2. Diagnosed with type 2 diabetes mellitus ≥ 180 days prior to the day of screening.
3. HbA_{1c} of 7.0-10.0% (53.0-85.8 mmol/mol) (both inclusive) as assessed by central laboratory.
4. Treated with once daily or twice daily basal insulin analogue (insulin degludec, insulin detemir, insulin glargine U100 or U300, total daily dose of 10-50 U, both inclusive) ≥ 90 days prior to the day of screening.
5. Stable daily dose(s) for 90 days prior to the day of screening of any of the following anti-diabetic drug(s) or combination regime(s):
   - Any metformin formulations ≥ 1500 mg or maximum tolerated or effective dose (as documented in subjects medical records)
   - Any metformin formulations ≥ 1500 mg or maximum tolerated or effective dose with DPP4i ≥ half of the maximum approved dose according to local label or maximum tolerated or effective dose (as documented in subjects medical records)
6. Body mass index (BMI) ≤ 40.0 kg/m^2

The main exclusion criterions for this trial are:

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method.
3. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.
4. Any disorder, except for conditions associated with type 2 diabetes mellitus, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
5. Any episodes of diabetic ketoacidosis within the past 90 days prior to the day of screening and between screening and randomisation.
6. Known hypoglycaemic unawareness as indicated by the Investigator according to Clarke's questionnaire question 8.

7. Recurrent severe hypoglycaemic episodes within the last year as judged by the Investigator.
8. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening and between screening and randomisation.

- There will be three treatment arms in this trial. Two of the arms will be insulin 287 arms and a third arm which will be for subjects on insulin glargine U100.

Number of subjects:

200 subjects will be screened for this trial. 150 subjects will be randomized and put on trial product for the duration of the trial.

Treatment groups and duration:

All subjects will be centrally randomised in a 1:1:1 manner, and assigned to receive either insulin 287, 700 U/mL or insulin glargine 100 U/mL throughout the 16-week treatment period. The trial products will be provided as prefilled pens containing 3 mL solution for s.c. injection once weekly (insulin 287) and once daily (insulin glargine U100) respectively.

The dose and dosing frequency of metformin ± DPP4i should not be changed at any time during the trial, unless due to safety concerns.

At the screening visit, Novo Nordisk will provide all subjects with a CGM device for continuous glucose monitoring and a BG meter for self-measuring of plasma glucose, during the first 18 weeks in the trial. Subjects will be carefully trained in handling of the trial product and devices, and will be closely monitored and retrained during the trial.

When discontinuing trial products, either at the scheduled end of treatment visit (V18) or if trial product is discontinued prematurely, the subject should be transferred to a suitable marketed product at the discretion of the investigator.

2 Flowchart

Trial Periods	Screening	Randomisation	Treatment															End of treatment	Follow up		Discontinuation Follow up visit[1]
Visit (V) **Phone contact (P)**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11**	**V12**	**P13**	**V14**	**P15**	**V16**	**P17**	**V18**	**V19 FU1**	**V20 FU2**	**V18A**
Time of visit (weeks)[2]	≤ -2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18	21	16
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	+3	+3	±3
SUBJECT RELATED INFORMATION AND ASSESSMENTS																					
Informed consent	X																				
In/exclusion criteria	X	X																			
Randomisation criteria		X																			
Concomitant illness/medical history[3]	X																				
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[4]	X[4]	X[4]
Demography[5]	X																				
Diabetes history	X																				
Hypoglycaemia unawareness	X[6]																				
Date of Diagnosis of Diabetes	X																				

[1] If subjects discontinue trial product prematurely they will be asked to attend the end of treatment visit (V18) as soon as possible and have the follow up visits scheduled 3 weeks (V19) and 6 weeks (V20) after the last day of dosing for insulin 287 and 2 weeks (V19) and 5 weeks (V20) after the last day of dosing for insulin glargine. Subjects will be asked to stay in site contact and continue wearing CGM (changed weekly) throughout the remaining weeks, finalised by a last visit (V18A) 16 weeks after randomisation.
[2] Time of visit is relative to randomisation (V2).
[3] Diabetes complications should be reported under medical history case report form (CRF) form.
[4] Only antidiabetic medication to be collected
[5] Demography consists of date of birth or year of birth and/or age, sex, ethnicity and race (according to local regulation).
[6] Information on hypoglycaemia unawareness will be recorded according to Clarke's questionnaire, question 8.[1] 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?" Subjects answering 'never, rarely or sometimes' are considered to have impaired awareness of hypoglycaemia

Trial Periods	Screening	Randomisation	Treatment															End of treatment	Follow up		Discontinuation Follow up visit[1]
Visit (V) **Phone contact (P)**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11**	**V12**	**P13**	**V14**	**P15**	**V16**	**P17**	**V18**	**V19 FU1**	**V20 FU2**	**V18A**
Time of visit (weeks)[2]	≤ -2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18	21	16
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	+3	+3	±3
Childbearing potential	X																				
Tobacco use[7]	X																				
Body measurements																					
Height	X																				
Body weight	X	X								X								X			
	EFFICACY																				
Glucose metabolism																					
HbA_{1c}	X	X				X				X				X				X			X
Fasting plasma glucose		X								X								X			
Self-measured plasma glucose (SMPG)[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
	OTHER ASSESSMENTS																				
Continuous glucose monitoring, fitting and training[9]	X	X	X	X	X	X															
Continuous glucose monitoring, sensor check[10]							X	X	X	X	X	X	X	X	X	X	X	X			
Continuous glucose monitoring, upload		X	X	X	X	X		X		X		X		X		X		X			X
Diabetes Treatment Satisfaction Questionnaire		X																X			
Insulin Preference Questionnaire[11]																		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
Hypoglycaemic episodes		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Technical complaints		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ECG[12]	X																	X			

[7] Smoking is defined as smoking at least one cigarette or equivalent daily.
[8] Subjects will measure once daily pre-breakfast SMPG.
[9] Subjects will be instructed by investigator to fit the CGM sensor on site at V1-V6. After V6, sensor should be changed by subjects.
[10] At each phone contact or site visit, investigator should check if subject have correctly fitted sensor, and last sensor was only used for 7 days.
[11] Only applicable for subjects randomised to insulin 287 arms.

Trial Periods	Screening	Randomisation	Treatment															End of treatment	Follow up		Discontinuation Follow up visit[1]
Visit (V) **Phone contact (P)**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11**	**V12**	**P13**	**V14**	**P15**	**V16**	**P17**	**V18**	**V19 FU1**	**V20 FU2**	**V18A**
Time of visit (weeks)[2]	≤ -2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18	21	16
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	+3	+3	±3
Eye Examination	X[13]																	X[14]			
Physical Examination	X																	X			
Vital signs	X	X								X								X			
Biochemistry	X	X				X				X				X				X			
Lipids		X								X								X			
Haematology	X	X								X								X			
Pregnancy test[15]	X	X																		X	
	TRIAL MATERIAL																				
Drug accountability		X				X				X				X				X			
Dispensing visit		X				X				X				X							
Dose of trial insulin[16]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[17]	X			
	REMINDERS																				
Handout ID card	X																				
Attend visit fasting		X								X								X			
Hand out direction for use[18]		X																			
Training in trial product, pen handling		X	X	X	X	X		X		X		X		X		X					
Hand out and instruct in BG meter	X																				

[12] Electrocardiogram (ECG) obtained within 2 weeks prior to V2 and V18 are acceptable if results are available for evaluation at the visits.
[13] Eye examination obtained within 90 days prior to V2 as part of routine practise may replace the screening assessment if results are available for evaluation at V2.
[14] Eye examinations performed within 2 weeks prior to V18 are acceptable if results are available for evaluation at the visit.
[15] For females of childbearing potential a serum pregnancy test must be performed at V1 and V20. At V2 and if a menstrual period is missed anytime during the trial, a urine pregnancy test will be taken. If a urine pregnancy test is positive, a serum sample should be taken and sent to the central laboratory for analysis.
[16] The first 5 doses of once weekly insulin 287 will be taken at the site (V2 to V6).
[17] The last dose of once weekly insulin 287 must be taken 15 weeks after randomisation, whereas the last dose of the once daily insulin glargine U100 must be taken 16 weeks after randomisation where the subjects come in for the end of treatment visit (V18). This is due to the longer half life of insulin 287.
[18] Directions for use can be handed out as needed at subsequent visits.

Trial Periods	Screening	Randomisation	Treatment															End of treatment	Follow up		Discontinuation Follow up visit[1]
Visit (V) **Phone contact (P)**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11**	**V12**	**P13**	**V14**	**P15**	**V16**	**P17**	**V18**	**V19 FU1**	**V20 FU2**	**V18A**
Time of visit (weeks)[2]	≤ -2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18	21	16
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	+3	+3	±3
IWRS session	X	X				X				X				X				X			
Hand out and instruct in diary	X	X	X	X	X	X		X		X		X		X		X		X	X		
Collect, review and transcribe diaries		X	X	X	X	X		X		X		X		X		X		X	X	X	
End treatment																		X			
End of trial																				X	X

3 Introduction

3.1 Trial rationale

NNC0148-0287 formulation C (referred to as insulin 287) is a novel long-acting insulin analogue designed for subcutaneous (s.c.) administration, with the aim to develop a once weekly injectable basal insulin treatment with the potential of becoming a more convenient choice, and to improve treatment adherence, and quality of life, for subjects with type 2 diabetes mellitus.

The present trial, seeks to investigate the optimal switch algorithm for insulin 287 by examining the effect on glycaemic control and safety parameters of insulin 287 once weekly using either the 'unit to unit switch' (e.g. 30 U of once daily insulin glargine U100 switch to 210 U of once weekly insulin 287), or the 'unit to unit switch with additional 100% loading dose' (e.g. switch from 30 U of once daily insulin glargine U100 to 210 U of once weekly insulin 287 and additional 210 U of once weekly insulin 287 as 100% loading dose) compared to insulin glargine U100 once daily. Subjects with type 2 diabetes mellitus (T2DM) on a basal insulin analogue will be investigated during 16 weeks of treatment. The trial results will be used as guidance for the selection of the optimal switch approach of insulin 287 in the phase 3 development programme of insulin 287.

3.2 Background

Diabetes mellitus

Diabetes mellitus is a metabolic disorder characterised by the presence of hyperglycaemia due to defective insulin secretion, insulin action or both. The chronic hyperglycaemia of diabetes mellitus is associated with significant long term sequelae, particularly damage, dysfunction and failure of various organs, especially the kidney, eye, nerves, heart and blood vessels.

Type 2 diabetes is a complex disorder which involves various degrees of decreased beta-cell function, peripheral insulin resistance and abnormal hepatic glucose metabolism. Glucose control in type 2 diabetes may deteriorate progressively over time. The American Diabetes Association (ADA) recommend a pre-meal glucose target of 80–130 mg/dL (4.4–7.2 mmol/L) to achieve glycaemic control.[2] On average, after failure of diet and exercise alone, subjects require a new intervention with glucose-lowering agents every 3-4 years in order to obtain/retain good glycaemic control.[3] Despite combination therapy and/or insulin treatment, a sizeable proportion of subjects remain poorly controlled.[3]

Improvement in long-term glucose control, as obtained with intensified insulin therapy, was shown in the UK Prospective Diabetes Study[4] to reduce the incidence of microvascular complications and delay the progression of existing complications in people with T2DM. For subjects with T2DM who are not achieving glycaemic goals with oral antidiabetic drugs, drug intensification, including insulin therapy, should not be delayed.[5]

Insulin 287

Insulin 287 is a novel long-acting basal insulin analogue with a terminal elimination half-life of approximately 196 hours (trial NN1436-4314). The molecule consists of a peptide backbone and a side-chain (coupled by acylation). The peptide backbone is more resistant towards proteolytical degradation compared to human insulin and the side chain gives a strong binding to albumin. Insulin 287 has been formulated as a 4200 nmol/mL solution, equivalent to 700 units/mL, anticipating that the insulin 287 molecule is equipotent to once-daily basal insulins. A first human dose trial with single doses in healthy subjects and in subjects with type 1 diabetes mellitus (T1DM) and two multiple-dose trials in subjects with T2DM have been completed. The PK properties of subcutaneous insulin 287 following 5 weeks of once weekly dosing in subjects with type 2 diabetes were investigated in trial NN1436-4314. This trial showed that insulin 287 exposure was well distributed across the dosing interval, with a PK profile suitable for once weekly dosing (the geometric mean terminal t½ of insulin 287 was approximately 196 hours), and a peak around 16 hours followed by a slow decline.

For the pharmacodynamic (PD) properties of s.c. insulin 287, evaluated by glucose clamp, the glucose infusion rate response was evenly distributed across the dosing interval. In addition, insulin 287 was well tolerated in subjects with T2DM. No safety concerns were identified after multiple once-weekly dosing in the dose range of 12−24 nmol/kg (2-4 U/kg). No serious or severe adverse events (AEs) were reported. No hypersensitivity reactions were reported.

For further information on previous trials, please refer to the Investigators Brochure (IB).

Insulin glargine U100

Insulin glargine U100 is a once daily long-acting insulin analogue, indicated for treatment of diabetes mellitus in combination with oral antidiabetic agents and as part of a basal-bolus insulin regimen. Insulin glargine U100 is widely used basal insulin world-wide and has therefore been selected as comparator in the current trial. For further details, please refer to the European Medicines Agency (EMA) Summary of Product Characteristics for insulin glargine (Lantus®)[6], U.S. Label Information[7] and manufactures label.

Metformin

Together with life style interventions metformin is considered a first-line antidiabetic therapy in subjects with T2DM.[5] Metformin is a product from the biguanide compound group. Metformin lowers plasma glucose levels without increasing the circulating insulin concentrations through lowering of the hepatic glucose output and increased insulin sensitivity. For further details, please refer to the EMA Summary of Products Characteristics for Metformin[8] or locally approved Product Information.

Dipeptidyl peptidase 4 inhibitors

Dipeptidyl peptidase 4 inhibitors (DPP4i) can be used as second line oral anti-diabetic drugs in combination with Metformin.[9] DPP4i prevent the hydrolysis of incretin hormones, thereby increasing plasma concentrations of the active forms of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. Incretin hormones are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. By enhancing active incretin levels, DPP4i increase insulin release and decrease glucagon levels in a glucose-dependent manner. For further details, please refer to the EMA Summary of Products Characteristics for the relevant DPP4i or locally approved Product Information.

3.3 Benefit-risk assessment

3.3.1 Benefits

Insulin 287 is currently in development for treatment of diabetes mellitus. Insulin 287 has in first human dose and multiple dose trials been shown to have a long and stable PK and PD profile supporting a once-weekly treatment. Currently available long-acting basal insulin products need to be administered once daily to provide 24-hour coverage. Research has shown that people with T2DM put value in reducing the number of insulin injections.[10] Therefore, the compliance and quality of life are expected to increase by introducing a once-weekly basal insulin treatment.

