Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03751657
Sponsor trial ID:	NN1436-4383
Official title of study:	An investigational trial comparing the efficacy and safety of once weekly NNC0148-0287 C (insulin 287) versus once daily insulin glargine, both in combination with metformin, with or without DPP-4 inhibitors, in insulin naïve subjects with type 2 diabetes mellitus
Document date:	29 May 2020

16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

.

Protocol

Protocol title: An investigational trial comparing the efficacy and safety of once weekly NNC0148-0287 C (insulin 287) versus once daily insulin glargine, both in combination with metformin, with or without DPP-4 inhibitors, in insulin naïve subjects with type 2 diabetes mellitus

Substance: NNC0148-0287 C (insulin 287)

Universal Trial Number: U1111-1208-4124

EUdraCT Number:2018-000322-63

Trial phase: 2

Table of Contents

1 Synopsis

Rationale:

NNC0148-0287 formulation C (referred to as insulin 287) may provide an efficacious, safe and convenient once weekly alternative to once daily basal insulin, which could improve treatment adherence and quality of life for subjects with type 2 diabetes mellitus.

The purpose of the present randomised, treat-to-target trial is to investigate efficacy and safety of once-weekly insulin 287 versus once-daily insulin glargine, both in combination with metformin with or without dipeptidyl peptidase-4 inhibitors, for 26 weeks in subjects with type 2 diabetes insufficiently controlled on metformin ±dipeptidyl peptidase-4 inhibitors. Glycated haemoglobin (HbA_{1c}) will be included as the primary endpoint since it is considered the most widely accepted measure of overall, long-term glucose control by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) guidance documents.

Objectives and endpoints

Primary objective
To investigate the effect on glycaemic control after 26 weeks treatment of once weekly insulin 287 versus once daily insulin glargine both in combination with metformin with or without dipeptidyl peptidase-4 inhibitors in insulin-naïve type 2 diabetes mellitus subjects inadequately treated with metformin with or without dipeptidyl peptidase-4 inhibitors.

Secondary objective
To investigate the safety and tolerability during 26 weeks of treatment with once weekly insulin 287 versus once daily insulin glargine both in combination with metformin with or without dipeptidyl peptidase-4 inhibitors in insulin-naïve subjects with type 2 diabetes mellitus inadequately treated with metformin with or without dipeptidyl peptidase-4 inhibitors.

Primary endpoint
Change from baseline (visit 2, week 0) to week 26 (visit 28) in HbA_{1c} (%-point and [mmol/mol])

Estimand
The primary estimand is defined as the treatment difference in change of HbA_{1c} from baseline to week 26 between once weekly insulin 287 and once daily insulin glargine for all randomised subjects, if all subjects had adhered to treatment and did not receive ancillary treatment.
This is a 'hypothetical' estimand aiming to reflect the treatment effect for subjects that are actually able to take the drug during the intended treatment period.

Overall design:

This is a 26-week, randomised, double-blind, double-dummy, active-controlled, parallel-group, stratified, multicentre, multinational trial with 2 arms comparing the efficacy and safety of

treatment with insulin 287 once weekly versus insulin glargine once daily in insulin-naive subjects with type 2 diabetes mellitus inadequately controlled on metformin with or without dipeptidyl peptidase-4 inhibitors.

Subjects will be randomised in a 1:1 manner to receive once weekly insulin 287 and once daily placebo or once weekly placebo and once daily insulin glargine. The randomisation of subjects will be stratified based on use of dipeptidyl peptidase-4 inhibitors.

Key inclusion criteria:

- Male or female, aged 18-75 years (both inclusive) at the time of signing informed consent.
- Diagnosed with type 2 diabetes mellitus ≥ 180 days prior to the day of screening.
- HbA_{1c} of 7.0-9.5% (53-80 mmol/mol) (both inclusive) as assessed by central laboratory.
- 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):
  a) Any metformin formulations ≥ 1500 mg or maximum tolerated or effective dose (as documented in subject's medical record)
  b) Any metformin formulations ≥ 1500 mg or maximum tolerated or effective dose (as documented in subject medical record) with DPP4i (≥ half of the maximum approved dose according to local label or maximum tolerated or effective dose (as documented in subject's medical records)
- Insulin naïve. However, short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed, as is prior insulin treatment for gestational diabetes.
- Body mass index (BMI) ≤ 40.0 kg/m^2

Key exclusion criteria:

- Any episodes of diabetic ketoacidosis within the past 90 days prior to the day of screening and between screening and randomisation.
- 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.
- Presently classified as being in New York Heart Association (NYHA) Class IV.
- 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. However, short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed, as is prior insulin treatment for gestational diabetes.
- Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).

- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a pharmacologically pupil-dilated fundus examination performed by an ophthalmologist or another suitably qualified health care provider within the past 90 days prior to screening or in the period between screening and randomisation.

Randomisation criterion:

- Subject able and willing to adhere to the protocol including self-administered daily injections using vial and syringe based on the Investigator's judgment.

Number of subjects:

- Number of subjects planned to be randomised: 250 subjects
- Estimated number of subjects to complete the trial (on trial product): 215.

Treatment groups and duration:

The total trial duration for the individual subject will be approximately 33 weeks. The trial includes a 2 week screening period, followed by a 26-week randomised treatment period and a 5-week follow-up period.

Trial products:

Investigational medical products:

- Test product:
  - NNC0148-0287 C 4200 nmol/mL in a 3 mL PDS290 pre-filled pen-injector with for subcutaneous injection
- Reference therapies:
  - Insulin glargine 100U/ml, 10 ml vials for subcutaneous injection
  - NNC0148-0287 C and insulin glargine placebo (double dummy trial)

2 Flowchart

Trial Periods	Screening	Randomisation	Treatment																			End of treatment[1]	Follow up		Discontinuation phone contacts (Px)	Discontinuation follow-up
Visit (V) **Phone contact (P)**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11**	**V12**	**P13**	**V14**	**P15** **P16** **P17**	**V18**	**P19** **P20** **P21**	**V22**	**P23** **P24** **P25**	**V26**	**V27**	**V28**	**V29** **FU1**	**V30** **FU2**	**Every 4 weeks**	**V28A**
Time of visit (weeks)[2]	≤-2	0	1	2	3	4	5	6	7	8	9	10	11	12	13 14 15	16	17 18 19	20	21 22 23	24	25	26	28	31		26
Visit window (days)			±1	±1	±1	±1	±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 criterion		X																								
Concomitant illness/ medical history	X																									
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[3]	X[3]	X[3]	X[3]
Demography[4]	X																									
Diabetes history/Diabetes complications	X																									
Date of Diagnosis of Diabetes	X																									
Childbearing potential	X																									
Tobacco use [5]	X																									
Body measurements																										
Height	X																									

[1] If subjects are discontinuing trial product prematurely they will be asked to attend the end of treatment visit (V28) as soon as possible and the follow up visits (V29 and V30) must be scheduled 2 and 5 weeks after discontinuation of trial product. After the follow-up period, the subjects discontinuing trial product prematurely should have phone contacts (Px) scheduled every 4 weeks until the discontinuation follow-up visit (28A) performed at week 26.
[2] Time of visit is relative to randomisation (V2).
[3] Only antidiabetic medication to be collected
[4] Demography consists of date of birth or year of birth and/or age, sex, ethnicity and race (according to local regulation).
[5] Smoking is defined as smoking at least one cigarette or equivalent daily.