The trial population will consist of subjects with type 2 diabetes insufficiently controlled on basal insulin and, metformin ±DPP4i. For all subjects participating in this 16 week trial, the anticipated benefits include improved glycaemic control. Titration algorithms, specifying recommended adjustments of basal insulin dose at different plasma glucose levels, are used in order to ensure that subjects receive an optimal treatment. Subjects will receive intense medical care by means of close contact to the clinical sites with weekly contacts.

3.3.2 Risks

Identified risks for insulin 287 describe undesirable clinical outcomes for which there is sufficient evidence that they are caused by insulin 287. Potential risks in this section describe undesirable clinical outcomes for which there is scientific evidence to suspect the possibility of a causal relationship with insulin 287, but where there is currently insufficient evidence to conclude that this association is causal.[11]

Identified risks

- Hypoglycaemia

Hypoglycaemia is a common undesirable effect related to the pharmacological mechanism of insulin. To mitigate the risk of hypoglycaemia in this trial, blood glucose (BG) measurements will be made throughout the drug exposure period, and will prevent worsening of hypoglycaemia by early detection and administration of carbohydrates and medical treatment, if necessary.

Potential risks

- Injection site reactions

Injection site reactions may occur with all injectable drugs. No injection site reactions were reported in trial NN1436-4314 with insulin 287. However, in this trial investigators and subjects will be asked to pay careful attention to injection site reactions at the place of injection; investigators should ensure careful monitoring and medical evaluation in case of injection site reaction occurrence. For further information on injection site reactions, please refer to Section 9.4.5.

- Hypersensitivity reactions

Severe systemic hypersensitivity reactions may potentially occur following injection of therapeutic proteins. No hypersensitivity reactions were reported in trial NN1436-4314 with insulin 287. During the treatment period in this trial, subjects will have weekly contacts with the site either at visits to the site or with phone contacts. Subjects and investigators will be instructed for signs and symptoms of allergic reactions and be instructed to contact the site immediately in case of signs of hypersensitivity. For further information on hypersensitivity reactions, please refer to Section 9.4.5.

- Antibody formation leading to change in clinical effect

An increase in anti-insulin 287 specific antibodies and anti-human insulin antibodies were observed for some subjects in trial NN1436-4314 trial with insulin 287. No hypersensitivity reactions were observed in this trial. Moreover, in trial NN1436-4314 higher antibody levels seemed to be associated with a longer terminal half-life and reduced clearance for insulin 287. In case of a systemic hypersensitivity reaction, blood sampling for assessment of antibodies against insulin 287 will be conducted. For more information, please refer to Section 9.4.5.

- Increase in hepatic enzymes

Transient increases in hepatic enzymes upon initiation of s.c. insulin are considered as potential risks due to the pharmacological mechanism of insulin. An increase in hepatic enzyme was observed in nonclinical studies in rats and dogs. No clinically significant changes in hepatic biomarkers have been observed in humans following the administration of insulin 287. In this trial, measurements of hepatic biomarkers will be performed at frequent intervals.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of insulin 287 may be found in the investigator's brochure and any updates hereof.

3.3.3 Conclusion on the benefit risk profile

Based on the non-clinical and clinical development programme, it has been concluded that insulin 287 is similar to human insulin with respect to pharmacological action and non-clinical safety. Insulin 287 was generally well tolerated within the evaluated dose ranges in the first-in-human, single dose escalation trial conducted in healthy subjects, in subjects with T1DM and in the multiple dose trial in subjects with T2DM. No safety concerns have been observed with insulin 287; neither elevation in hepatic enzymes nor clinical consequences following antibody formation have been reported. With insulin 287, no hypersensitivity reactions and injection site reactions were observed. To mitigate the risk of hypoglycaemia in this trial, frequent blood glucose measurements will be made throughout drug exposure. Therefore, it can be concluded that the risk to the subjects in this trial is considered low. The risk is acceptable in view of the benefits a basal insulin with a longer action profile than currently available would provide to subjects with diabetes. The overall benefit-risk profile of insulin 287 is anticipated to be favourable.

4 Objectives and endpoints

4.1 Primary, secondary and exploratory objectives

4.1.1 Primary objective

To compare the effect on glycaemic control of treatment with once weekly insulin 287 using two different switch approaches versus once daily insulin glargine U100 both in combination with metformin ± DPP4i in basal insulin analogue treated T2DM subjects

4.1.2 Secondary objective

To compare the safety and tolerability of once weekly insulin 287 using 2 different switch approaches versus once daily insulin glargine U100 both in combination with metformin ± DPP4i in basal insulin analogue treated T2DM subjects

Primary estimand

The primary estimand is defined as the mean difference in 'time in target range 3.9-10.0 mmol/L (70–180 mg/dL)' during the last 2 weeks of treatment (week 15 and 16) between each of the 2 different switch approaches of once weekly insulin 287 and once daily insulin glargine U100 for all randomised subjects, if all subjects had adhered to the randomised insulin treatment and had 70% of the planned continuous glucose monitoring (CGM) measurements recorded.

The following intercurrent events for the primary estimand will be handled by the hypothetical strategy: initiation of insulin treatment other than the randomised treatment, discontinuation of randomised insulin treatment, withdrawal from the trial, and recording of less than 70% of planned CGM measurements in the last two weeks of treatment. Other intercurrent events will be handled by the treatment policy strategy. This estimand aims to reflect the estimated treatment effect for subjects that had adhered to the planned insulin treatment during the planned treatment period.

4.2 Primary, secondary and exploratory endpoints

4.2.1 Primary endpoint

Endpoint title*	Time frame	Unit
Time in target range 3.9–10.0 mmol/L (70-180 mg/dL) measured using CGM	During the last 2 weeks of treatment (week 15 and 16)	Percent

*The primary endpoint is based on data recorded by continuous glucose monitoring (CGM) system, Dexcom G6 ®.

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

Not applicable in this trial.

4.2.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline week 0 (V2) to week 16 (V18)	%-point
Change in fasting plasma glucose (FPG)	From baseline week 0 (V2) to week 16 (V18)	mmol/l
Change in body weight	From baseline week 0 (V2) to week 16 (V18)	Kg
Weekly insulin dose**	During the last 2 weeks of treatment (week 15 and 16)	U

**Investigators will record administered insulin dose for both insulin glargine U100 and insulin 287 subjects. For insulin glargine U100, investigators will enter the daily administered doses in the CRF and for those on the insulin 287 treatment, enter the weekly administered doses.

Supportive secondary safety endpoints

Endpoint title	**Time frame**	**Unit**
Number of treatment emergent adverse events (TEAEs)	From baseline week 0 (V2) to week 21 (V20)	Count of events
Number of severe hypoglycaemic episodes (**level 3**)	From baseline week 0 (V2) to week 16 (V18)	Count of events
Number of clinically significant hypoglycaemic episodes (**level 2**) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (**level 3**)	From baseline week 0 (V2) to week 16 (V18)	Count of events
Number of hypoglycaemic alert episodes (**level 1**) (≥3.0 and <3.9 mmol/L (≥54 and <70 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 16 (V18)	Count of events

5 Trial design

5.1 Overall design

This is a 16 weeks exploratory, multicentre, randomised, open label, active-controlled, parallel-group trial with 3 arms investigating the effect on glycaemic control and safety of treatment with once weekly insulin 287 using 2 different switch approaches (either 'unit to unit switch with an additional 100% loading dose' approach, referred in the trial design as arm A or 'unit to unit switch' approach, referred in the trial design as arm B) versus once daily insulin glargine U100 (arm C) in basal insulin analogue treated subjects with T2DM inadequately controlled on basal insulin analogue with metformin, with or without DPP4i. The overall trial design and visit schedule are outlined in Figure 5-1 and trial flowchart (see Section 2) respectively.

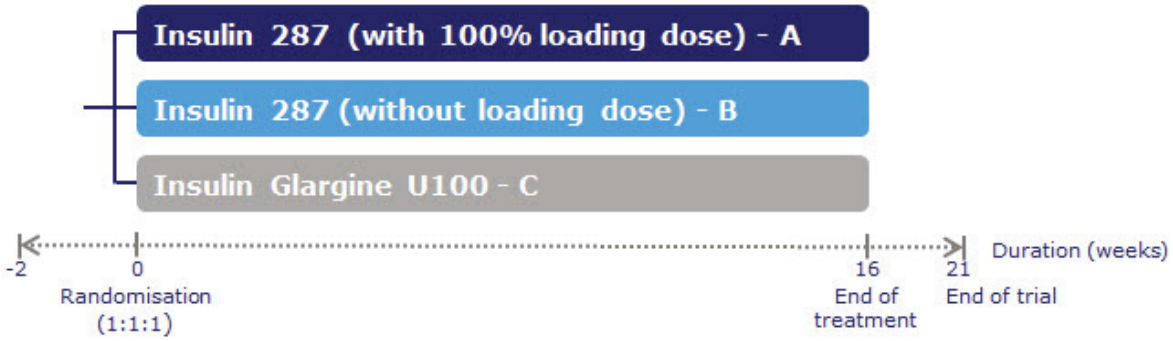


Figure 5-1 Trial design

Subjects will be randomly allocated to receive once weekly insulin 287 using one of the 2 switch approaches (arm A and B) or once daily insulin glargine U100 (arm C). The randomisation will be stratified based on prior basal insulin analogue twice daily treatment or insulin glargine U300 treatment. The trial duration is approximately 23 weeks and consists 2 weeks of screening period, 16 weeks of randomised treatment period, and 5 weeks follow-up period. The trial includes a screening visit (Visit 1) to assess subject's eligibility. From screening visit (after signed informed consent) until randomisation, all subjects will be required to measure daily pre-breakfast self-measured plasma glucose (SMPG) and have 10 days baseline continuous glucose monitoring (CGM) profile collected. After screening, all eligible subjects will be randomised (1:1:1) at Visit 2. During the 16 weeks treatment period, subjects will have weekly contact with the site either at site visits (9 visits) or by phone (6 phone contacts). To evaluate the effect on glycaemic control, subjects will have CGM profiles collected during the 16 weeks treatment period. The CGM will be blinded for both subjects and investigator.

After 16 weeks of treatment subjects will come in for their end of treatment visit (V18). The end of treatment visit will be one week after the last dose of insulin 287 and on the day of or the day after the last dose of insulin glargine U100. This will be followed by 2 follow up visits (V19 and V20). The last follow up visit (V20) is scheduled to take place 6 weeks after the last dose of once weekly insulin 287 and 5 weeks after the last dose of once daily insulin glargine U100. This will allow for appropriate wash-out of trial drug, following at least 5 half-lives of insulin 287.

The dose and dosing frequency of metformin ± DPP4i should not be changed at any time during the trial, unless due to safety concerns. This will be done at the discretion of the investigator.

Event adjudication will be performed for major adverse cardiovascular events (MACE), death, and hypersensitivity reactions (see Section 9.2.1.1 and Appendix 4).

The follow-up period is 5 weeks.

5.2 Subject and trial completion

Approximately 200 subjects will be screened to achieve 150 subjects randomly assigned to trial product. The estimated number of subjects to complete the trial (on trial product) is 143.

Trial period completion for a subject:

Trial period completion is defined as when the randomised subject has completed the final scheduled visit V18 ('end of trial' according to the flowchart).

'Date of trial completion' is the date the subject completed the final scheduled visit (V20).

Treatment period completion for a subject:

Treatment period completion is defined as when the randomised subject has received the 16 weeks required treatment, and attended the 'end of treatment' visit (V18) according to the flowchart.

Treatment emergent period for a subject:

The treatment emergent period represents the period where subjects are considered exposed to trial product. It starts at the first date of exposure to the randomised treatment and ends at the last follow-up visit (V20), thus includes a time period after last dose of randomised treatment corresponding to approximately 5 half-lives of insulin 287 once weekly dose.

For subjects who discontinues treatment, but do not attend the last follow up visit (V20): Last dosing day of randomised treatment + 5 weeks for insulin glargine U100 once daily, and last dosing day of randomised treatment + 6 weeks for insulin 287 once weekly.

5.3 End of trial definition

The end of the trial is defined as the date of the last visit of the last subject in the trial.

5.4 Scientific rationale for trial design

The trial is designed to investigate the effect on glycaemic control and safety of once-weekly insulin 287 using two different switch algorithms with either a 'unit to unit switch', or a 'unit to unit switch with an additional 100% loading dose' versus once-daily insulin glargine U100 during 16 weeks of treatment.

Currently, basal insulins with the longest duration are dosed once daily. In order to compare to well-established and widely used basal insulin with once daily dosing, insulin glargine U100 has been chosen as comparator. The treatment arms will be open label as it was not considered feasible to blind the two insulin 287 arms and the insulin glargine U100 arm due to the high number of injections required to make a double-blind, double dummy trial resulting in an increased burden on the subjects.

The treatment duration of 16 weeks has been chosen as an adequate time to assess effect on glycaemic control as well as safety and tolerability. This duration will also allow for up-titrating the basal insulin. The treat-to-target approach has been chosen in order to ensure optimal titration of insulin based on self-measured plasma glucose (SMPG) values with the aim of improving HbA_{1c} in the period.

Subjects included in the trial will already be on basal insulin treatment, ensuring trial population representative for the relevant patient group (see Section 6 regarding the subject population). All will use first line treatment metformin. Use of DPP4i in addition to metformin is allowed but not a requirement. To include a more homogenous study population, other oral antidiabetic drugs are not allowed.

Titration of insulin 287 and insulin glargine are based on three pre-breakfast SMPG values measured on two days prior to titration and on the day of the contact. CGM values will be used to generate profiles for evaluating the effect on glycaemic control.

To safeguard subjects, the inclusion and exclusion criteria defined in this trial will limit the trial population to subjects not suffering from underlying diseases other than T2DM and related diseases, such as hypertension or dyslipidaemia. This is to avoid compromising the safety of the subjects participating in the trial and to strengthen conclusions regarding the efficacy and, safety of once-weekly insulin 287.

During the treatment period, the subjects will have weekly contacts with the site either at site visits or phone contacts and the first 5 administrations of once-weekly insulin 287 will be done at the site. After the injections at the site, the subjects should stay at least one hour for observation. This applies only for those treated on the insulin 287 arms. The last follow-up visit is planned to be 6 weeks after last dose of insulin 287, allowing appropriate time for wash-out of trial drug, following at least 5 half-lives of insulin 287.

Ethical considerations

All subjects must only be included after a thorough evaluation with regards to defined in- and exclusion criteria in order to ensure that subjects are eligible for trial treatment. Subjects will be treated with a treat-to-target insulin regimen anticipated to improve glycaemic control compared to their pre-trial treatment. To participate in the trial subjects will have to spend some extra time, as additional assessments and visits to the clinic are required. Three of the visits will also require that the subject is fasting for blood sampling. In case of lack of efficacy of trial product, the subject will be prematurely discontinued, see Section 8.1 regarding discontinuation of trial treatment.

The trial products may be associated with adverse reactions, of which hypoglycaemia is the most common. For further information, please refer to the Investigator's Brochure for insulin 287[12] and local label for insulin glargine U100. Relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation. These precautions include thorough information regarding the correct administration of the trial products and handling of the CGM device. The first 5 doses (V2-V6), along with handling and fitting of the CGM will be administered at the site by the site personnel. The insulin dose will be adjusted gradually and closely supervised. Furthermore, subjects will be informed about possible adverse reactions and inconveniences and will be instructed to contact the investigator in case of any concerns regarding the trial participation.

5.5 Justification for dose

Insulin glargine U100 will be initiated at the same dose as the pre-trial basal insulin and insulin 287 will be initiated at 7 times the pre-trial basal insulin dose.

One unit (U) of Insulin 287 has similar glucose lowering effect as one U of insulin glargine U100, and therefore once-weekly dosing corresponds to 7 times the daily dose of the once daily comparator.

The PK/PD properties of Insulin 287 following 5 weeks of once weekly dosing in subjects with T2DM (trial NN1436-4314) showed that insulin 287 exposure was well distributed across the dosing interval, with a PK profile suitable for once weekly dosing. Insulin 287 was well tolerated in subjects with T2DM and no safety concerns were identified after multiple once-weekly dosing in the dose range of 12−24 nmol/kg (2-4 U/Kg).

For subjects randomised to insulin 287 100% loading dose arm: It takes 3-5 doses before reaching the full effect of insulin 287. Theoretically subjects may therefore need additional insulin to maintain glycaemic control the first weeks after initiation. Modelling data suggest that adding a 100% loading dose may prevent deterioration of the glycaemic control during the first weeks of treatment without jeopardising safety. Therefore the approach of 100% loading dose has been chosen; hence no additional insulin is permitted after V2.

To reduce the risk of subjects experiencing hypoglycaemia in the initial treatment phase subjects switching from a twice daily basal insulin regiment and a once daily regimen with insulin glargine U300 will have their dose reduced by 20%. This is applicable for all treatment arms.

After randomisation at V2, subjects will start once daily and once-weekly injections on the same day. This treatment will continue until 15 weeks after randomisation. At this time point the last once weekly injection must be taken while the once daily injections are taken until 16 weeks after randomisation where the subjects come in for the end of treatment visit (V18). This is due to the longer half-life of insulin 287.

Further details on dose adjustment can be found in Appendix 9, titration guideline

6 Trial population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 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, aged 18-75 years (both inclusive) at the time of signing informed consent.
3. Diagnosed with type 2 diabetes mellitus ≥ 180 days prior to the day of screening.
4. HbA_{1c} of 7.0-10.0% (53.0-85.8 mmol/mol) (both inclusive) as assessed by central laboratory.
5. Treated with once daily or twice daily basal insulin analogue (insulin degludec, insulin detemir, insulin glargine U100 or U300, total daily dose of 10-50 U, both inclusive) ≥ 90 days prior to the day of screening.
6. Stable daily dose(s) for 90 days prior to the day of screening of any of the following anti-diabetic drug(s) or combination regime(s):
   - Any metformin formulations ≥ 1500 mg or maximum tolerated or effective dose (as documented in subjects medical records)
   - Any metformin formulations ≥ 1500 mg or maximum tolerated or effective dose with DPP4i ≥ half of the maximum approved dose according to local label or maximum tolerated or effective dose (as documented in subjects medical records)
7. Body mass index (BMI) ≤ 40.0 kg/m^2

6.2 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. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method.
   For Czech Republic and Germany, please see country specific requirements in Appendix 10.
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.
5. Any disorder, except for conditions associated with type 2 diabetes mellitus, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
6. Any episodes of diabetic ketoacidosis within the past 90 days prior to the day of screening and between screening and randomisation.
7. Known hypoglycaemic unawareness as indicated by the Investigator according to Clarke's questionnaire question 8.[1]
8. Recurrent severe hypoglycaemic episodes within the last year as judged by the Investigator.
9. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening and between screening and randomisation.
10. Presently classified as being in New York Heart Association (NYHA) Class IV.
11. Planned coronary, carotid or peripheral artery revascularisation, between screening and randomisation.
12. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR <60 ml/min/1.73 m^2 as defined by KDIGO 2012.[13]
13. Impaired liver function, defined as Alanine Aminotransferase (ALT) ≥ 2.5 times or Bilirubin >1.5 times upper normal limit at screening
14. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic ≥180 mmHg or diastolic ≥110 mmHg) at screening.
15. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening.
16. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.
17. Presence or history of malignant neoplasms within 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed

6.3 Lifestyle restrictions

Not applicable for this trial.

6.4 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 fasting visit until blood sampling and body weight 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 to the next day.

6.5 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to in/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAE). A screen failure session must be made in the interactive web response system (IWRS).

Individuals who do not meet the criteria for participation in this trial may not be rescreened. Re-sampling is not allowed if the subject has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

6.6 Randomisation criteria

To be randomised, the randomisation criterion must be answered "yes".

- Subject able and willing to adhere to the protocol including daily SMPG measurements and wearing CGM sensor based on the Investigator’s judgment.

7 Treatments

7.1 Treatments administered

- All investigational medical products (IMPs) are listed in Table 7-1
- Trial product must only be used, if it appears clear and colourless.
- The investigator must document that directions for use are given to the subject orally and in writing at the first dispensing visit (as specified in the flowchart).

Table 7-1 Trial products provided by Novo Nordisk A/S

Trial product name and strength:	**(NNC0148-0287 C) 4200 nmol/mL (insulin 287)** **(Investigational medicinal product (IMP), test product)**	**Insulin glargine, 100 U/mL** **(IMP, reference therapy)**
Dosage form & Route of administration:	solution for s.c. injection	solution for s.c. injection
Site of injection	Thigh	Thigh
Dosing instructions (see Appendix 9for titration guidelines):	Insulin 287 should be injected subcutaneously once weekly at the same day of the week, anytime during the day, preferably at the same time of the day throughout the trial.	Insulin glargine U100 should be injected subcutaneously once daily at anytime of the day, but at the same time every day throughout the trial.
Packaging:	3 ml pre-filled PDS290 pen-injector with 7U increments	3 mL SoloSTAR® pre-filled pen-injector with 1U increments.

For Germany: For country specific information please refer to Appendix 10.

7.1.1 Background medication

After randomisation subjects must continue their pre-trial oral anti-diabetic background medication with metformin ± DPP4i throughout the trial. The background medication must be maintained at the stable, pre-trial dose and at the same frequency during the entire treatment period unless due to safety concerns related to the background medication. In addition, the background medication:

- is considered to be non-investigational medicinal product
- will not be provided by Novo Nordisk A/S unless required by local law and should be purchased or otherwise delivered to subjects in accordance with local health plans
- should be used in accordance with standard of care or local label in the individual country
- any changes to the background medication must be updated in the case report form (CRF).

7.1.2 Medical devices

PDS290 Pen Device

- Insulin 287 will be provided in a PDS290 pre-filled pen with 7U increments, each pen-injector contains 3 ml insulin 287 corresponding to 2100 units, solution for injection.
- The subjects must be trained according to the direction for use in how to handle the PDS290 pen-injector when handed out the first time.
- Training must be repeated during the trial at regular intervals in order to ensure correct use of the PDS290 pen-injector.
- The following should be emphasized:
  - Always use a new needle for each injection as this will prevent contamination and ensure correct dose.
  - Only needles provided and/or approved by Novo Nordisk must be used for administration of trial product.
  - Remember to prime the pen-injector to ensure product flow

The PDS290 pen-injector to be used in this trial has not been approved for marketing. The PDS290 pen-injector has been documented to be in compliance with the relevant essential requirements of Annex I of the Council directive 93/42/EEC 14, and compliance for the indication for use in adults with T2DM has been verified by the notified body, Lloyds. In this trial, the PDS290 pen-injector will be used in accordance with the verified intended use and indication for use.

The PDS290 pen-injector is not under investigation and there is no intent to use the results from this trial to support a new marketing application or extension of an existing marketing approval.

SoloSTAR Pen®

- Insulin Glargine U100 will be provided as the marketed SoloSTAR® pen, containing 3 ml insulin glargine corresponding to 300U solution for injection. The pens will not be modified but labelled for clinical trial use.
- The subjects must be trained according to the direction for use in how to handle the SoloSTAR ® pen when handed out the first time.
- Training must be repeated during the trial at regular intervals in order to ensure correct use of the SoloSTAR® pen.
- The following should be emphasized:
  - Always use a new needle for each injection as this will prevent contamination and ensure correct dose.
  - Only needles provided and/or approved by Novo Nordisk must be used for administration of trial product.
  - Remember to prime the pen-injector to ensure product flow

Continuous Glucose Monitoring (CGM)

For monitoring of continuous glucose during the first 18 weeks in the trial, Novo Nordisk will provide all subjects with a CGM device (sensor, transmitter, receiver, and guide).

A PC with internet connection must be available at site (same PC as used for the CRF system can be utilised). For further instruction and requirements, please see the user manual and guides provided.

Novo Nordisk will ensure that trial site staff receives appropriate training with regards to the use of the CGM devices. Furthermore site staff should familiarise themselves with the CGM user manual and guides before using the CGM devices. Subjects must be instructed in handling of the CGM and sensor change according to Section 9.1.3 as indicated in the flowchart, Section 2.

The CGM receiver should be collected at site at end of treatment visit (V18) and returned to Novo Nordisk after the trial.

Blood glucose meters

For self-measuring of blood glucose during the trial, Novo Nordisk will provide subjects with a BG meter at the screening visit (V1) including auxiliaries and instructions for use.

The subjects must be instructed in how to use the BG meter as indicated in the flowchart, Section 2. The BG meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display

7.2 Dose modification

Doses are adjusted according to plasma glucose values as described in details in Titration guideline Appendix 9.

7.3 Method of treatment assignment

All subjects will be centrally randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed at the trial visits summarised in the flowchart Section 2.

7.4 Blinding

This is an open-label trial.

7.5 Preparation/Handling/Storage/Accountability

Only subjects randomized in the trial may receive trial product and only authorised site staff may supply or administer trial product. The subject must return all used, partly used and unused trial product including empty packaging materials during the trial as instructed by the investigator.

- The investigator must document, that directions for use are given to the subject verbally and in writing, at the first dispensing visit (V2). Directions for use can be handed out as needed at subsequent visits.
- Conditions for storage are specified on the label and in the trial materials manual.
- Each trial site will be supplied with sufficient trial products for the trial on an on-going basis, controlled by the IWRS. Trial product will be distributed to the trial sites, according to screening and randomisation.
- The investigator is responsible for the confirmation of that appropriate temperature conditions have been maintained during transit, for all trial products received and any discrepancies are reported and resolved, before use of the trial products.
- All trial products must be stored in a secure, access controlled, and temperature monitored (manual or automated) area in accordance with the labelled storage conditions, with access limited to the investigator and authorised site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the trial materials manual.
- 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 is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- The subject should return all used, partly used and unused trial product including empty packaging materials, during the trial as instructed by the investigator.
- Drug accountability should be performed on pen level and must be documented in the IWRS.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- Destruction of trial products must be documented in the IWRS.
- All returned, expired or damaged trial products (for technical complaint samples see Appendix 6) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the trial site.

7.6 Treatment 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 contact (visit or phone contact) by evaluating the glycaemic control and adherence to the visit schedule, completion of the subject´s diary; including SMPG values, dose and hypoglycaemia reporting. If a subject is found to be non-compliant the investigator will remind the subject of the importance of following the instructions including taking the trial products as prescribed. Re-training will be provided as needed by the site.

To limit the risk of using multiple pens simultaneously, subjects randomised to insulin 287 and insulin glargine U100 will only receive the lowest possible amount of pen-injectors, still ensuring sufficient supplies, allowing for up-titration between the dispensing visits, see flowchart, Section 2.

7.7 Concomitant medication

Any medication other than the trial product that the subject is receiving at the time of the first visit (V1) or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates

7.7.1 Concomitant medication (diabetes)

For metformin and DPP4i (if used), the following additional information must be recorded:

- Start date of current dose and total daily dose. The dose should not be changed at any time during the trial, unless due to safety concerns
- For new anti-diabetic medication prescribed in the follow up period, start date of current dose and total daily dose must also be recorded

Until end of treatment (V18) only randomised treatment (trial products and metformin with or without DPP4i) are allowed. If the investigator chooses to initiate other anti-diabetic medication, or change dose of metformin, or DPP4i prior to end of treatment (V18), this should be registered in the CRF as change in concomitant medication (diabetes).

Changes in concomitant medication must be recorded at each visit. If a change is due to an adverse event (AE) or serious adverse event (SAE), then this must be reported according to Section 9.2

7.8 Treatment after the end of the trial

When discontinuing trial products, either at the scheduled end of treatment visit (V18) or if trial product is discontinued, the subject should be transferred to a suitable marketed product at the discretion of the investigator. If the switch to post-trial treatment includes a new insulin treatment, please refer to the titration guideline Appendix 9 for more information

8 Discontinuation/Withdrawal criteria

All efforts should be made to keep subjects on trial products.

The subject may be discontinued at any time during the trial, at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Efforts must be made to have the subjects, who discontinue trial product prematurely, attend the end of treatment visit (V18) and have the follow up visits V19 and V20 performed. Subjects should be asked to continue wearing CGM (changed weekly) throughout the remaining weeks, finalised by a last visit (V18A) 16 weeks after randomisation. To support the subjects with this, sites should stay in contact e.g. by phone calls or site visits to collect the required data for the analysis of the primary endpoint.

Only subjects who withdraw consent will be considered as withdrawn from the trial. Subjects must be educated about the continued scientific importance of their data, even if they discontinue trial product.

8.1 Discontinuation of trial treatment

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

1. Safety concern related to trial product or unacceptable intolerability
2. Included in the trial in violation of the inclusion and/or exclusion criteria
3. Pregnancy
4. Intention of becoming pregnant
5. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.
6. Lack of efficacy, defined as fulfilment of all 4 criteria below:
   a. No reduction in HbA_{1c} measured by central laboratory from randomisation (V2) to visit 6, to visit 10, or to visit 14, AND
   b. The pre-breakfast SMPG readings on 3 consecutive days higher than 240 mg/dL (13.3 mmol/L) within the last two weeks period despite appropriate dose adjustments AND
   c. A confirmatory fasting plasma glucose (FPG) exceeding 240 mg/dL (13.3 mmol/L) measured by central laboratory. The subject should come in for an unscheduled visit as soon as possible (within one week). The next scheduled visit should not be awaited AND
   d. No treatable intercurrent cause (e.g. non-compliance) for the hyperglycaemia at the investigator's judgment

If a subject is discontinued, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to end of treatment visit (V18) and to come in for the follow up visits V19 and V20. Subjects should be asked to continue wearing CGM (changed weekly) throughout the remaining weeks finalised by a last visit (V18A) 16 weeks after

randomisation. To support the subjects with this, sites should stay in contact e.g. by phone calls or site visits.