Trial Periods	Screening	Randomisation	Treatment																			End of treatment[1]	Follow up		Discontinuation phone contacts (Px)	Discontinuation follow-up
Visit (V) **Phone contact (P)**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11**	**V12**	**P13**	**V14**	**P15** **P16** **P17**	**V18**	**P19** **P20** **P21**	**V22**	**P23** **P24** **P25**	**V26**	**P27**	**V28**	**V29** **FU1**	**V30** **FU2**	**Every 4 weeks**	**V28A**
Time of visit (weeks)[2]	≤-2	0	1	2	3	4	5	6	7	8	9	10	11	12	13 14 15	16	17 18 19	20	21 22 23	24	25	26	28	31		26
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	+3	+3		±3
Body weight[6]	X	X												X								X				X
EFFICACY																										
Glucose metabolism																										
HbA_{1c}	X	X				X				X				X		X		X				X				X
Fasting plasma glucose		X												X								X				
Fasting C-peptide		X												X								X				
Self-measured plasma glucose (SMPG)[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
9-point profile[8]		X												X								X				
PK sampling				X				X						X		X		X				X		X		
OTHER ASSESSMENTS																										
Flash glucose monitoring, fitting		X		X		X														X		X				
Flash glucose monitoring, removal and upload				X		X		X														X	X			
SAFETY																										
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Technical complaints		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
ECG[9]	X																					X				

[6] Body weight should be measured fasting except for V1 and V28A.
[7] Subjects will measure once daily pre-breakfast SMPG.
[8] The 9-point profile must be performed in the week prior to visits, on a day where the subject does not anticipate unusual strenuous exercise
[9] ECG obtained within 2 weeks prior to V2 and V28 are acceptable if results are available for evaluation at the visits.

Trial Periods	Screening	Randomisation	Treatment																			End of treatment[1]	Follow up		Discontinuation phone contacts (Px)	Discontinuation follow-up
Visit (V) **Phone contact (P)**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11**	**V12**	**P13**	**V14**	**P15** **P16** **P17**	**V18**	**P19** **P20** **P21**	**V22**	**P23** **P24** **P25**	**V26**	**V27**	**V28**	**V29** **FU1**	**V30** **FU2**	**Every 4 weeks**	**V28A**
Time of visit (weeks)[2]	≤-2	0	1	2	3	4	5	6	7	8	9	10	11	12	13 14 15	16	17 18 19	20	21 22 23	24	25	26	28	31		26
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	+3	+3		±3
Eye Examination	X[10]																					X[11]				
Physical Examination	X																					X				
Vital signs	X	X												X								X				
Biochemistry	X	X				X				X				X		X		X				X				
Lipids		X												X								X				
Free Fatty Acids		X												X								X				
Haematology	X	X												X								X				
Pregnancy test[12]	X	X																						X		
Antibodies		X		X				X								X						X		X		
	TRIAL MATERIAL																									
Drug accountability		X				X				X				X		X		X				X				
Dispensing visit		X				X				X				X		X		X								
Dose of trial insulin[13]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[14]	X				
	REMINDERS																									
Handout ID card	X																									
Attend visit fasting		X												X								X				

[10] 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.
[11] Eye examinations performed within 2 weeks prior to V28 are acceptable if results are available for evaluation at the visit. For treatment-discontinued subjects, eye examination can be performed up to 2 weeks after V28.
[12] For females of childbearing potential a serum pregnancy test must be performed at V1 and V30. At V2 and if a menstrual period is missed, a urine pregnancy test will be taken.
[13] The first 5 doses of once-weekly insulin 287 or once-weekly placebo will be taken at the site (V2 to V6).
[14] The last dose of once weekly insulin/placebo must be taken 25 weeks after randomisation, whereas the last dose of the once daily insulin/placebo must be taken 26 weeks after randomisation where the subjects come in for the end of treatment visit (V28). This is due to the longer half life of Insulin 287.

Trial Periods	Screening	Randomisation	Treatment																			End of treatment[1]	Follow up		Discontinuation phone contacts (Px)	Discontinuation follow-up
Visit (V) **Phone contact (P)**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**P7**	**V8**	**P9**	**V10**	**P11**	**V12**	**P13**	**V14**	**P15** **P16** **P17**	**V18**	**P19** **P20** **P21**	**V22**	**P23** **P24** **P25**	**V26**	**P27**	**V28**	**V29** **FU1**	**V30** **FU2**	**Every** **4** **weeks**	**V28A**
Time of visit (weeks)[2]	≤-2	0	1	2	3	4	5	6	7	8	9	10	11	12	13 14 15	16	17 18 19	20	21 22 23	24	25	26	28	31		26
Visit window (days)			±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	+3	+3		±3
Hand out direction for use[15]		X																								
Training in trial product handling and titration	X[16]	X[17]	X	X	X	X		X		X		X		X		X		X		X						
Hand out and instruct in BG meter	X																									
IWRS session	X	X				X				X				X		X		X				X				
Hand out and instruct in diary	X	X	X	X	X	X		X		X		X		X		X		X		X		X	X			
Collect and review diary		X	X	X	X	X		X		X		X		X		X		X		X		X	X	X		
End treatment																						X				
End of trial																								X[18]		X

[15] Directions for use can be handed out as needed at subsequent visits.
[16] Subjects must be trained in the use of vial and syringe at V1, by having the subjects inject themselves with saline solution at site. If deemed necessary by the investigator, it could be considered to have the subjects inject themselves with saline solution at home between V1 and V2. At V2 the ability to self-administer daily injections will have to be assessed prior to randomisation.
[17] Subjects must be trained in handling of the PDS290 pre-filled pen-injector at V2.
[18] Not applicable for subjects discontinuing trial product prematurely, these will have "end of trial" at V28A.

3 Introduction

3.1 Trial rationale

NNC0148-0287 formulation C (referred to as insulin 287) is a novel long-acting insulin analogue which is designed for subcutaneous (s.c.) administration with the aim to develop a once weekly injectable basal insulin treatment. Currently the basal insulin products with the longest duration are administered once daily.

Research has shown that people with diabetes would prefer fewer injections and increased flexibility than provided by the current once-daily treatment regimen.[1] Development of sustained release formulations or compounds with prolonged action has in several treatment areas been demonstrated to improve subject compliance and treatment outcomes. Hence, insulin 287 would be a convenient basal insulin which could improve treatment adherence and quality of life for subjects with type 2 diabetes mellitus (T2DM).