See the flowchart in Section 2 for data to be collected at the time of treatment randomisation and follow up visits V19, V20, and V18A.

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

A subject who does not fulfil the eligibility (inclusion/exclusion/randomisation) criteria must not be randomised. Randomisation in violation of any of the eligibility criteria is Good Clinical Practice (GCP) non-compliance and must be reported to the sponsor without delay. This will be handled as an important protocol deviation, and the Independent Ethics Committee/Institutional Review Board (IEC/IRB) and regulatory authorities must be notified according to local requirements. If there is no safety concerns, trial treatment may be continued or resumed at the discretion of the investigator after agreement with the sponsor's global medical expert.

8.2 Withdrawal from the trial

A subject may withdraw consent at any time at his/her own request. If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to end-of-treatment visit V18 and to come in for the follow up visits V19, and V20. See the flowchart in Section 2 for data to be collected.

Final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be made in the IWRS.

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the medical record.

If the subject withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

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

8.2.1 Replacement of subjects

Subjects who discontinue trial product or withdraw from trial will not be replaced.

8.3 Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a subject fails to return to the trial site for a required visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

9 Trial assessments and procedures

Trial procedures and their timing are summarised in the flowchart in Section 2. Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.

- Informed consent must be obtained before any trial related activity, see Appendix 3.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a clinical trial and giving contact details of relevant trial site staff.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the flowchart in Section 2 and the laboratory manual.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons See Appendix 2 for further details on laboratory samples.
- Review of completed diaries, electrocardiograms (ECGs), laboratory reports, eye and physical examinations must be documented either on the documents (by signing and dating) or in the subject's source documents, including patient diaries.
- If clarification of entries or discrepancies in the diary is needed, the subject must be questioned and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.
- Source data of clinical assessments performed and recorded in the CRF must be available and will usually be in the subject's medical records. Additional recording to be considered source data includes, but is not limited to diary data, laboratory reports, Dexcom G6 ® data, BG meter, pictures and electrocardiogram (ECG) recordings.
  For United States: Please refer to country specific information in Appendix 10.

9.1 Efficacy assessments

The efficacy laboratory assessments HbA_{1c} and FPG are collected according to the time points provided in the flowchart, Section 2. For further details on laboratory tests see Appendix 2.

9.1.1 Insulin Dose

During the trial, starting at the screening visit (V1), subjects must be instructed to report daily SMPG measurements in the diary.

From V2 subjects should be instructed to record insulin glargine U100 doses taken the last two days prior to titration and on the day of the contact, in the diary, exception being week 15 and 16 where doses must be collected every day. All insulin 287 doses must be entered in the diary.

At each visit or phone contact the Investigator will recommend to either titrate up or down or remain on the same dose based on the SMPG values measured on the two previous days and the day of the contact. The investigator must base the new recommended dose on the applicable titration algorithm assigned to that subject as per randomisation, see titration guideline Appendix 9, for further information.

The Investigator must record the following in the CRF:

- Date, dose and injection time of insulin 287 or insulin glargine U100
- Prescribed doses of insulin 287 and insulin glargine U100; i.e. what the investigator tells the subject to take
- Reason for deviation from the recommended dose, as applicable

For dosing of anti-diabetic medication prescribed in the follow up period please see Section 7.7

9.1.2 Self-measured plasma glucose

Subjects will be provided with a BG meter including auxiliaries as well as instructions for use. The subjects will be instructed in how to use the device and the instruction will be repeated at regular intervals as indicated in the flowchart, Section 2.

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

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

Subjects should be instructed in how to record the results of the SMPG values in the diaries. The record of each SMPG value should include date, time and value. All data from the diary must be transcribed into the CRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the CRF must be corrected.

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

9.1.3 Continuous glucose monitoring (CGM)

As indicated in the flowchart (see Section 2), all subjects will wear CGM during screening and, throughout the 16 week treatment period from V1 to V18.

The CGM system used in this trial will be the Dexcom G6® which consists of three parts:

- the sensor, applied under the skin on the subjects abdomen.

- the transmitter, which is placed on top of the sensor
- the receiver, a hand held device used to store the data received from the transmitter

The sensor is pre-calibrated during manufacturing and requires no finger stick calibration during use. The sensor measurements performed in the interstitial fluid are automatically calibrated to plasma equivalent glucose values. The CGM readings will be blinded to both the subject and investigator and will not be used for any insulin dose titration or hypoglycaemic episode reporting.

CGM fitting and training

The sensor must be applied under the skin of the subject's lower abdomen, using the sensor applicator as described in the Operator's user guide. When applied, a thin, flexible, and sterile fibre is inserted just under the skin of the subject, allowing the measurement of glucose concentration in the interstitial fluid.

For this trial the subject will change their CGM sensor at every site visit and phone contact (see flow chart Section 2) during the 18 week treatment period. The site staff will fit the sensor and transmitter on the subject during the first 6 clinic visits (V1 to V6). The site staffs are responsible for providing appropriate training during visit V1 to V6, to the subject on how to apply the sensor by themselves.
From P7 to V18, including phone contacts (P7 to P15), the subject will change the sensor by themselves. At V10, the site will replace the transmitter during sensor change.

When a new sensor is applied to the subject it is important to enter the new sensor code into the receiver and to check that date and time is correct on the receiver. This will ensure that the sensor is calibrated to the receiver.

For further information on fitting, and changing of the CGM parts, please refer to the user manual.

If a subject withdraws consent during the trial, a site visit must be scheduled in order to remove the sensor and download the data from the receiver. At the end of the trial, the subject must return all CGM material, including any unused sensor, receiver and other materials to the site staff.

CGM sensor check

From P7 till V18, the site staff should ensure that the subject has correctly fitted the sensor, the receiver is working, and sensors are changed at every site visit and phone contact. This will be done in person during the clinic visit and over the phone during phone contacts.

CGM upload

Data stored on the receiver must be uploaded at the site to the provided CGM software program, following the instructions from the user guide provided to sites.

The upload will be documented by the system directly.
The following information must be recorded and transferred into the CRF for every CGM period:

- Serial number of the CGM receiver
- Sensor fitting date and time
- Sensor removal date and time

9.1.4 Patient Reported Outcomes

There are two patient reported outcome questionnaires in this trial. They are:

- Diabetes Treatment Satisfaction Questionnaire (DTSQ)
- Insulin Preference Questionnaire

All subjects (in all three arms of treatment) taking part in this trial will complete the Diabetes Treatment Satisfaction Questionnaire at V2 and V18. The questionnaire is in paper format and will be completed at site by the subject.

Only subjects who are treated on the insulin 287 arms must also complete the Insulin Preference Questionnaire at V18 during their end of treatment clinic visit.

9.2 Adverse events

The definitions of AEs and SAEs can be found in Appendix 4.

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE.

9.2.1 Time period and frequency for collecting AE and SAE information

All AEs will be collected from the first trial-related activity after obtaining informed consent and until the follow up visit/end of trial visit (V20), at the time points specified in the flowchart.

All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours, as indicated in Appendix 4. The investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former trial subjects. However, if the investigator becomes aware of any SAE, including a death, at any time after a subject has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related to the investigational trial product or trial participation, the investigator must promptly notify Novo Nordisk.

The method of recording, evaluating and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4. Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about events.

Timelines for reporting of AEs, and events for adjudication, are listed in Figure 9-1.

Some AEs require additional data collection via a specific event form. This includes medication errors observed during the trial. The relevant specific events are listed in Table 9-1and the reporting timelines in Figure 9-1.

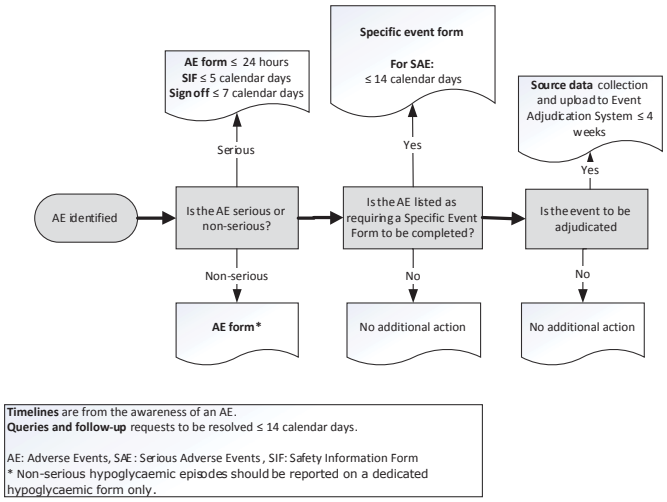


Figure 9-1 Decision tree for determining the event type and the respective forms to complete with associated timelines

Table 9-1 AEs requiring additional data collection (via specific event form), and events for adjudication

	AE requiring additional data collection via event specific form (Appendix 4)	**AE for adjudication requiring source document upload to Event Adjudication System (EAS)** (Section 9.2.1.1, Appendix 4 and Event Adjudication Site Manual)
Acute coronary syndrome		**X**
Cerebrovascular event		**X**
Heart failure		**X**
Death		**X**
Hypersensitivity		**X**
Injection site reactions	**X**	**X**
Medication error	**X**	
Hypoglycaemic episode [a,b]	**X**	

[a] Non-serious hypoglycaemic and hyperglycaemic episodes should be reported on dedicated hypoglycaemic and hyperglycaemic forms only.
[b] For details about specific event forms, see Section 9.2.6.

9.2.1.1 Event for adjudication

Event adjudication will be performed for adverse events in randomised subjects. The list of events for adjudication can be found in Figure 9-1 and the reporting timelines in Figure 9-1. These events are reviewed by an independent external event adjudication committee (EAC) in a blinded manner; refer to Appendix 3 for further details.

There are 3 ways to identify events relevant for adjudication as described below:

1. Investigator reported events for adjudication:
   - All AEs reported with a relevant AE category (Figure 9-1) selected based on predefined criteria (Appendix 4)
   - All AEs reported with a fatal outcome
2. Preferred term search (standardised screening):
   - All AEs recorded in the CRF but not directly reported by the investigator as requiring adjudication, will undergo screening to identify potential events for adjudication.
3. Event Adjudication Committee (EAC)-identified events:
   - During review of source documents provided for another event for adjudication, the EAC may identify additional events in scope for adjudication that were not initially reported by the investigator. In these instances, the investigator will be notified of the newly identified event and has the option to report the EAC-identified event. Regardless of whether the investigator decides to report the event, it will undergo adjudication.

For all the scenarios listed above, investigator must collect copies of all relevant source documents specific to the event type as outlined in the Event Adjudication Site Manual. All source documents should be labelled with trial ID, subject number and AE number, anonymised of any treatment or personal identifiers and uploaded to the Event Adjudication System (EAS) as soon as possible and preferably within 4 weeks according to instructions in the Event Adjudication Site Manual. Specific labelling and redaction requirements apply to digital pictures (see Section 9.4.5 and the Event Adjudication Site Manual for details). All follow up regarding source documents will be handled in the EAS. If no, or insufficient source documents are provided to the adjudication supplier, the investigator can be asked to complete a clinical narrative to be uploaded to the EAS.

If new information related to a reported event where source documents have previously been provided becomes available, it is the responsibility of the investigator to ensure that the new information is reflected in both the CRF and uploaded to the EAS.

The assessments made by both the EAC and the investigator will be analysed and included in the clinical trial report.

9.2.2 Method of detecting AEs and SAEs

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about events.

9.2.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, or if the event is otherwise explained (e.g. chronic condition) or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial product under clinical investigation are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Novo Nordisk policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs), from Novo Nordisk will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to AE/SAEs description in Section 9.2.1.

9.2.6 Disease-related events and/or disease-related outcomes not qualifying as an AE or SAE

The following Disease-Related Events (DREs) are common in subjects with T2DM and can be serious/life threatening:

- Hypoglycaemic episodes

Definitions, classification and reporting requirements are described in Appendix 4.

Hypoglycaemia

Non-serious hypoglycaemia must be reported on a hypoglycaemic episode form only (refer to Figure 9-1).

If the hypoglycaemic episode fulfils the criteria for an SAE then in addition to the above, an AE form and a safety information form must also be filled in. One AE form and safety information form can cover several hypoglycaemic episode forms, if the subject has not recovered between the episodes.

9.2.7 Pregnancies and associated adverse events

Details of pregnancies in female subjects will be collected after the first-trial-related activity after obtaining informed consent and until the pregnancy outcome and the new born infant is one month of age.

If a pregnancy is reported in female subjects, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Figure 9-2 and Appendix 5.

Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.

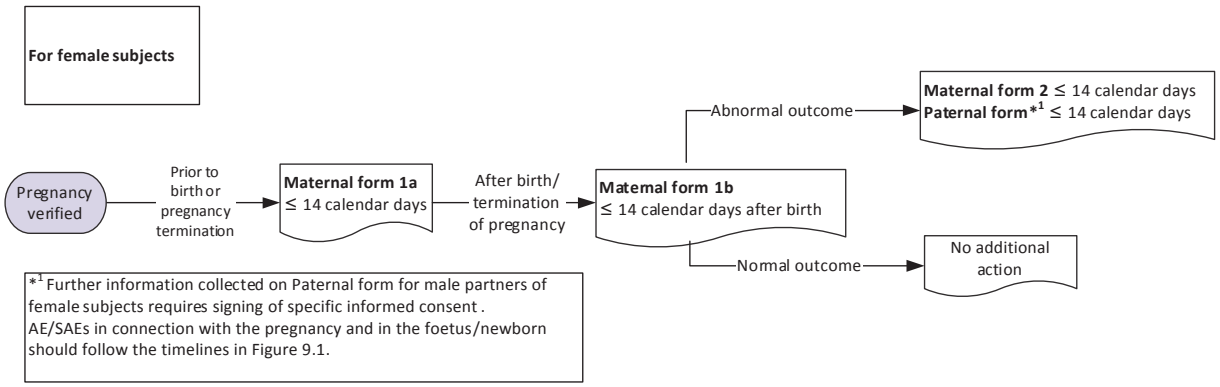


Figure 9-2 Decision tree for determining the forms to complete with associated timelines for pregnancy.

9.2.8 Medical device incidents (including malfunctions)

Refer to technical complaints in Section 9.2.9.

9.2.9 Technical complaints

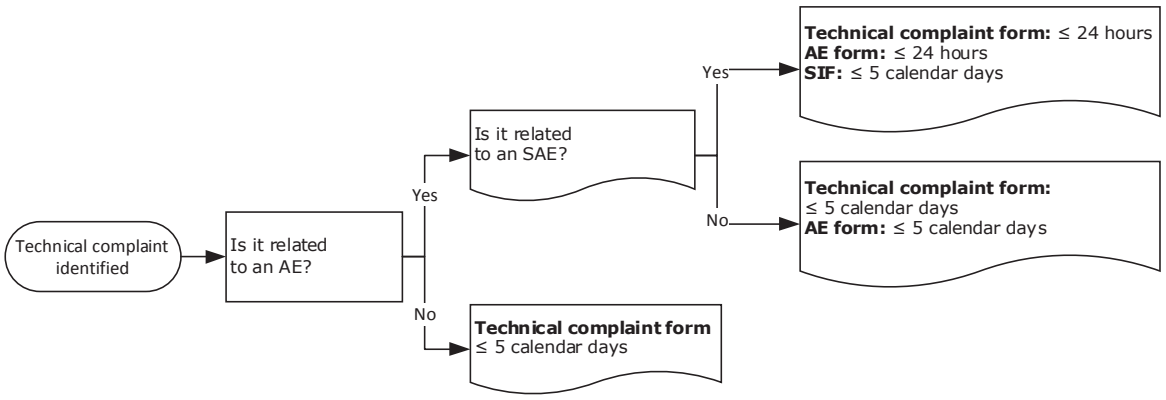
Technical complaints will be collected for all trial products listed on the technical complaint (TC) form in the CRF.

The investigator must assess whether a technical complaint is related to an AE.

The definitions and reporting process for technical complaints can be found in Appendix 6.

Timelines for reporting technical complaints are listed in Figure 9-3.

Technical Complaints related to the CGM devices or BG meters and associated auxiliaries must be reported directly to the supplier/manufacturer.



AE: Adverse Event, SAE: Serious Adverse Event, SIF: Safety Information Form

Figure 9-3 Decision tree for determining the forms to complete with associated timelines for technical complaints.

9.3 Treatment of overdose

Accidental overdose must be reported as a medication error. Intentional overdose is considered abuse or misuse of trial product and must be reported as an AE. Refer to Section 9.2.1 and Figure 9-1 for further details.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAE and laboratory abnormalities until the blood glucose is normalised and (or) signs/symptoms have been relieved.

The administration of insulin, including an overdose of insulin, may result in hypoglycaemia. Symptoms usually occur suddenly and may include cold sweat, nervousness or tremor, anxious feelings, unusual tiredness, confusion, difficulty in concentration, excessive hunger, temporary vision changes, headache, nausea and palpitation. Prolonged or severe hypoglycaemia can lead to a loss of self-control, spasms, and/or unconsciousness and, in extreme cases, death. As with all long-acting insulin preparations, their prolonged effect may delay recovery from a hypoglycaemic episode.

A specific overdose for insulin 287 cannot be defined; however, hypoglycaemia may develop over sequential stages if the doses administered are too high relative to the subject's requirements:

- Mild hypoglycaemia can be treated by oral administration of glucose or sugary products.

- Severe hypoglycaemia, where the subject is not able to treat him/herself, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or s.c. by a trained person, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the subject does not respond to glucagon within 10-15 minutes. If the subject has been unconscious, administration of oral carbohydrates is recommended for the subject upon regaining consciousness, in order to prevent a relapse.

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the subject.

For more information on overdose, also consult the current version of Investigator's Brochure (IB) for insulin 287[12] and Summary of Product Characteristics for insulin glargine U100.[6]

9.4 Safety assessments

Planned time points for all safety assessments and subject relation information are provided in the flowchart Section 2.

Medical history is a medical event that the subject has experienced in the past. Only relevant concomitant illness and medical history as judged by the investigator should be reported.

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

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

In case of an abnormal and clinically significant finding, the investigator must record the finding on the Medical History/Concomitant Illness form if it is present at screening. Any new finding fulfilling the AE definition (see Appendix 4) during the trial and any clinically significant worsening from baseline (V1) must be reported as an AE (see Section 9.2).

For handling of hypoglycaemic episodes; see Appendix 8

9.4.1 Physical examinations

A physical examination will include assessments of:

- Head, ears, eyes, nose, throat, neck
- Cardiovascular system
- Respiratory system
- Gastrointestinal system including mouth
- Musculoskeletal system

- Central and peripheral nervous system
- Skin

Body measurements will also be measured and recorded as specified in the flowchart.

- Body weight should be measured in kilogram (kg) or pounds (lb) without coat and shoes wearing only light clothing. Body weight will be recorded to one decimal.
- Body weight should be assessed with the same equipment throughout the trial, if possible.
- Height should be assessed without shoes. Height is measured in centimetres (cm) or inches (in) at screening visit (V1) and recorded to the nearest whole number
- From the body weight and height the BMI will be calculated in the CRF.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2 Vital signs

- Pulse rate as well as diastolic and systolic blood pressure will be assessed.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting, in the same position at each of the 4 visits, without distractions (e.g. television, cell phones).
- Blood pressure at screening will consist of 3 diastolic and systolic blood pressure measurements with intervals of at least 1 minute. All three readings must be entered in the CRF and the average of the 3 blood pressure readings will be calculated in the CRF. At the subsequent visits, the blood pressure should only be measured once.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

9.4.3 Electrocardiograms

- A 12-lead electrocardiogram (ECG) must be performed by the investigator or delegated staff as outlined in the flowchart, Section 2 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals.
- 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 before randomisation in order to determine the eligibility of the subject.

9.4.4 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the flowchart in Section 2.

9.4.5 Assessments in case of suspicion of hypersensitivity reaction to trial product

Subjects and investigators will be instructed to detect signs and symptoms of hypersensitivity reactions to trial product:

- Local reactions, including injection site reactions and
- Systemic reactions, including anaphylaxis

In the event of a hypersensitivity reaction:

- The subject should contact the site for advice on further action as soon as possible.
- Treatment should be provided by the investigator according to local clinical practice.

Digital pictures

- The investigator or the subject should take digital pictures of the hypersensitivity reaction at time of identification and thereafter as often as judged necessary by the investigator.
- The pictures should include subject identification number, date and time, time after dosing and a ruler for scaling. All pictures should be stored as part of source documentation at site.

Additional blood samples

In the event of a systemic hypersensitivity reaction (defined in Appendix 4), as judged by the investigator, the subject should be called in as soon as possible to have additional blood samples taken in order to analyse the following parameters:

- Tryptase (optimal 0.5 – 2 hours post reaction)
- Total IgE
- Anti-NNC0148-0287 IgE antibodies
- Anti-NNC0148-0287 binding antibodies
- Histamine release (basophil) assay
- Anti-human insulin IgE antibodies

The blood sampling should be repeated 2 to 4 weeks following the systemic hypersensitivity reaction. The results will be provided from the central laboratory and should be included in the documentation provided for event adjudication on the systemic and local hypersensitivity reaction.

Refer to Appendix 4 for further information about evaluation and reporting of hypersensitivity reactions. For information about sample retention; see Appendix 7.

9.5 Eye Examination

Subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy are not eligible as this indicates retinopathy that has recently progressed to a level that requires intervention or is approaching intervention, but has yet to be brought under control. Results of an eye examination performed by an ophthalmologist or another suitably qualified health care provider

(e.g. optometrist) must be available and evaluated by the investigator before randomisation to assess eligibility.

The eye examination should be performed as a fundus photography (e.g. 2-field 60 degree or better, colour or red-free) or by slit-lamp biomicroscopy examination (e.g. using a pre-corneal or corneal contact lens examination). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination. If the subject had such an eye examination performed within 90 days prior to screening, the investigator may base his/her evaluation upon the results of that examination.

The examination must be repeated before randomisation if the subject has experienced worsening of visual function since the last examination. If the applicable eye examination was performed before the subject signed the informed consent form, it must be documented that the reason for performing the examination was not related to this trial. After randomisation an eye examination performed according to above must be performed as per the flowchart in Section 2.

The investigator should indicate the outcome of each eye examination. Relevant findings prior to randomisation must be recorded as concomitant illness/medical history, while relevant findings occurring after randomisation should be reported as an AE, if applicable according to Section 9.2.

9.6 Pharmacokinetics

Not applicable for this trial.

9.7 Pharmacodynamics

Not applicable for this trial.

9.8 Genetics

Not applicable for this trial.

9.9 Biomarkers

Not applicable for this trial.

10 Statistical considerations

10.1 Sample size determination

The primary estimand is defined as the mean difference in 'time in target range 3.9-10.0 mmol/L (70–180 mg/dL)' during the last 2 weeks of treatment (week 15 and 16) between each of the 2 different switch approaches of once weekly insulin 287 (arm A and B) and once daily insulin glargine U100 (arm C) for all randomised subjects, if all subjects had adhered to the randomised insulin treatment and had 70% of the planned CGM measurements recorded during the last two weeks of the planned treatment period (week 15 and 16). The following intercurrent events for the primary estimand will be handled by the hypothetical strategy: initiation of insulin treatment other than the randomised treatment (hereafter defined as rescue medication), discontinuation of randomised insulin treatment, recording of less than 70% of planned CGM measurements in the last two weeks of treatment, and withdrawal from the trial. Hence, measurements collected after these intercurrent events are handled as missing data for the primary estimand.

The sample size calculation is based on the width of the 95% confidence interval (CI). Data from insulin degludec treated subjects in trial NN9068-3697 showed a standard deviation (SD) of 2.5 hour for a 24h period after 26 weeks of treatment and for time in range defined as 3.9-10.0 mmol/L (70–180 mg/dL). NN9068-3697 was conducted in insulin naïve subjects with T2DM and used older CGM devices (iPro1 and iPro2). Another trial in T1DM subjects NN1250-3874 with insulin glargine U100 as comparator used the Dexcom SEVEN® PLUS CGM device which is considered more representative for the present trial as there have been notable improvements in the CGM-devices. In this trial a SD of 3.0 hour in the last maintenance period was observed for time in range defined as 3.9-10.0 mmol/L (70–180 mg/dL). However, the titration periods were only four weeks in NN1250-3874. The SD for the current trial is assumed to be 3.0 based on observations from these two trials. Table 10-1 shows the width of the 95% confidence interval for any pairwise comparison that can be obtained with 80% probability for a range of sample sizes and assumed values of SD.

Table 10-1 Width of the 95% CI for various SD and number of subjects per treatment arm

	Number per treatment arm		
SD	40	50	60
2.5	2.4	2.1	1.9
3.0	2.9	**2.5**	2.3
3.5	3.3	3.0	2.7

CI: confidence interval. SD: standard deviation.

With 50 subjects randomised to each treatment arm in a 1:1:1 manner, the width of the 95% for any pairwise comparison is 2.5 h/24h with a probability of 80%. Two-and-a-half hour corresponds to approximately 10%-point for percent time in range.

10.2 Definition of analysis sets

The following analysis sets will be defined:

Full analysis set (FAS): includes all randomised subjects. Subjects in the FAS will contribute to evaluation "as randomised".

Safety analysis set (SAS): includes all subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation based on the trial product received for the majority of the period they were on treatment. This will be referred to as contributing to the evaluation "as treated".

The relevant observations periods are

In-trial: This observation period represents the time period after randomisation where subjects are considered to be in the trial, regardless of discontinuation of trial product or initiation of rescue medication. The in-trial observation period starts at randomisation (as registered in IWRS) and ends at the date of:

- The last direct subject-site contact, which is scheduled to take place 6 weeks after planned last dose of once weekly trial product and 5 weeks after last dose of once daily trial product at a follow-up visit (phone visit)
- Withdrawal for subjects who withdraw their informed consent
- The last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up
- Death for subjects who die before any of the above
- For subjects not randomised but exposed to trial product the in-trial period starts at the date of first dose of trial product.

On-treatment: This observation period represents the time period where subjects are considered exposed to trial product. The observation period is a sub-set of the in-trial observation period. It starts at the date of first dose of trial product, the observation period ends at the first date of any of the following:

- The follow-up visit (FU2)
- The last date on trial product + 5 weeks for once daily insulin and +6 weeks for once weekly insulin
- The end-date for the in-trial observation period

On-treatment without rescue medication: This observation period is a sub-set of the on-treatment observation period, where subjects are considered treated with randomised insulin product, and have not initiated a non-randomised inulin treatment. Specifically, the period starts at the date of first dose of trial product and ends at the first date of any of the following:

- The last dose of trial product + 5 weeks for once daily insulin and +6 weeks for once weekly insulin
- Initiation of a non-randomised insulin treatment

The 'on-treatment without rescue medication' observation period will be the primary observation period for efficacy evaluations. Safety will be evaluated based on the in-trial and the on-treatment observation periods unless otherwise specified.

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period. Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group.

Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion will 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.

10.3 Statistical analyses

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

All statistical analysis of efficacy and safety endpoints will be based on the FAS unless otherwise specified. Confirmatory analysis addressing the primary estimand will be based on on-treatment data without rescue medication.

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

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

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

In the statistical models baseline value of the endpoint value will be included as a covariate and explanatory factors will be categorized as follows:

- Treatment: switch approach with 100% loading dose, switch approach without loading dose, insulin glargine U100

10.3.1 Primary endpoint

The primary endpoint is 'time in target range 3.9–10.0 mmol/L (70-180 mg/dL)' during the last 2 weeks of treatment (week 15 and 16). The percentage of time spent in glycaemic target range will be calculated as 100 times the number of recorded measurements in glycaemic target range 3.9–10.0 mmol/L (70-180 mg/dL), both inclusive divided by the total number of recorded measurements.

Following international consensus criteria[14] it will be required that at least 70% of the planned CGM measurements, during the last two weeks of treatment is available, for endpoint data to be included in the analysis.

The primary estimand will be estimated based on the Full Analysis Set (FAS) using measurements obtained while subjects are adhering to randomised treatment without initiation of rescue medication. Measurements obtained after initiation of rescue treatment and endpoint data from which the required 70% of the planned CGM measurements during the last two weeks of treatment are not available will be regarded as missing. Missing endpoint data will be imputed from trial participants who are from the same randomised group, and who have completed and adhered to their randomised insulin treatment without initiation of a non-randomised insulin treatment i.e., data will be imputed based on the assumption that, within treatment groups, subjects with missing endpoint data will behave like subjects completing randomised treatment. Specifically, the imputations and analyses will be carried out as follows:

- First, one thousand (1000) copies of the dataset will be generated for time in range.
- Second, for each dataset copy, each assessment and each treatment group, an analysis of variance (ANOVA) model with baseline 'time in target range' as covariate will be fitted to the time in range values for subjects having completed their randomised treatment. The estimated mean, and variances, from the model will be used to impute missing values in the same treatment group.
- For each of the complete data sets, the primary endpoint will be analysed using an ANOVA model with randomised treatment as fixed factor and baseline 'time in target range' as covariate, the analysis will be stratified according to pre-trial insulin treatment (twice daily or insulin glargine U300). The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.[15]
- Each pairwise treatment contrast with 95% CI will be presented.

Baseline 'time in target range' will be derived the same way as the primary endpoint.