The present randomised, treat-to-target trial will investigate efficacy and safety of once-weekly insulin 287 (formulation C) versus once-daily insulin glargine (IGlar), both in combination with metformin with or without dipeptidyl peptidase-4 inhibitors (DPP4i), for 26 weeks in subjects with type 2 diabetes insufficiently controlled on metformin ±DPP4i . HbA_{1c} will be included as the primary endpoint since it is considered the most widely accepted measure of overall, long-term glucose control by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) guidance documents.[2, 3]

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 premeal glucose target of 80–130 mg/dL (4.4–7.2 mmol/L) to achieve glycaemic control.[4] 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.[2] Despite combination therapy and/or insulin treatment, a sizeable proportion of subjects remain poorly controlled.[2]

Improvement in long-term glucose control, as obtained with intensified insulin therapy, was shown in the UK Prospective Diabetes Study (UKPDS)[5] 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 (OADs), drug intensification, including insulin therapy, should not be delayed.[6]

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 and two multiple-dose trials in subjects with type 2 diabetes have been completed. The pharmacokinetics (PK) properties of subcutaneous insulin 287 (formulation C) 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 pharmacodynamics (PD) properties of s.c. insulin 287 (formulation C), 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 type 2 diabetes. No safety concerns were identified after multiple once-weekly dosing in the dose range of 12−24 nmol/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.[7]

Insulin glargine

Insulin glargine 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 is a widely used basal insulin world-wide and has therefore been selected as comparator in the current trial. For further details, please refer to the EMA Summary of Product Characteristics for insulin glargine (Lantus®)[8], U.S. Label Information[9] and manufactures label.

Metformin

Together with life style interventions metformin is considered a first-line antidiabetic therapy in subjects with T2DM.[6] 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[10] or locally approved Product Information.

Dipeptidyl peptidase 4 inhibitors

Dipeptidyl peptidase 4 inhibitors (DPP4i) can be used as second line OADs in combination with Metformin[11]. DPP4i prevent the hydrolysis of incretin hormones, thereby increasing plasma concentrations of the active forms of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). 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 (FHD) and multiple dose (MD) 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.[12] 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 insulin naïve subjects with type 2 diabetes insufficiently controlled on metformin ±DPP4i. For all subjects participating in this 26 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 LAI 287 describe undesirable clinical outcomes for which there is sufficient evidence that they are caused by LAI287. Potential risks in this section describe undesirable clinical outcomes for which there is scientific evidence to suspect the possibility of a causal relationship with LAI287, but where there is currently insufficient evidence to conclude that this association is causal.[13]

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, frequent blood glucose (BG) measurements will be made throughout drug exposure, 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 formulation C of 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 9.4.6.1.

- **Hypersensitivity reactions**

  Severe systemic hypersensitivity reactions may potentially occur following injection of therapeutic proteins. No hypersensitivity reactions were reported in trial NN1436-4314 with optimised formulation C. 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 9.4.6.1.

- **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 optimised formulation C. 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 this trial blood samples will be analysed for serum antibodies against insulin 287 at pre-dose time points and at the follow-up visit. 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 9.4.6.1.

- **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.[7]

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 type 1 diabetes and in the multiple dose trial in subjects with type 2 diabetes mellitus. No safety concerns have been observed with LAI287 formulation C; neither elevation in hepatic enzymes nor clinical consequences following antibody formation have been reported. With formulation C, 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 improved with the optimised formulation C and is anticipated to be favourable.[7]

4 Objectives and endpoints

4.1 Primary, secondary and exploratory objectives

4.1.1 Primary objective

To investigate the effect on glycaemic control after 26 weeks treatment of once weekly insulin 287 versus once daily IGlar both in combination with metformin with or without DPP4i in insulin-naïve T2DM subjects inadequately treated with metformin with or without DPP4i.

4.1.2 Secondary objective

To investigate the safety and tolerability during 26 weeks of treatment with once weekly insulin 287 versus once daily IGlar both in combination with metformin with or without DPP4i in insulin-naïve subjects with T2DM inadequately treated with metformin with or without DPP4i.

4.1.3 Exploratory objectives

- To investigate the pharmacokinetics (PK) of insulin 287 using population PK during 26 weeks of treatment in insulin naïve subjects with T2DM inadequately treated with metformin with or without DPP4i
- To investigate the effect on glycaemic control (using [redacted] FreeStyle Libre Pro) of insulin 287 and IGlar during 26 weeks of treatment in insulin naïve subjects with T2DM inadequately treated with metformin with or without DPP4i

4.2 Primary estimand

The primary estimand is defined as the treatment difference in change of HbA_{1c} from baseline to week 26 between once weekly insulin 287 and once daily IGlar for all randomised subjects, if all subjects had adhered to treatment and did not receive ancillary treatment.

This is a 'hypothetical' estimand aiming to reflect the treatment effect for subjects that are actually able to take the drug during the intended treatment period.

4.2.1 Secondary estimand

The secondary estimand is defined as the treatment difference in change of HbA_{1c} from baseline to week 26 between once weekly insulin 287 and once daily IGlar for all randomised subjects, regardless of the treatment actually received.

This estimand aims to reflect the treatment effect for all subjects regardless of treatment adherence, i.e., a 'treatment policy' estimand.

4.3 Primary, secondary and exploratory endpoints

4.3.1 Primary endpoint

Endpoint title	Time Frame	Unit
Change in HbA_{1c}	From baseline (V2) to week 26 (V28)	%-point and [mmol/mol]

4.3.2 Secondary endpoints

4.3.2.1 Confirmatory endpoints

Not applicable for this trial.

4.3.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

Endpoint title	Time Frame	Unit
Change in fasting plasma glucose	From baseline (V2) to week 26 (V28)	[mmol/l]
9-point profile (individual SMPG values)	Week 26 (V28)	[mmol/l]
Change in mean of the 9-point profile, defined as the area	From baseline (V2) to week 26 (V28)	[mmol/l]

under the profile		
Fluctuations of the 9-point profile (defined as the integrated absolute distance from the mean profile value divided by measurement time)	Week 26 (V28)	[mmol/l]
Change in fasting C-peptide	From baseline (V2) to week 26 (V28)	[mmol/l]
Change in body weight	From baseline (V2) to week 26 (V28)	Kilogram
Weekly dose of insulin 287 and weekly dose of IGlar	Week 24-26 (V26-V28)	U

Supportive secondary safety endpoints

Endpoint title	**Time Frame**	**Unit**
Number of treatment emergent adverse events (TEAEs)	From baseline (V2) to week 31 (V30)	Number 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 (V2) to week 26 (V28)	Number 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 (V2) to week 26 (V28)	Number of events
Number of severe hypoglycaemic episodes (level 3)	From baseline (V2) to week 26 (V28)	Number of events
Change in anti-insulin 287 antibodies level	From baseline (V2) to week 31 (V30)	%B/T*
Change in anti-insulin 287 antibody titres	From baseline (V2) to week 31 (V30)	No unit
Change in cross-reactive anti-human insulin antibody status	From baseline (V2) to week 31 (V30)	Positive/negative for cross-reactivity

(positive/negative)		

* %B/T is % bound radioactivity-labelled insulin 287/Total added radioactivity-labelled insulin 287.