Efficacy endpoints

The secondary efficacy endpoints will be addressed in terms of the frame work of the primary estimand.

The secondary efficacy endpoints addressing glycaemic control and body weight will be analysed using the same model as specified for the primary model with the exception that baseline value of the endpoint will be used as covariate. Missing data will be imputed similarly as for the primary endpoint, but using a sequential approach where available data from scheduled visits during the trial are used to impute missing data for subsequent scheduled visits.

The insulin doses will be analysed log-transformed and without a covariate reflecting baseline dose but otherwise using the same statistical model as specified for the primary model.

Safety endpoints

Adverse events

A treatment-emergent AE is an event that has onset date (or increase in severity) during the on-treatment observation period. These will therefore be referred to as 'on-treatment AEs' hereafter. On-treatment AEs are summarised descriptively in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). These summaries are replicated by outputs including all 'in-trial' AEs (i.e., AEs with onset date [or increase in severity] during the 'in-trial' observation period).

The most frequent AEs will be defined as preferred terms that are experienced by at least 5% of the subjects in any of the treatment arms.

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding.

Hypoglycaemic episodes

Hypoglycaemia endpoints will be summarized similarly to the treatment emergent AE's for the on-treatment observation periods based on the SAS.

10.4 Pharmacokinetic and/or pharmacodynamic modelling

Not applicable for this trial.

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12 Appendices

Appendix 1 Abbreviations and Trademarks

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
CGM	continuous glucose monitoring
CI	confidence interval
CRF	case report form
DUN	dispensing unit number
DPP4i	dipeptidyl peptidase 4 inhibitors
EAS	event adjudication system
ECG	electrocardiogram
EMA	European Medicines Agency
FAS	full analysis set
FPG	fasting plasma glucose
GCP	Good Clinical Practice
HbA_{1c}	glycated haemoglobin
HRT	hormone replacement therapy
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IWRS	interactive web response system
PD	pharmacodynamics
PG	plasma glucose
PK	pharmacokinetics
SAE	serious adverse event
SD	standard deviation

SMPG	self-measured plasma glucose
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
WOCBP	woman of child bearing potential

Appendix 2 Clinical laboratory tests

- The tests detailed in Table 12-1 and Table 12-2 will be performed by the central laboratory, unless otherwise specified.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- Laboratory samples will be destroyed on an ongoing basis and no later than at finalisation of the clinical trial report.
- Samples to assess systemic hypersensitivity reactions will be stored as described in Appendix 7.
- 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.
- Antibody samples taken in case of a suspected hypersensitivity reaction related to the trial product will be stored as described in Appendix 7.

Table 12-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• FPG (Fasting plasma glucose) • HbA_{1c}
NOTES : [a] A FPG result < 3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as an adverse event at the discretion of the investigator (Appendix 4).	

Table 12-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	• Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Thrombocytes • Differential count (eosinophils, neutrophils, basophils, monocytes and lymphocytes)
Biochemistry[1]	• Alanine Aminotransferase (ALT) • Albumin • Alkaline phosphatase • Aspartate Aminotransferase (AST) • Creatinine • Potassium

	• Sodium • Bilirubin
Lipids	• Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein cholesterol • Triglycerides • Free fatty acid
Pregnancy Testing	• Serum or urine human chorionic gonadotropin (hCG) pregnancy test (for women of childbearing potential)
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation • Additional blood samples in case of a systemic hypersensitivity reaction: o Tryptase o Total IgE o Anti-NNC0148-0287 IgE antibodies o Anti-NNC0148-0287 binding antibodies o Histamine release (basophil) assay o Anti-human insulin IgE antibodies
Notes : [a]Details of required actions for increased liver parameters are given in Appendix 4 (Hy's Law)	

Trial-required laboratory assessments will be performed by a central laboratory, with the exception of:

- Urine pregnancy tests which are performed locally
- Anti-insulin 287 antibodies, anti-insulin glargine antibodies, pharmacokinetics and additional blood samples in case of a systemic and local hypersensitivity reaction which are performed at special lab.

Appendix 3 Trial governance considerations

1) Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[16], applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[17] and ISO 14155[18]
- Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements), must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
  - providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
  - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
  - ensuring submission of the clinical trial report synopsis to the IRB/IEC.

2) Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and one year after completion of the trial.

For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

3) Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the subject and answer all questions regarding the trial.
- The investigator must inform the subject about the long-term storage of additional blood samples e.g. for exploratory investigation of antibodies or further development of anti-insulin antibody assays or to assess systemic hypersensitivity reactions. The subject must be informed that he/she is free to refuse to participate and may withdraw consent to the long term storage of the additional blood samples at any time and for any reason during the storage period.
- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.
- Subjects must be informed that their participation is voluntary.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[17], Declaration of Helsinki[16] and the IRB/IEC or trial site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the trial.
- A copy of the informed consent form(s) must be provided to the subject.

4) Information to subjects during trial

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

5) Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.
- The subject must be informed that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

6) Committee structure

Novo Nordisk safety committee

Novo Nordisk will constitute an internal insulin 287 safety committee to perform ongoing safety surveillance. The insulin 287 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.

Event adjudication committee

An independent external EAC is established to perform ongoing blinded adjudication of selected AEs and death (see Table 9-1and Appendix 4). The EAC will evaluate events sent for adjudication using pre-defined definitions and guidelines in accordance with the EAC Charter. The evaluation is based on review of pre-defined clinical data collected by the investigational sites.

The EAC is composed of permanent members covering all required medical specialities. EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk. The EAC will have no authority to impact on trial conduct, trial protocol or amendments.

Hypersensitivity reactions were observed with previous Formulation A, which was subsequently optimised to the current Formulation C. No hypersensitivity reactions have so far been observed with Formulation C. However, event adjudication for hypersensitivity reactions (local reactions, including injection site reactions and systemic reactions, including anaphylaxis) is introduced in the present trial to ensure standardised and objective assessment by an independent adjudication committee of experts within the specialty.

The cardiovascular events will be adjudicated in accordance with U.S. Food and Drug Administration requirements[19].

The AEs for adjudication are listed in Table 9-1 and Appendix 4.

Global expert panel

A global expert panel will consist of investigators participating in the trial in different countries and of designated Novo Nordisk employees. The panel will discuss and advice on global and local operational issues related to trial conduct.

7) Publication policy

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 investigators who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

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

One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications.[20]

Communication of results

Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed 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. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This

includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

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

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. 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.

Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the trial concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[21]

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned 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.

Site-specific publications by investigators

For a multicentre 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. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the trial.

Investigator access to data and review of results

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

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

8) Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[21], the Food and Drug Administration Amendment Act[22], European Commission Requirements[23] 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.

The Primary Completion Date is the last assessment of the primary endpoint, and is for this trial Last Subject First Treatment (LSFT) + 16 weeks corresponding to visit V18. If the last subject is withdrawn early, the Primary Completion Date is considered the date when the last subject would have completed visit V18. The Primary Completion Date determines the deadline for results disclosure at clinicaltrials.gov according to Food and Drug Administration Amendment Act.

9) Data quality assurance

Case Report Forms (CRFs)

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory and CGM Dexcom G6 ® data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The following will be provided as paper CRFs:
  - Pregnancy forms
- The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:
  - AE forms
  - Safety information forms
  - Technical complaint forms (also to be used to report complaints that are not subject related, e.g. discovered at trial site before allocation)
- 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 when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

- The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

Monitoring

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records), including electronic medical 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).

- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

- Monitoring will be conducted using a risk based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to trial sites.

- Monitors will review the subject's medical records and other source data e.g. the diaries and PROs, to ensure consistency and/or identify omissions compared to the CRF.

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 CRF or via listings from the trial database.

10) Source documents

All data entered in the CRF must be verifiable in source documentation other than the CRF.

- The original of the completed diaries must not be removed from the trial site.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the trial site.
- Data reported on paper CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify subject's medical history in source documents such as subject's medical record.
- All subject data relating to the trial will be recorded on CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory and diary data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each trial site. There will only be one source document defined at any time for any data element.

11) Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) must be retained by the trial site. If the provided electronic 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.
- Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice

12) Trial and site closure

Novo Nordisk reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or 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.

Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by Novo Nordisk or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines
- inadequate recruitment of subjects by the investigator
- discontinuation of further trial product development.

13) Responsibilities

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

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

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents, including the subject identification code list must be kept in a secure locked facility so that 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).

14) 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:

- The Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal of Laws of 2008 No.45 item 271 with amendments).

Appendix 4 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting

AE definition
• An AE is any untoward medical occurrence in a clinical trial subject administered or using a medicinal product, whether or not considered related to the medicinal product or usage. • An AE can be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product. Note 1: This includes events related to the procedures involved (any procedure in the protocol). Note 2: For users or other persons this is restricted to events related to the investigational medical device.

Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • A clinical abnormal laboratory finding 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 • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms or the clinical sequelae of a suspected overdose of trial product regardless of intent. • A "lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition. • Abuse and misuse of trial product must be reported as an AE. • Abuse is defined as: Persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm) • Misuse is defined as: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol or the terms of the marketing authorisation.
Events NOT meeting the AE definition
• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product. • Note: pre-existing conditions should be recorded as medical history/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.

Definition of an SAE
An SAE is an AE that fulfils at least one of the following criteria:
• Results in death
Is life-threatening • The term 'life-threatening' in the definition of 'serious' 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 were more severe.
Requires inpatient hospitalisation or prolongation of existing hospitalisation • Hospitalisation signifies that the subject has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Note: • 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.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experience of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Important medical event: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion. The following adverse events must always be reported as SAEs using the important medical event criterion, if no other seriousness criteria are applicable: • Suspicion of transmission of infectious agents via the trial product. • Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law)

Description of AEs requiring additional data collection (via specific event form) and/or events for adjudication.
AEs requiring additional data collection (via specific event form): **Injection site reaction** If an event of injection site reaction is observed the following additional information must be obtained if available on the injection site reaction form: • Symptoms associated with the event • Treatment given for the reaction

- Association with the trial product(s)
- Relevant risk factors associated with the event

Additionally, the following information must be recorded on the injection site reaction form:

- Timing and duration of the injection site reaction
- Timing and dose of last injection prior to the onset of reaction
- Relieve of symptoms
- Information about the injection (incl. needle angle and site of reaction)
- Skin condition before injection site reaction
- Size of reaction
- Needle information

Hypoglycaemic episode

See Appendix 8

Medication error: A medication error concerning trial products is defined as:

- Administration of wrong drug
  Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in administration of wrong drug
- Wrong route of administration, such as intramuscular instead of subcutaneous
- Accidental administration of a lower or higher dose than intended. 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

Events for adjudication

Event type	Description	Adjudication outcome
Acute coronary syndrome	Acute Coronary Syndrome conditions include all types of acute myocardial infarction and hospitalisation for unstable angina pectoris	• Acute myocardial infarction (including subgroup classifications) • Hospitalisation for unstable angina pectoris
Cerebrovascular events	Episode of focal or global neurological dysfunction that could be caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction	• Ischaemic stroke • Haemorrhagic stroke • Undetermined stroke
Heart failure	Presentation of the subject for an urgent, unscheduled clinic/office/emergency department visit or hospital admission, with a primary diagnosis of heart failure (new episode or worsening of existing heart failure)	• Heart failure hospitalisation • Urgent heart failure visit
Death	All cause death	• Cardiovascular death (including undetermined cause of death)

		• Non-Cardiovascular death
Hypersensitivity • Local reactions, including injection site reactions • Systemic reactions, including anaphylaxis	Hypersensitivity is defined as episodes of objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons Anaphylaxis is defined as serious hypersensitivity reactions that is rapid in onset and may cause death	• Hypersensitivity reaction

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the CRF.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.
- For all non-serious AEs the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE related forms refer to "SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

The investigator will assess intensity for each event reported during the trial and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: Severe is a category used for rating the intensity of an event; and both an AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the outcomes described in the definition of an SAE and not when it is rated as severe

Assessment of causality

The investigator is obligated to assess the relationship between trial product and the occurrence of each AE/SAE.

Relationship between an AE/SAE and the relevant trial product(s) should be assessed as:

- 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.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to trial product administration will be considered and investigated.

The investigator should use the investigator's brochure for insulin 287 and/or product information for marketed non-Novo Nordisk's products, for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data**.

The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate 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 sequelae meet 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 a fatal outcome must be reported as an SAE.
- **Unknown**: This term is only applicable if the subject is lost to follow-up.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.
New or updated information will be recorded in the CRF.

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

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

SAE reporting via electronic CRF

- Relevant forms (AE and safety information form) must be completed in the CRF.
- For reporting and sign-off timelines, see box below.
- If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form and if the CRF is unavailable for more than 5 calendar days then the site will use the safety information form (see box below).
- The site will enter the SAE data into the CRF as soon as it becomes available, see 9.2.1.
- After the trial is completed at a given site, the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after CRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

SAE reporting via paper CRF

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by fax, e-mail or courier.
- Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting time frames (as illustrated in Figure 9-1):
- AE form within 24 hours.
- Safety information form within 5 calendar days.
- Both forms must be signed within 7 calendar days.
- Contact details for SAE reporting can be found in the investigator trial master file.

Appendix 5 Contraceptive guidance and collection of pregnancy information

It must be recorded in the CRF whether female subjects are of childbearing potential.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP

Premenarcheal

Premenopausal female with one of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of subject's medical records, medical examination or medical history interview.

Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or Hormonal Replacement Therapy (HRT). However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrolment.

Contraception guidance

Male subjects

No contraception measures are required for male subjects as the risk of teratogenicity/fetotoxicity caused by transfer of insulin 287 or insulin glargine U100 in seminal fluid is unlikely.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly as described in table(s) below:

Table 12-3 Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent [a] Failure rate of <1% per year when used consistently and correctly.
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • oral • injectable
Highly effective methods that are user independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine Device • Intrauterine hormone-releasing System • Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.
Notes: [a]Failure rates may differ from < 1% per year, if not used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials.

Pregnancy testing

- WOCBP should only be included after a negative highly sensitive serum pregnancy test.
- Urine Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of pregnancy information

Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy.

- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to Novo Nordisk. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the trial product by the investigator will be reported to Novo Nordisk as described in Appendix 4. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the trial will discontinue trial product.

Appendix 6 Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

Technical complaint definition
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:

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

Time period for detecting technical complaints
All technical complaints, which occur from the time of receipt of the product at trial site until the time of the last usage of the product, must be collected for products predefined on the technical complaint form.

Reporting of technical complaints to Novo Nordisk
Contact details (fax, e-mail and address) for Customer Complaint Center – refer to Attachment I Technical complaints must be reported on a separate technical complaint form: 1. One technical complaint form must be completed for each affected DUN 2. If DUN is not available, a technical complaint form for each batch, code or lot number must be completed

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within the timelines specified in Figure 9-3. If the CRF 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 Centre, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

Follow-up of technical complaints
The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.
Collection, storage and shipment of technical complaint samples
The investigator must collect the technical complaint sample and all associated parts that were packed in the same DUN and notify the monitor within 5 calendar days of obtaining the sample at trial site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together. Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

Reporting of technical complaints for Novo Nordisk products not included in technical complaint form
Technical complaints on Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk affiliate with a reference to trial ID.