4.3.3 Exploratory endpoints

Endpoint title	Time Frame	Unit
Insulin 287 concentrations, evaluated in a population PK analysis	From baseline (V2) to week 26 (V28)	pmol/L
Time in target-range 3.9–7.8 mmol/L (70-140 mg/dL) measured by flash glucose monitoring (FGM) (FreeStyle Libre Pro)	During the last 2 weeks of treatment (week 25 and 26)	Time unit

5 Trial design

5.1 Overall design

This is a 26-week, randomised, double-blind, double-dummy, active-controlled, parallel-group, stratified, multicentre, multinational trial with 2 arms comparing the efficacy and safety of treatment with insulin 287 once weekly versus insulin glargine once daily in insulin-naive subjects with T2DM inadequately controlled on metformin with or without DPP4i.

Subjects will be randomised in a 1:1 manner to receive once weekly insulin 287 and once daily placebo or once weekly placebo and once daily insulin glargine. The randomisation of subjects will be stratified based on use of DPP4i.

The total trial duration for the individual subject will be approximately 33 weeks. The trial includes a 2 week screening period, followed by a 26-week randomised treatment period and a 5-week follow-up period.

After screening, all eligible subjects will be randomised (1:1) to insulin 287 or insulin glargine at the randomisation visit (V2). During the 26-week treatment period, the subjects will have weekly contact with the site either at site visits or by phone.

After 26 weeks of treatment the subjects will come in for their end-of-treatment visit. The end of-treatment visit will be one week after the last dose of once weekly insulin/once weekly placebo and on the day of or the day after the last dose of once daily insulin/once daily placebo.

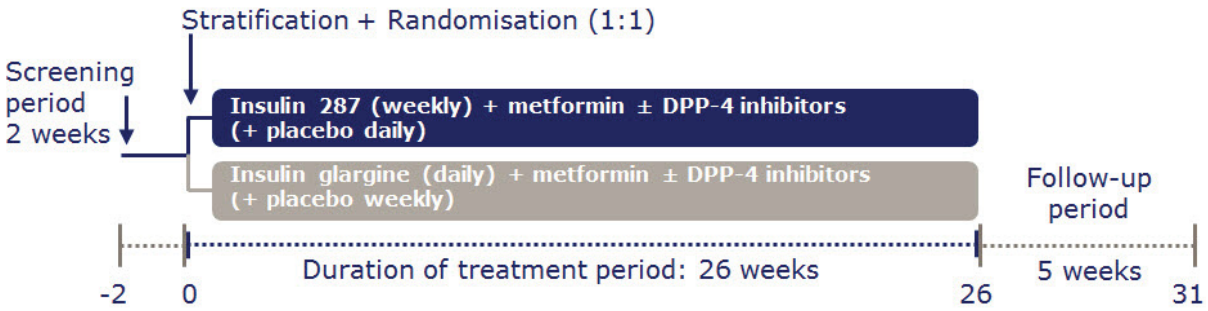
The end of-treatment visit will be followed by two follow up visits (V29 and V30). The last follow up visit (V30) is scheduled to take place 6 weeks after the last dose of once weekly insulin/once weekly placebo and 5 weeks after the last dose of once daily insulin/once daily placebo.

The dose and dosing frequency of metformin with or without DPP4i should not be changed at any time during the trial, unless due to safety concerns.

Event adjudication will be performed for major adverse cardiovascular events (MACE) and hypersensitivity reactions (see section 9.2.1.1).

The overall trial design and visit schedule are outlined in the trial diagram Figure 5-1 and trial flowchart (section 2) respectively.

Figure 5-1 Trial Design



5.2 Subject and trial completion

250 subjects will be randomly assigned to trial product. The estimated number of subjects to complete the trial (on trial product) is 215.

Trial period completion for a subject:

Trial period completion is defined as when the randomised subject has completed the final scheduled visit V30, (‘end of trial' according to the flowchart, section 2).
'Date of trial completion' is the date the subject completed the final scheduled visit (V30).

Treatment period completion for a subject:

Treatment period completion is defined as when the randomised subject has received the required treatment, and attended the 'end of treatment' visit (V28) according to the flowchart, section 2

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 Treatment emergent period

The treatment emergent period represents the period where subjects are considered exposed to trial product. It starts at the first date of exposure to randomised treatment and ends at the last follow-up visit (FU2), thus includes a time period after last dose of randomised treatment corresponding to approximately 5 half-lives of insulin 287. Specifically, it ends at one of the following:

- For subjects completing the trial: Last follow-up visit (FU2)
- For subjects who discontinue: Last follow-up visit (FU2) as defined in section 8.1
- For subjects who discontinue, but do not attend FU2 visit: Last dosing day of randomised treatment + 5 weeks for glargine, and last dosing day of randomised treatment + 6 weeks for insulin 287

5.5 Scientific rationale for trial design

The trial is designed to investigate the effect on glycaemic control, safety and tolerability between a once-weekly insulin and a once-daily insulin, while minimising bias of the results. 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 has been chosen as comparator. The treatment arms will be blinded to increase the scientific value of the results as compared to an open design, thus avoiding bias from investigators and subjects. To ensure blinding between the two treatments with different duration of action and dosing frequency, a double-dummy approach is applied. The treatment duration of 26 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 as well as a sufficient maintenance period. The first 16 weeks will be defined as the titration period and the following 10 weeks until end-of-treatment as the maintenance period. 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 be insulin naïve, but all will use first line treatment metformin. Use of DPP4i in addition to metformin is allowed but not a requirement. Subjects will be stratified on use of DPP4i to ensure an equal distribution of subjects in both treatment arms. To include a more homogenous study population, other oral antidiabetic drugs are not allowed.

Titration of insulin 287 and IGlar are based on three pre-breakfast SMPG values measured on two days prior to titration and on the day of the contact.

Furthermore, to collect data to characterise the effect of insulin 287, FGM data will be collected during the trial.

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 type 2 diabetes 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, safety and the PK properties of once-weekly insulin 287.

Furthermore, during the treatment period, the subjects will have weekly contacts with the site either at visits to the site or phone contacts and the first 5 administrations of once-weekly insulin 287 or once-weekly placebo will be done at the site. After the injections at the site, the subjects should stay at least one hour for observation. The last follow-up visit is planned to be 6 weeks after last once-weekly insulin/once-weekly placebo dose 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. Some 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 with reference to premature discontinuation criteria, section 8.1

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[7] and local label for insulin glargine. Relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation in the trial. These precautions include thorough information regarding the correct administration of the trial products and gradual dose adjustment. 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. The double-dummy study design introduces a potential risk of mix-up between treatments. To minimise this risk, injections of the weekly insulin 287/insulin 287 placebo will be performed at the site during the first month while the once daily injections are performed by the subjects at home. To further mitigate the risk, instructions will be given to consistently use the same thigh for injection, left for the once weekly injection and right for the once daily injection throughout the study period.

5.6 Justification for dose

Insulin glargine will be initiated at 10 units (U) once daily and insulin 287 will be initiated at 70U once weekly. One U of insulin 287 has similar glucose lowering effect as one U of a standard insulin analogue, such as insulin glargine, and therefore once-weekly dosing corresponds to 7 times the daily dose of the once daily comparator. Starting dose is based on insulin glargine label.

The starting dose is considered to be safe and conservative for insulin naïve subjects with type 2 diabetes. The PK/PD properties of insulin 287 following 5 weeks of once weekly dosing in subjects

with type 2 diabetes (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 type 2 diabetes and no safety concerns were identified after multiple once-weekly dosing in the dose range of 12−24 nmol/kg.

After randomisation at V2, subjects will start once daily and once-weekly injections on the same day. This treatment will continue until 25 weeks after randomisation. At this time point the last once weekly injection must be taken while the once daily injections are taken until 26 weeks after randomisation where the subjects come in for the end of treatment visit (V28). This is due to the longer half-life of Insulin 287. Further details 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

Subjects are eligible to be included in the trial only if all of the following criteria apply:

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 7.0-9.5% (53-80 mmol/mol) (both inclusive) as assessed by central laboratory.
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):
    (a) Any metformin formulations ≥ 1500 mg or maximum tolerated or effective dose (as documented in subject's medical record)
    (b) Any metformin formulations ≥ 1500 mg or maximum tolerated or effective dose (as documented in subject medical record) with DPP4i (≥ half of the maximum approved dose according to local label or maximum tolerated or effective dose (as documented in subject's medical records)
6. Insulin naïve. However, short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed, as is prior insulin treatment for gestational diabetes.
7. Body mass index (BMI) ≤ 40.0 kg/m^2

6.2 Exclusion criteria

Subjects are excluded from the trial if any of the following criteria apply:

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 adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).
   For Czech Republic and Greece, please see Appendix 10 for country specific requirements.
4. Receipt of any investigational medicinal product within 90 days prior to the day of 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. 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.
8. Presently classified as being in New York Heart Association (NYHA) Class IV.
9. Planned coronary, carotid or peripheral artery revascularisation.
10. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR <60 ml/min/1.73 m2 as defined by KDIGO 2012 using the CKD-Epi for eGFR calculation*
11. Impaired liver function, defined as Alanine Aminotransferase (ALT) ≥ 2.5 times or Bilirubin >1.5 times upper normal limit at screening*
12. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic ≥180 mmHg or diastolic ≥110 mmHg) at screening.
13. 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. However, short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed, as is prior insulin treatment for gestational diabetes.
14. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).
15. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a pharmacologically pupil-dilated fundus examination performed by an ophthalmologist or another suitably qualified health care provider within the past 90 days prior to screening or in the period between screening and randomisation.
16. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed.

*Result from the screening visit as provided by the central lab.

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 (if applicable) have been performed. Any other prescribed medication should be taken as usual. If the subject attends a fasting visit in a non-fasting state the blood sampling and body weight procedures should be re-scheduled 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 and/or randomisation 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 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".

1) Subject able and willing to adhere to the protocol including self-administered daily injections using vial and syringe based on the Investigator's judgment.

7 Treatments

7.1 Treatments administered

- All investigational medical products (IMPs) are listed in table Table 7-1
- Trial product must only be used, if it appears clear and colourless.
- Trial products must not be dispensed to any person not included in the trial

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

Trial product name:	NNC0148-0287 C 4200 nmol/mL or placebo (IMP, test product or double dummy)	Insulin glargine 100 U/mL or placebo (IMP reference therapy or double dummy)

Dosage form:	Solution for injection	Solution for injection
Route of administration:	Subcutaneously into the **left thigh.** Rotation of injection site on the left thigh is recommended	Subcutaneously into the **right thigh**. Rotation of injection site on the right thigh is recommended.
Recommended initial dose.	Initial dose 70U. For details refer to Appendix 9.	Initial dose 10U. For details refer to Appendix 9.
Dosing instructions:	Once weekly at the same day of the week, anytime during the day, preferably at the same time of the day. For details on dose titration. See Appendix 9, Titration Guideline.	Once daily anytime of the day, preferably at the same time every day For details on dose titration. See Appendix 9, Titration Guideline.
Packaging.	3 mL PDS290 pre-filled pen-injector.	10 ml vial

- After randomisation at V2, subjects will start once daily and once-weekly injections on the same day. During the treatment period, the subjects will have weekly contacts with the site either at visits to the site or phone contacts and the first 5 administrations of once-weekly insulin 287 or once-weekly placebo will be done at the site. After the injections at the site, the subjects should stay at least one hour for observation.
- Once daily and once-weekly injections will continue until 25 weeks after randomisation. At this time point the last once weekly injection must be taken while the once daily injections are taken until 26 weeks after randomisation where the subjects come in for the end of treatment visit (V28).
- Subjects must be trained in the use of vial and syringe at V1, by having the subjects inject themselves with saline solution at site. If deemed necessary by the investigator, it could be considered to have the subjects inject themselves with saline solution at home between V1 and V2. At V2 the ability to self-administer daily injections will have to be assessed prior to randomisation.
- Subjects must be trained in handling of the PDS290 pre-filled pen-injector at V2.
- Training in handling the pen-injector and vials/syringes must be repeated during the trial as needed.
- Subjects should be instructed to discard the injector needle and syringe after each injection and store the pen-injector without an injection needle attached.
- The investigator must document that directions for use (DFU) 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.

7.1.1 Non-investigational medical products

The oral antidiabetic drugs metformin and DPP4i are considered as Non Investigational Medicinal Products (NIMPs) and hence will not be provided by Novo Nordisk, unless required by local law and should be purchased or otherwise delivered to subjects in accordance with the local health plan.

For Slovakia, please see Appendix 10 for country specific requirements.

7.1.2 Auxiliary supplies

The following will be provided by Novo Nordisk:

- DFU for PDS290 pre-filled pen-injector and vials
- Needles for PDS290 pre-filled pen-injectors. Only needles provided by Novo Nordisk must be used for administration of trial product.
- Syringes for injection of insulin glargine (for use with vial)
- Diary
- Blood glucose (BG) meter and related auxiliaries
- [redacted] FreeStyle Libre Pro supplies (sensor, reader, operator's manual and user guides)

Subjects must be instructed in how to use the diary, FreeStyle Libre Pro and BG meter. The instruction should be repeated during the trial, as needed.

For complaints related to the BG meter or the FreeStyle Libre Pro, the investigator must contact the device manufacturer's technical support according to Operator's Manuals provided with the devices.

7.1.3 Medical devices

Investigational medical device: 3 mL PDS290 pre-filled pen-injector

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 T2D has been verified by the notified body, [redacted]. 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 in that there is no intent to use the results from this trial to support a new marketing application or extension of an existing marketing approval.

Training in the 3 mL PDS290 pre-filled pen-injector

The subjects must be trained according to the direction for use in how to handle the PDS290 pen-injector. Training must be repeated during the trial at regular intervals in order to ensure correct use of the PDS290 pen-injector.

7.2 Dose modification

Doses are adjusted according to plasma glucose values as described in Appendix 9 (Titration Guideline).

7.3 Method of treatment assignment

All subjects will be centrally randomised using IWRS and assigned to the next available treatment according to randomisation schedule. Subjects will be stratified based on use of DPP4i. Within each stratum, each subject will be randomly allocated to receive once weekly insulin 287 and once daily placebo or once weekly placebo and once daily insulin glargine.

Trial products will be dispensed at the trial visits summarised in the flowchart, section 2.