Appendix 7 Retention of human biosamples

Anti-insulin 287 antibodies, anti-insulin glargine antibodies samples and samples to assess systemic and local hypersensitivity reactions (if taken) will be stored at a central bio-repository after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.
Antibody samples may be used for later analysis for further characterisation of antibody responses towards drug, if required by health authorities or for safety reasons, or for exploratory investigation of antibodies or further development of anti-insulin antibody assays.

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

Only Novo Nordisk staff and biorepository personnel will have access to the stored samples.

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

Appendix 8 Hypoglycaemic episodes

Classification of hypoglycaemia

Classification of hypoglycaemia		
Level	Glycaemic criteria	Description
Hypoglycaemia alert value (**level 1**)	< 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (**level 2**)	< 3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (**level 3**)	No specific glucose threshold	Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery
Notes: Novo Nordisk terms adapted from IHSG[24], ADA-2018 [2], ISPAD[25], Type 1 diabetes outcomes program[26], ATTD[14]. Severe hypoglycaemia as defined by Seaquist[27].		

Reporting of hypoglycaemic episodes:

Plasma Glucose (PG) should always be measured by the study provided BG meter and recorded in the diary and CRF when a hypoglycaemic episode is suspected.

PG values <3.9 mmol/L (70 mg/dL) should be reported as a hypoglycaemic episode according to the instructions below. When a subject experiences a hypoglycaemic episode, subject/investigator should record the general information in relation to the hypoglycaemia (timing, PG measurements, symptoms etc.) as described in the diary/CRF, respectively. In case a subject is not able to fill in the diary (e.g. in case of hospitalisation), the investigator should report the hypoglycaemic episode in the hypoglycaemic episode CRF.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the SMPG value is ≥3.9 mmol/L (70 mg/dL) and in case of severe hypoglycaemia, that the condition have been resolved in accordance with current guidelines[27].Furthermore, subjects should be encouraged to measure and follow their SMPG values 1-2 hours after the episode.

Repeated SMPG measurements and/or symptoms will by default be considered as one hypoglycaemic episode until a succeeding SMPG value is ≥ 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved. The episode should be reported as only one hypoglycaemic episode on the hypoglycaemic episode CRF. In case of several low SMPG values within the hypoglycaemic episode, 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 low SMPG value and/or symptom. The remaining values will be kept as source data in the diary.

If the severity of a hypoglycaemic episode changes, only one hypoglycaemic episode should be reported, reflecting the most severe degree of hypoglycaemia.

Regarding the question: "To feel better, did you need help to get a sugary drink, food, or medicine?" the investigator must instruct subjects that the answer should be "Yes", if the episode is an event requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery following the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.[27]

Additional information (e.g. description of symptoms, alleviation of symptoms, seizure or coma) in relation to severe hypoglycaemic episodes must be recorded in the hypoglycaemic episode CRF.

Diary Review

At each visit or phone contact, the investigator must review all SMPG values in the diary and identify any 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 could have handled the episode (by getting a sugary drink and/or food) him/herself. If the subject could not have handled the episode him/herself, it has to be reported as a hypoglycaemic episode in the hypoglycaemic episode CRF describing that the subject could not have handled the episode him/herself.

For low SMPG values for hypoglycaemic episodes where the subject could handle the episode him/herself:

- If a hypoglycaemic episode form in the diary is not completed by the subject within 7 calendar days of the SMPG measurement, the episode should be described in the source documents and reported by the investigator on a hypoglycaemic episode CRF with as much information as possible: Novo Nordisk will not query for additional data except for the start date and whether the subject could have handled the episode him/herself due to the decreased validity of such data.[28] [29]

Re-training of subjects

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

Appendix 9 Titration guideline

Introduction

Titration guidelines have been developed, providing recommended dose adjustments at different plasma glucose (PG) levels to ensure that subjects receive an optimal treatment. However, it is recognised that insulin treatment should be individualised and the specific titration algorithms may not be applicable in certain clinical situations. Hence, it is important that other information, such as symptoms of hypo/hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the subject's level of glycaemic control, is taken into consideration when decisions on dosing are made. The investigator is responsible for the treatment of the subjects and can therefore overrule the guidelines to avoid safety hazards.

Initiation of trial products

At randomisation eligible subjects will be randomised to receive insulin 287 or to receive insulin glargine U100.

Insulin 287 should be taken once weekly at the same day of the week. Dependent on randomisation and previous insulin regimen the subjects should either initiate insulin 287 with or without a 100% loading dose as follows:

A. If the subject prior to randomisation received a once daily regimen with insulin degludec, insulin detemir or insulin glargine U100 the initial dose of insulin 287 after randomisation should be according to the table below.

	Weekly dose at randomisation visit (V2)	**Weekly dose at V3**
Without loading dose	Current daily dose x 7	Same dose as V2, then follow titration algorithm
With additional 100% loading dose	Current daily dose x 7 x 2	Divide V2 dose by 2, then follow titration algorithm

In Table 12-4, please find the calculated weekly doses for V2 and V3 based on current daily doses between 10 and 50U:

Table 12-4 Doses for subject that prior to randomisation received a once daily regimen with insulin degludec, insulin detemir or insulin glargine U100

Current daily dose	V2 without loading dose	V3 without loading dose	V2 with loading dose	V3 with loading dose
10	70	70	140	70
11	77	77	154	77
12	84	84	168	84
13	91	91	182	91
14	98	98	196	98
15	105	105	210	105
16	112	112	224	112
17	119	119	238	119
18	126	126	252	126
19	133	133	266	133
20	140	140	280	140
21	147	147	294	147
22	154	154	308	154
23	161	161	322	161
24	168	168	336	168
25	175	175	350	175
26	182	182	364	182
27	189	189	378	189
28	196	196	392	196
29	203	203	406	203
30	210	210	420	210
31	217	217	434	217
32	224	224	448	224
33	231	231	462	231
34	238	238	476	238
35	245	245	490	245
36	252	252	504	252
37	259	259	518	259
38	266	266	532	266
39	273	273	546	273
40	280	280	560	280
41	287	287	574	287
42	294	294	588	294
43	301	301	602	301
44	308	308	616	308
45	315	315	630	315
46	322	322	644	322
47	329	329	658	329
48	336	336	672	336
49	343	343	686	343
50	350	350	700	350

B. If the subject prior to randomisation received a twice daily regimen with any basal insulin analogue or an once daily regimen with insulin glargine U300, the total daily insulin dose prior to randomisation should be reduced by 20%. The initial doses of insulin 287 should be according to the table below.

	Weekly dose at randomisation visit (V2)	**Weekly dose at V3**
Without loading dose	Current total daily dose x 0.8 x 7	Same dose as V2, then follow titration algorithm
With additional 100% loading dose	Current total daily dose x 0.8 x 7 x2	Divide V2 dose by 2, then follow titration algorithm

In Table 12-5, below, please find the calculated weekly doses for V2 and V3 based on current daily doses between 10 and 50U:

Table 12-5 Doses for subjects that prior to randomisation received a twice daily regimen with any basal insulin analogue or a once daily regimen with insulin glargine U300

Current daily dose	V2: weekly dose without loading dose	V3 weekly dose without loading dose:	V2 weekly dose with loading dose	V3: weekly dose with loading dose
10	56	56	112	56
11	56	56	119	56
12	63	63	133	63
13	70	70	140	70
14	77	77	154	77
15	84	84	168	84
16	84	84	175	84
17	91	91	189	91
18	98	98	196	98
19	105	105	210	105
20	112	112	224	112
21	112	112	231	112
22	119	119	245	119
23	126	126	252	126
24	133	133	266	133
25	140	140	280	140
26	140	140	287	140
27	147	147	301	147
28	154	154	308	154
29	161	161	322	161
30	168	168	336	168
31	168	168	343	168
32	175	175	357	175
33	182	182	364	182
34	189	189	378	189
35	196	196	392	196
36	196	196	399	196
37	203	203	413	203
38	210	210	420	210
39	217	217	434	217
40	224	224	448	224
41	224	224	455	224
42	231	231	469	231
43	238	238	476	238
44	245	245	490	245
45	252	252	504	252
46	252	252	511	252
47	259	259	525	259
48	266	266	532	266
49	273	273	546	273
50	280	280	560	280

Insulin glargine U100 should be taken once daily at any time of the day, but at the same time every day.

If the subject prior to randomisation received a once daily regimen with insulin degludec, insulin detemir or insulin glargine U100 the initial dose at randomisation should be the same as prior to randomisation

If the subject prior to randomisation received a twice daily regimen with any basal insulin analogue or a once daily regimen with insulin glargine U300 the total daily insulin dose prior to randomisation should be reduced by 20% and taken once daily.

The treat-to-target approach will be applied to all three treatment arms to optimise glycaemic control throughout the trial. There are no maximum or minimum insulin doses.

Dose adjustment of trial products during the trial

After randomisation the trial products will be adjusted once weekly by the investigator in connection with the scheduled visits/phone contacts as described below.

The dose adjustment will be based on the three pre-breakfast SMPG values measured on the two days prior to titration and on the day of the contact, and in accordance with Table 12-6. If there are values below 4.4 mmol/L (80 mg/dL) the reduction will be based on the lowest SMPG value. If there are no low values the dose will be adjusted according to the mean of the SMPG values. If one or more SMPG values are missing, the dose adjustment should be performed on the remaining SMPG value(s).

Table 12-6: Insulin glargine U100 and insulin 287 titration algorithm

Pre-breakfast SMPG			Insulin glargine U100 dose adjustment	Insulin 287 dose adjustment
Value to use	mmol/L	mg/dL	U	U
Lowest of the SMPG values	<4.4	<80	–4	–28
Mean of the SMPG values	4.4–7.2	80–130	No adjustment	No adjustment
	>7.2	>130	+4	+28

Deviations from the algorithm

It is recommended that the algorithm is followed. However, it is also important that the decision to adjust insulin doses is based on all relevant information. A reason for deviating from the algorithm should be entered into the CRF by the investigator as applicable.

Missing dose guidance for insulin 287

The dosing window for insulin 287 is ±1 day.

- If a dose is missed for ≤ 4 days after the planned dosing day, subjects should inject the planned full dose as soon as possible and perform control SMPG measurements.
- If the missing dose is observed from day 5 to day 7 (which is the next planned dosing day), subject should inject 50% of the missed dose rounded down to the nearest possible dose which can be divided with 7, e.g. if a subject forgot to take the prescribed dose of 77U, then 50% of 77U is 38.5U and hence the dose should be rounded down to 35U. On day 7, the next scheduled full prescribed dose should still be taken. Additional SMPG measurement should be performed to control BG.

Dose recommendation from end of treatment (EOT) and during follow up for insulin 287

If it is decided that the individual subject should continue on insulin after EOT it is recommended that the subject is switched from insulin 287 to any available basal insulin at the discretion of the investigator. The initial post-trial basal dose is estimated as follows:

- Calculate 50% of the latest weekly insulin 287 dose and divide by 7
- Initiate the new daily basal insulin based on above calculated dose
- Consider titrating the basal insulin once or twice weekly according to the pre-breakfast SMPG values and the local label of the chosen insulin

Data collection

The following data should be entered into the diary every day by the subject and reviewed by the investigator during the clinic visit:

- Per protocol pre-breakfast SMPG values measured since last visit/phone contact
- Insulin glargine U100 doses taken the last two days prior to titration and on the day of the contact. Exception being week 15 and 16 where doses are collected every day. All insulin 287 doses must be entered in the diary.

The following should be entered by investigator into the CRF within 24 hours after each contact:

- Per protocol pre-breakfast SMPG values measured since last visit/phone contact
- Date, actual dose and injection time of insulin 287 since the last contact or date, actual dose and injection time of insulin glargine U100 taken the last two days prior to titration and on the day of the contact. Exception being week 15 and 16 where all daily doses are collected and must be entered into the CRF.
- Insulin glargine U100 or insulin 287 doses prescribed at this contact.
- Reasons for deviation from the titration algorithms, if applicable
- Hypoglycaemic episodes

Data surveillance

Surveillance of titration data will be performed centrally by Novo Nordisk in an unbiased or, if possible, a blinded manner. The data will be reviewed and significant changes from the titration algorithm will be followed up.

It is important that data regarding titration is entered into the diary and into the CRF. 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 titration data should be reviewed by Novo Nordisk within 24 hours (on workdays). The reviewer may contact the investigator by e-mail or phone to clarify reasons 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 workdays).

In addition, Novo Nordisk will monitor changes in HbA_{1c}. Novo Nordisk may visit or phone sites to discuss progress in glycaemic control and titration of individual subjects.

Appendix 10 Country-specific requirements

For Czech Republic: Adequate contraceptive measures are always one highly reliable method (such as intrauterine device, sterilisation of one of the partners, hormonal birth control methods) plus one supplementary barrier method (such as condom, diaphragm) with a spermicide. In justified cases, this combination may be replaced with a double-barrier method with a spermicide. Total sexual abstinence may also be considered contraception. (Please note: Hormonal contraception should always be discussed with a gynaecologist).

For Germany: Section 6.2Exclusion criteria about pregnancy and use of contraceptive: Contraception requirements as per: CTFG guideline

Section 7: Treatments: In section regarding trial products, please distinguish between IMPs and non-IMPs otherwise all Trial products are considered as IMPs and must be mentioned in the CTA.

Other: Subject's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth.

For United States: Section 9 Trial assessments and procedures: For eye examinations: Funduscopy/fundusphotography will be performed by the Investigator or a local Ophthalmologist/Optometrist according to local practice

Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Protocol Amendment

no 1

to Protocol, version 2.0 dated 01 February 2019

Trial ID: NN1436-4466

Protocol title: A trial comparing NNC0148-0287 C (insulin 287) versus insulin glargine U100, both in combination with metformin, with or without DPP4 inhibitors and with or without SGLT2 inhibitors, in basal insulin treated subjects with type 2 diabetes mellitus

Trial phase: 2a
Applicable to all countries

Table of Contents "Double click to update Table of Content"

1 Introduction including rationale for the protocol amendment

Allowing few OADs (metformin and DPP4i) in the target population was to aim for a pure and homogeneous population. Current clinical practice however has moved towards increasing the use of other OADs as SGLT2i prior to initiating insulin. We therefore update the protocol to align with clinical practice. With allowing metformin, DPP4i and SGLT2i the protocol will closer reflect the clinical practice while at the same time securing a relatively homogeneous population.