7.4 Blinding

This is a double-dummy, double-blinded trial.
The following trial products will be packed blinded and are visually identical for the following trial product:

- Insulin 287 or once weekly placebo, 3 mL PDS290 pre-filled pen-injector
- Insulin glargine or once daily placebo, 10 mL vial

The specific trial product for a subject will be assigned using the IWRS. The site will access the IWRS before the start and each dispensation of trial product administration for each subject.

The IWRS is used for blind-breaking instructions. The blind may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Novo Nordisk will be notified immediately after breaking the blind. The date when and reason why the blind was broken must be recorded in the source documentation.

Whenever the blind is broken, the person breaking the blind must print the "code break confirmation" notification generated by the IWRS and sign and date the document.

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

If the blind has been broken by investigator, the subject must discontinue treatment with trial product and a treatment discontinuation session must be completed in IWRS.

The laboratory responsible for pharmacokinetics and antibodies analyses and the responsible scientific monitor of bioanalysis at Novo Nordisk will have access to the treatment allocation in the IWRS.

7.5 Preparation/Handling/Storage/Accountability

Only subjects enrolled in the trial may receive trial product and only authorised site staff may supply or administer trial product.

Storage conditions, in-use conditions and in-use time for trial products will be available on the product label and in the TMM.

- 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 must confirm 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, controlled, and 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 TMM.
- Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk.
- The subject must return all used and unused trial product including empty packaging materials during the trial as instructed by the investigator.
- The investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- Drug accountability should be performed on a pen/vial 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 their 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 the SMPG profiles, 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.

7.7 Concomitant medication

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

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

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.
- Until end of treatment (V28) 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/DPP4i prior to end of treatment (V28), this is defined as ancillary treatment (see section 7.7.1)
- For new anti-diabetic medication prescribed in the follow up period start date of current dose and total daily dose must also be recorded.

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE/SAE, then this must be reported according to Section 9.2.

7.7.1 Ancillary treatment

Until end of treatment (V28) only randomised treatment (trial products and metformin with or without DPP4i) are allowed. Ancillary treatment is defined as any diabetes medication - other than randomised treatment (trial products and metformin with or without DPP4i) initiated due to for example safety reasons. It should be registered as concomitant medication (diabetes) in the electronic case report form (eCRF).

For subjects not treated with DPP4i prior to the randomisation, initiation of long term use of DPP4i is considered as ancillary treatment. A medication error (see Appendix 4) is as such not considered as ancillary treatment.

7.8 Treatment after the end of the trial

When discontinuing trial products, either at the scheduled end of treatment visit (V28) 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, attend the end of treatment visit corresponding to V28 as soon as possible after discontinuation of trial product (preferably the same day) to collect the required data for the analysis of the primary endpoint. The two follow up visits must also be performed. FU1 must be scheduled at least 2 weeks (+3 days) after and FU2 must be scheduled 5 weeks (+3 days) after discontinuation of the trial product respectively.

Once the two follow-up visits after discontinuation of trial product are completed the subject should be contacted by phone every 4 weeks. Information on antidiabetic medication must be collected and recorded in the eCRF. Phone contacts must be documented in the medical record and in the eCRF. The subject should finally come in for the discontinuation follow-up visit (V28A), 26 weeks after randomisation and have the assessments performed stated in the flow chart (section 2).

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

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

Only subjects who withdraw consent will be considered as withdrawn from the trial. See section 8.2

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. Pregnancy
3. Intention of becoming pregnant
4. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.

5. Lack of efficacy, defined as fulfilment of **all** 4 criteria below:
   - No reduction in HbA_{1c} measured by central laboratory from randomisation (V2) to visit 10, or to visit 14, or to visit 18, or to visit 22 or to visit 26 **AND**

- 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**
- 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**
- No treatable intercurrent cause (e.g. non-compliance) for the hyperglycaemia at the investigator's judgment

See the flowchart 2 for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

The primary reason for discontinuation of trial product must be specified in the eCRF, 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 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 assessments performed according to V28 and come in for the follow up visits (V29 and V30). See the flowchart 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 samples 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 reason(s) for withdrawing, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the eCRF.

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 2.
- 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 trial and giving contact details of relevant trial site staff.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- 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. 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.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 for further details on laboratory samples.

- Source data of clinical assessments performed and recorded in the eCRF 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, Libre Pro data, BG meter, pictures and ECG recordings.

9.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart 2.

9.1.1 Self-measured plasma glucose

At the screening visit (V1), subjects must be provided with a BG meter including auxiliaries and a diary as well as instructions for use. The subjects must be instructed in how to use the devices and the instruction should be repeated at regular intervals as indicated in the flowchart 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.

The BG meter provided by Novo Nordisk must be used for the measurements required in the protocol, as described in the flow chart 2.

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 eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF must be corrected.

Occasional review by the investigator of the 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.

Selected titration data (e.g. certain SMPGs and insulin doses) will only be used during the trial for central titration surveillance, to ensure compliance with the titration guideline Appendix 9. Only SMPGs obtained as part of the 9-point profiles will be reported in the clinical trial report (CTR).

Once daily pre-breakfast SMPG
Subjects should perform daily pre-breakfast SMPG from randomisation visit (V2) to end of treatment visit (V28). These SMPG values should be performed in a fasting condition.

9-point SMPG profile
Subjects will be instructed to perform 9-point profiles in the week prior to visits as specified in section 2, on a day where the subject does not anticipate unusual strenuous exercise.

The SMPG values obtained should be recorded in the diary (including actual clock time and date of measurement) according to the time points listed below:

- Before breakfast
- 90 minutes after the start of breakfast
- Before lunch
- 90 minutes after the start of lunch
- Before main evening meal (dinner)
- 90 minutes after the start of main evening meal (dinner)
- At bedtime
- At 4 am
- Before breakfast the following day

SMPG values measured before breakfast should be performed in a fasting condition.
The measurements will be used to evaluate the glucose profile.

9.1.2 Insulin dose

During the trial, starting at the randomisation visit (V2), subjects must be instructed to report date, dose and time of once weekly and date and dose of once daily insulin in the diary.

The recommended insulin doses will be calculated by the investigator based on recommendations from the Titration Guideline (see Appendix 9). At each visit/phone contact the Investigator will titrate the subjects by making prescribed dose adjustments based on the recommendation from the diary, if applicable.

The Investigator must record the following in the eCRF:

- Date, dose and injection time of once-weekly insulin/placebo
- Date and dose of once-daily insulin/placebo:
    - From V2 to V26: Insulin glargine/insulin glargine-placebo doses must be recorded two days prior to and on the day of the visit/contact.
    - From V26 to V28: Insulin glargine/insulin glargine-placebo doses must be recorded every day.
- Prescribed doses of once-weekly and once-daily insulin/placebo i.e. what the investigator tells the subject to take
- Reason for deviation from the recommended dose, if needed

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

9.1.3 Flash Glucose Monitoring

In order to evaluate the effect on glycaemic control at different time points during the trial, subjects will have FGM profiles generated 5 times during the trial. Please refer to the flowchart in section 2.

The FGM system used in this trial will be the FreeStyle Libre Pro system which consists of two parts:

- the sensor, applied on the back of the subjects' upper arm
- the reader, a hand held device kept at site and used to download data stored on the sensor

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, which will be shown on the display of the reader upon download of sensor data.

The FGM readings will be blinded to the subject as the reader will be kept at site.

The FGM values generated should not be used for insulin dose titration and/or hypoglycaemic episodes reporting.

9.1.3.1 FGM Reader setting

Each site will receive 2 readers; one to activate all subjects' sensors and download of their data and one as backup.

The FGM reader must be set up before use. The set up includes:

- Date and time setting
- Entry of the target glucose range. The range 3.9–7.8 mmol/L (70-140 mg/dL) should be used.

Time and date as well as level of battery should be verified each time the reader is used.

9.1.3.2 Fitting and removal of the FGM sensor

The sensor must be applied on the back of the upper arm of the subjects, using the sensor applicator as described in the Operator's manual. When applied, a thin, flexible and sterile fibre is inserted just under the skin of the subjects, allowing the measurement of glucose concentration in the interstitial fluid.

The sensor must be activated by holding the site reader within 4cm (1.5inch) of the sensor. Successful start of the sensor must be checked as described in the Operator's manual.

The sensor will store the subject's glucose readings every 15 minutes for up to 14 days.

For further information on preparing, fitting, and removal of the FGM system, please refer to the Operator's manual.

If a subject withdraws consent during one of the FGM periods, a site visit must be scheduled in order to remove the sensor and download data to the reader.

9.1.3.3 Duration of FGM periods

The sensor has an in-use period of 14 days and will automatically stop recording data 14 days after insertion and activation.

Subjects must aim to use the sensor for 14 days.
In cases where the sensor is dislodged prematurely, the subject must be fitted with a new sensor as soon as possible. Additional fitting visit at site will not be considered an unscheduled visit.

9.1.3.4 Wearing of the FGM sensor

Before each FGM periods, subjects must be instructed to follow the recommendations and limitations described in the Operator's manual and user guide while wearing the FGM sensor.

Subjects must be instructed to remove the FGM sensor prior to any X-ray, Computerised Tomography (CT) scan, high-frequency electrical heat (diathermy) treatment or magnetic resonance imaging (MRI).

9.1.3.5 Transfer of FGM data

Data stored on the sensor must be downloaded at the site by holding the reader within 4cm (1.5inch) of the sensor. Data on the reader device must then be uploaded to the provided FGM Software program that allows upload of the FGM data from the reader, 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 eCRF for every FGM period:

- Serial number of the FGM sensor
- Sensor fitting date and time
- Sensor removal date and time

9.1.4 Clinical efficacy laboratory assessments

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

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 second follow-up visit (V30), 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.

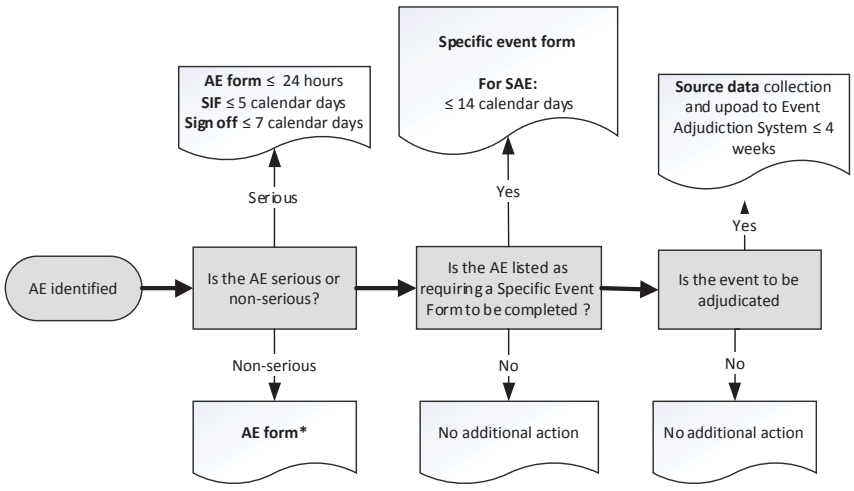
Investigators are not obligated to actively seek for AE or SAE in former trial subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related 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.

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 and hypoglycaemic episodes observed during the trial. The relevant specific events are listed in Table 9-1 and 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:



Timelines are from the awareness of an AE .
Queries and follow-up requests to be resolved ≤ 14 calendar days.

AE: Adverse Events, SAE: Serious Adverse Events , SIF: Safety Information Form
* Non-serious hypoglycaemic episodes should be reported on a dedicated hypoglycaemic form only.

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 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]	X	

[a]Refer to Section 9.2.6for reporting details

For details about specific event forms, see Appendix 4

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 Table 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 (Table 9-1) selected based on predefined criteria (Appendix 4)
   - All AEs reported with a fatal outcome
2) Preferred term (PT) search (standardised screening):
   - All AEs recorded in the eCRF 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 personal identifiers and uploaded to the EAS as soon as possible and preferably within 4 weeks according to instructions in the Event Adjudication Site Manual. Specific labelling requirements apply to digital pictures (see section 9.4.6.1 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 eCRF 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, stabilisation, 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 suspected unexpected serious adverse reactions (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 for standard AE collection

The following Disease-Related Event (DRE) is common in subjects with T2DM and can be serious/life threatening:

- Hypoglycaemic episodes

Definitions, classification and reporting requirements are described in Appendix 8.

Hypoglycaemia

Non-serious hypoglycaemia must be reported on a hypoglycaemic episode form.

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.

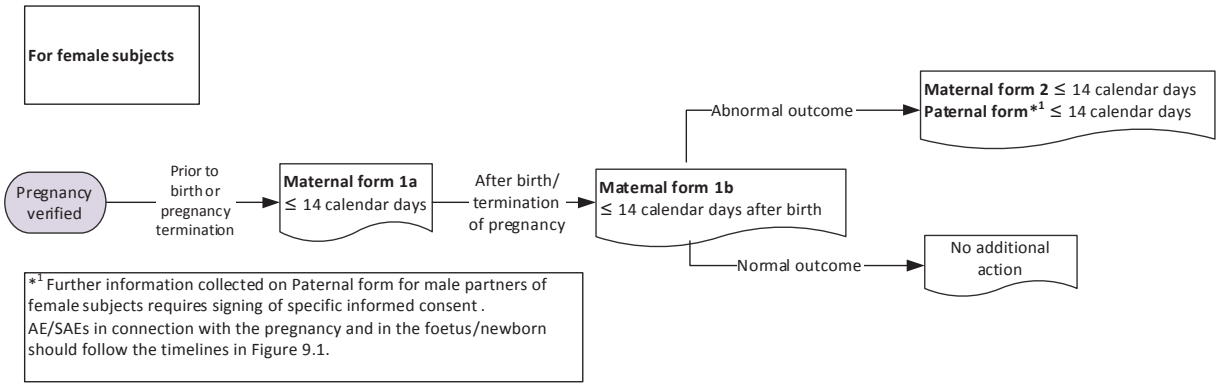


Figure 9-2 Decision tree for determining the forms to complete with associated timelines for pregnancy.

9.2.8 Medical device incidents (including malfunctions)

Section not applicable for this trial. Refer to technical complaints in Section 9.2.9.