2 Changes

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through.~~

Title, frontpage:

A trial comparing NNC0148-0287 C (insulin 287) versus insulin glargine U100, both in combination with metformin, with or without DPP4 inhibitors *and with or without SGLT2 inhibitors,* in basal insulin treated subjects with type 2 diabetes mellitus

Introduction, Background [3.2]:

sodium-glucose cotransporter 2 inhibitors (SGLT2i)

SGLT2i can be used as second line OADs in combination with Metformin. SGLT2i provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2. For further details, please refer to the EMA Summary of Products Characteristics for the relevant SGLT2i or locally approved Product Information.

Inclusion criteria [6]:

6. Stable daily dose(s) for 90 days prior to the day of screening of any of the following anti-diabetic drug(s) or combination regime(s):
    - Any metformin formulations ≥ 1500 mg or maximum tolerated or effective dose (as documented in subjects medical records).
    - *Free or fixed combination therapy: Metformin as outlined above ± DPP4i ± SGLT2i is allowed:*
        - DPP4i (≥ half of the maximum approved dose according to local label or maximum tolerated or effective dose)
        - *SGLT2i (≥ half of the maximum approved dose according to local label or maximum tolerated or effective dose*

Objectives and endpoints, Primary objective [4.1.1.]:

To compare the effect on glycaemic control of treatment with once weekly insulin 287 using two different switch approaches versus once daily insulin glargine U100 both in combination with metformin ± DPP4i ± *SGLT2i* in basal insulin analogue treated T2DM subjects

Objectives and endpoints, Secondary objective [4.1.2]:
To compare the safety and tolerability of once weekly insulin 287 using 2 different switch approaches versus once daily insulin glargine U100 both in combination with metformin ± DPP4i ± *SGLT2i* in basal insulin analogue treated T2DM subjects

Trial design, overall design [5.1]

Subjects will be randomly allocated to receive once weekly insulin 287 using one of the 2 switch approaches (arm A and B) or once daily insulin glargine U100 (arm C). *The randomisation will be stratified based on pre-trial insulin treatment and based on whether or not subjects are treated with SGLT2i.*

Statistical considerations, statistical analyses [10.3]
In the statistical models baseline value of the endpoint value will be included as a covariate and explanatory factors will be categorized as follows:

- Treatment: switch approach with 100% loading dose, switch approach without loading dose, insulin glargine U100
- Pre-trial insulin treatment: twice daily or insulin glargine U300: *yes or no*
- *SGLT2i use: yes or no*

Statistical considerations, Primary endpoint [10.3.1]
- First, one thousand (1000) copies of the dataset will be generated for time in range.
- Second, for each dataset copy, each assessment and each treatment group, an analysis of variance (ANOVA) model with baseline 'time in target range' as covariate will be fitted to the time in range values for subjects having completed their randomised treatment. The estimated mean, and variances, from the model will be used to impute missing values in the same treatment group.
- *For each of the complete data sets, the primary endpoint will be analysed using an ANOVA model with randomised treatment, pre-trial insulin treatment and SGLT2i use (yes/no) as fixed factors and baseline 'time in target range' as covariate.* The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.

Throughout protocol section 1-10: when mentioning backgound medication ± *SGLT2i* has been added.

END OF AMENDMENT 1

Protocol Amendment

no 2

to Protocol, version 1.0 dated 29 November 2018

Trial ID: NN1436-4466

A trial comparing NNC0148-0287 C (insulin 287) versus insulin glargine U100, both in combination with metformin, with or without DPP4 inhibitors, in basal insulin treated subjects with type 2 diabetes mellitus

Trial phase: 2a
Applicable to Germany

Table of Contents

1 Introduction including rationale for the protocol amendment

This protocol amendment is to update protocol version 1.0, dated 29 November 2018 to implement the objections received from the German Health Authority BfArM.

This protocol is amended for the following reasons:

- Inclusion of further clarification on the observation of hypersensitivity reactions in trial NN1436-4057. Explanation regarding different formulations of insulin 287 used in NN1436-4057 (formulation A) and NN1436-4314 (formulation C). Confirmation that no hypersensitivity reactions have been observed with the current formulation C in trial NN1436-4314.

- Additional information on introduction of event adjudication by an independent adjudication committee of experts for hypersensitivity reactions to ensure standardised and objective assessment.

- Further explanation that the potency of one unit (U) of Insulin 287 corresponds to one unit (U) of Insulin glargine U100, considering the different dosing schemes.

In this protocol amendment:
- Any new text is written *in italics*.
- Any text deleted from the protocol is written using ~~strike through.~~

2 Changes

2.1 Section 3.3.2 Risks

Identified risks for insulin 287 describe undesirable clinical outcomes for which there is sufficient evidence that they are caused by insulin 287. Potential risks in this section describe undesirable clinical outcomes for which there is scientific evidence to suspect the possibility of a causal relationship with insulin 287, but where there is currently insufficient evidence to conclude that this association is causal.[11]

Identified risks

- Hypoglycaemia

Hypoglycaemia is a common undesirable effect related to the pharmacological mechanism of insulin. To mitigate the risk of hypoglycaemia in this trial, blood glucose (BG) measurements will be made throughout the drug exposure period, and will prevent worsening of hypoglycaemia by early detection and administration of carbohydrates and medical treatment, if necessary.

Potential risks

- Injection site reactions

Injection site reactions may occur with all injectable drugs. No injection site reactions were reported in trial NN1436-4314 with insulin 287. However, in this trial investigators and subjects will be asked to pay careful attention to injection site reactions at the place of injection; investigators should ensure careful monitoring and medical evaluation in case of injection site reaction occurrence. For further information on injection site reactions, please refer to Section 9.4.5.

- Hypersensitivity reactions

Severe systemic hypersensitivity reactions may potentially occur following injection of therapeutic proteins. *Multiple doses of once-weekly insulin 287 (previous formulation A) in the dose range of 9–27 nmol/kg were generally well-tolerated by subjects with T2DM in trial NN1436-4057. However, the trial was put on hold due to 3 subjects experiencing hypersensitivity reactions. Trial NN1436 4314 was very similar to trial NN1436-4057, but with an optimised formulation of insulin 287 (formulation C) in subjects with T2DM.* No hypersensitivity reactions were reported in trial NN1436-4314 with insulin 287. During the treatment period in this trial, subjects will have weekly contacts with the site either at visits to the site or with phone contacts. Subjects and investigators will be instructed for signs and symptoms of allergic reactions. ~~and~~ *Subjects will* be instructed to contact the site immediately in case of signs of hypersensitivity. For further information on hypersensitivity reactions, please refer to Section 9.4.5.

- Antibody formation leading to change in clinical effect

An increase in anti-insulin 287 specific antibodies and anti-human insulin antibodies were observed for some subjects in trial NN1436-4314 trial with insulin 287. No hypersensitivity reactions were observed in this trial. Moreover, in trial NN1436-4314 higher antibody levels seemed to be associated with a longer terminal half-life and reduced clearance for insulin 287. In case of a systemic hypersensitivity reaction, blood sampling for assessment of antibodies against insulin 287 will be conducted. For more information, please refer to Section 9.4.5.

- Increase in hepatic enzymes

Transient increases in hepatic enzymes upon initiation of s.c. insulin are considered as potential risks due to the pharmacological mechanism of insulin. An increase in hepatic enzyme was observed in nonclinical studies in rats and dogs. No clinically significant changes in hepatic biomarkers have been observed in humans following the administration of insulin 287. In this trial, measurements of hepatic biomarkers will be performed at frequent intervals.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of insulin 287 may be found in the investigator's brochure and any updates hereof.

2.2 Section 3.3.3 Conclusion on the benefit risk profile

Based on the non-clinical and clinical development programme, it has been concluded that insulin 287 is similar to human insulin with respect to pharmacological action and non-clinical safety.

Hypersensitivity reactions were observed with a previous formulation A (see Investigator's Brochure for insulin 287[12]), which was subsequently optimised to the current formulation C. No hypersensitivity reactions have been observed with the current formulation C in the concluded trial NN1436-4314.

Event adjudication for hypersensitivity reactions (local reactions, including injection site reactions and systemic reactions, including anaphylaxis) is introduced in the present trial to ensure standardised and objective assessment by an independent adjudication committee of experts within the specialty.

Insulin 287 was generally well tolerated within the evaluated dose ranges in the first-in-human, single dose escalation trial *(NN1436-3955, previous formulation A)*, conducted in healthy subjects and in subjects with T1DM ~~and~~ *as well as* in the multiple dose trial in subjects with T2DM *using formulation C (NN1436-4314).*

~~No safety concerns have been observed with insulin 287;~~ Neither elevation in hepatic enzymes nor clinical consequences following antibody formation have been reported *with insulin 287*. With insulin 287 *formulation C*, no hypersensitivity reactions and injection site reactions were observed *in the completed trial*. To mitigate the risk of hypoglycaemia in this trial, frequent blood glucose measurements will be made throughout drug exposure. Therefore, it can be concluded that the risk to the subjects in this trial is considered low. The risk is acceptable in view of the benefits a basal insulin with a longer action profile than currently available would provide to subjects with diabetes. The overall benefit-risk profile of insulin 287 is anticipated to be favourable.

2.3 Section 5.5 Justification for dose

Insulin glargine U100 will be initiated at the same dose as the pre-trial basal insulin and insulin 287 will be initiated at 7 times the pre-trial basal insulin dose.

One unit (U) of Insulin 287 has similar glucose lowering effect as one U of insulin glargine U100, and therefore once-weekly dosing corresponds to 7 times the daily dose of the once daily comparator. *The assumption of equipotency is supported by results from trial NN1436-4314: in the period 24–48 hours after dosing, i.e. around the time for maximum glucose-lowering effect, the relative bio-efficacy of insulin 287 compared to OD insulin degludec was 109% [81; 146], and in the last 24 hours of the weekly dosing interval it was 93% [63; 136]. The potency of insulin degludec and insulin glargine (U100) has previously shown to be comparable.[30]*

The PK/PD properties of Insulin 287 following 5 weeks of once weekly dosing in subjects with T2DM (trial NN1436-4314) showed that insulin 287 exposure was well distributed across the dosing interval, with a PK profile suitable for once weekly dosing. Insulin 287 was well tolerated in subjects with T2DM and no safety concerns were identified after multiple once-weekly dosing in the dose range of 12−24 nmol/kg (2-4 U/Kg).

For subjects randomised to insulin 287 100% loading dose arm: It takes 3-5 doses before reaching the full effect of insulin 287. Theoretically subjects may therefore need additional insulin to maintain glycaemic control the first weeks after initiation. Modelling data suggest that adding a 100% loading dose may prevent deterioration of the glycaemic control during the first weeks of treatment without jeopardising safety. Therefore the approach of 100% loading dose has been chosen; hence no additional insulin is permitted after V2.

To reduce the risk of subjects experiencing hypoglycaemia in the initial treatment phase subjects switching from a twice daily basal insulin regiment and a once daily regimen with insulin glargine U300 will have their dose reduced by 20%. This is applicable for all treatment arms.

After randomisation at V2, subjects will start once daily and once-weekly injections on the same day. This treatment will continue until 15 weeks after randomisation. At this time point the last once weekly injection must be taken while the once daily injections are taken until 16 weeks after randomisation where the subjects come in for the end of treatment visit (V18). This is due to the longer half-life of insulin 287.

Further details on dose adjustment can be found in Appendix 9, titration guideline

2.4 Section 11 References

11. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 1) (EMA/838713/2011 Rev 1). 15 Apr 2014.

12. Novo Nordisk A/S. Investigator's Brochure, NNC0148-0287 (Insulin 287), NN1436(T2D), (edition 5), or any updates hereof. 2018.

30. Novo Nordisk A/S. Tresiba ® (insulin degludec), EU Summary of Product Characteristics (SmPC). Feb 2018.

~~CONFIDENTIAL~~

Memo

To:
[redacted]287 (NN1236-4466) TMFs in ITALY

From: [redacted]

02 September 2019

Protocol amendment no. 1 (Protocol, version 2.0 dated 01 February 2019) not submitted in Italy

This MEMO is to document that, for trial NN1436-4466, only Protocol version 1.0 dated 29 Nov 2018 was submitted, approved and currently used in Italy.

Protocol amendment no. 1 (Protocol, version 2.0 dated 01 February 2019 and all the updated related documents) was not submitted in Italy.
Substantial change of Protocol amendment no. 1 was to reflect the updated inclusion criteria allowing patient in treatment with SGLT2 as second line OAD prior to insulin treatment to be enrolled in the trial.

Due to local approval timelines and trial recruitment timelines, it was evaluated to not submit the protocol amendment, since all the regulatory approvals were not expected to be obtained before the planned date of global LPFV. In addition, in agreement with the clinical practice in Italy, protocol amendment has no impact on the Country recruitment.

At trial level, it was decided to not create a country specific version based on Protocol version 1.0 dated 29 Nov 2018 of the below trial systems.
The following trial systems based on Protocol version 2.0 dated 01 Feb 2019 are currently used in all the Italian sites too:
- EDC: Annotated Study Book for Study Design: NN1436-4466 Study Design Version: 1.4
- IWRS: Version: 2.0 Version date: 01APR2019

Italian sites have been informed on the major differences of the systems compared with the approved version of protocol.

Novo Nordisk S.p.A. [redacted] Telephone: [redacted] E-mail: [redacted] Fax: [redacted]

~~CONFIDENTIAL~~

Memo

To:
NN1436-4466 ISG

From: [redacted]

27-FEB-2019

NN1436-4466: Notification of error in document for Amendment 1, version 1.0 to Protocol 1.0

Please note the following document incorrectly identifies the protocol version corrected during Amendment 1 to Protocol Version 1.0 for NN1436-4466.

Document Name	NovoDocs Document ID	NovoDocs Object ID	Dated
4466-protocol-amendment-1-global	[redacted]	[redacted]	01-FEBRUARY-2019

In the above document, the title page (page 1) in error references 'Protocol Amendment no 1 to Protocol, version **2.0** dated 01 February 2019'. This is incorrect and should state ''Protocol Amendment no 1 to Protocol, version **1.0** dated **29 November 2018**" because Amendment no 1 was performed on Protocol version **1.0**.

Also, the protocol title listed on the title page is currently referring to protocol version 2.0 named "A trial comparing NNC0148-0287 C (insulin 287) versus insulin glargine U100, both in combination with metformin, with or without DPP4 inhibitors **and with or without SGLT2 inhibitors,** in basal insulin treated subjects with type 2 diabetes mellitus". The title should refer to the title of protocol version 1.0 named "A trial comparing NNC0148-0287 C (insulin 287) versus insulin glargine U100, both in combination with metformin, with or without DPP4 inhibitors, in basal insulin treated subjects with type 2 diabetes mellitus".

Please file this memo locally and notify relevant local authorities and ethics committees according to local procedures.

Thank you,

[redacted]
NN1436-4466

Novo Nordisk A/S [redacted] Telephone: [redacted] E-mail: [redacted]
Internet: www.novonordisk.com
CVR Number: [redacted]