9.2.9 Technical complaints

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.

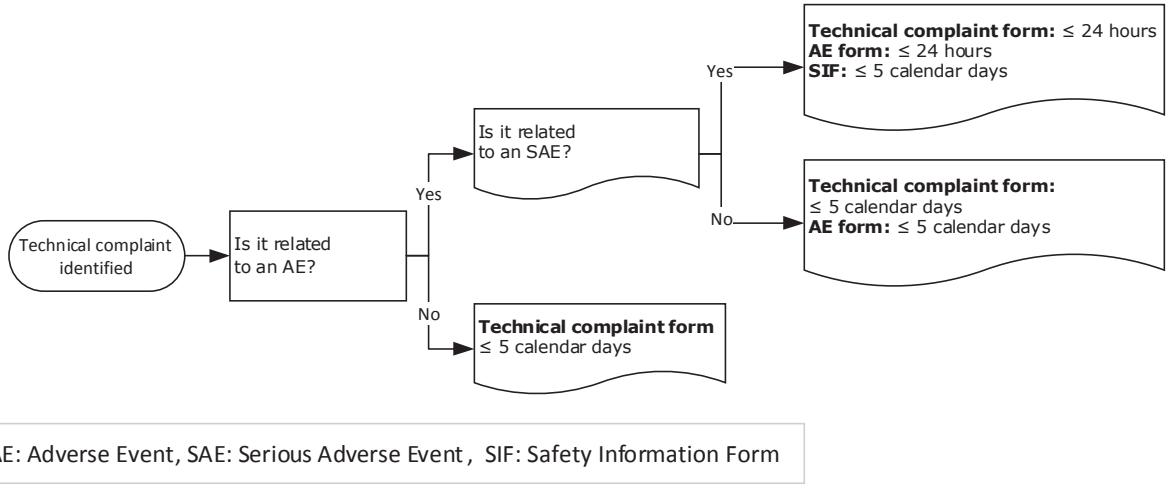


Figure 9-3 Decision tree for determining the forms to complete with associated timelines for technical complaints.

9.3 Treatment of overdose

The overdose must be reported as a medication error. Refer to Section 9.2.1 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 has 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 IB for insulin 287 and Summary of Product Characteristics for insulin glargine.[8]

9.4 Safety assessments

Planned time points for all safety assessments are provided in the flowchart 2.

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.
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.

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 (V2) must be reported as an AE (see Section 9.2).

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 eCRF.
- 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 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 eCRF 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 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 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 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) and performed with pharmacologically dilated pupils.

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.

9.4.5 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 2.

9.4.6 Immunogenicity assessments

Blood samples to be analysed for serum antibodies against insulin 287 or insulin glargine will be drawn at pre-specified time points according to the flowchart in section 2. For details on blood sampling, serum preparation, storage, labelling and shipments please refer to the laboratory manual.

Samples from the insulin 287 arm of the study will be analysed for anti-insulin 287 antibodies, and samples from the comparator arm will be analysed for anti-insulin glargine antibodies. Confirmed anti-insulin 287 or anti-insulin glargine antibody positive samples will have an antibody titre value determined, and will be further tested for cross-reactivity to endogenous insulin.

Residual anti-drug antibody samples may be used for exploratory investigation of antibodies or further development of anti-insulin antibody assays.

9.4.6.1 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:

- 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 – 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 hypersensitivity reaction.

9.5 Pharmacokinetics

Blood samples will be used to evaluate the pharmacokinetics (PK) of insulin 287. PK samples will be collected at the visits outlined in the flowchart, section 2. The investigator must record the exact date and clock time for blood sampling in the eCRF.

Each PK sample will be divided into 2 aliquots (one for pharmacokinetics and one for backup,). The back-up sample may be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial.

Procedures for sampling, handling, storage, labelling, and shipments of the specimens must be performed in accordance with the laboratory manual.

Bioanalysis of insulin 287 samples will be performed at a special laboratory using a validated[15, 16] Luminescent Oxygen Channelling Immunoassay (LOCI) with a range of 500 – 100.000 pmol/L. The exact method will be described in a bioanalytical report.

9.6 Pharmacodynamics

Not applicable for this trial.

9.7 Genetics

Not applicable for this trial.

9.8 Biomarkers

Not applicable for this trial.

10 Statistical considerations

10.1 Sample size determination

The primary estimand is defined as the treatment difference in change in HbA_{1c} from baseline to week 26 between once weekly insulin 287 and once daily IGlar for all randomised subjects, if all subjects had adhered to treatment and did not receive ancillary treatment. This is a “hypothetical” estimand. This estimand aims to reflect the treatment effect for subjects that are actually able to take the drug during the intended treatment period. With the aim of evaluating proof of concept this estimand is considered relevant.

The sample size is determined such that the width of the two-sided 95% confidence interval (CI) for the treatment difference assuming normally distributed data in change from baseline to 26 weeks in

HbA_{1c} is 0.5%-point. The standard deviation (SD) is expected to be 1.0%-point for all treatment arms based on observations with IGlar in insulin naïve T2DM trials (NN1250-3579, NN1250-3643 and NN1250-3672). A total of 246 subjects will ensure the required width of the 95% CI. The total number of subjects to be randomised is rounded from 246 to 250 with 125 in each treatment arm.

The required width of the confidence interval is independent of the choice of estimand and sensitivity analyses since all randomised subjects will contribute to all analyses. The SD is assumed to be 1.0 based on observations from finalised clinical trials with IGlar in insulin naïve T2DM subjects. Since the assumed SD of 1 is to the conservative side it is assumed that the SD will not be further increased by the choice of estimand.

Table 10-1 displays sample sizes for various alternative standard deviations and widths of the 95% CI.

Table 10-1 Sample size for various standard deviations and widths of the confidence interval

	Width of the 95% CI		
SD	0.40	0.50	0.60
0.9	312	200	140
1.0	384	**246**	172
1.1	466	298	208

Sample size is computed for 1:1 randomisation. SD: standard deviation.

10.2 Definition of analysis sets

The following analysis sets are defined in accordance with the International Council for Harmonisation (ICH)-E9 guidance[17].

- Full Analysis Set (FAS): includes all randomised subjects. In exceptional cases, subjects may be eliminated from the full analysis set. In such cases the elimination will be justified and documented. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation "as randomised".
- Safety Analysis Set (SAS): includes all subjects receiving at least one dose of the investigational product or comparator. Subjects in the safety set will contribute to the evaluation "as treated".

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

The on-treatment observation period is defined as the period from date of first dose of randomised Investigational Medicinal Product (IMP) until the end of the treatment emergent period.

The in-trial observation period is defined as the period from date of randomisation and until last scheduled subject-site contact (i.e. the end date is the last site/phone visit).

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

10.3 Statistical analyses

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

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

All efficacy endpoints will be summarised using the full analysis set (FAS) and safety endpoints will be summarised using the safety analysis set (SAS). All statistical analyses of efficacy and safety endpoints will be based on the FAS unless otherwise specified.

Endpoints are summarised by arithmetic mean, SD, median, and minimum and maximum value. Selected endpoints, e.g. endpoints that are analysed log-transformed, will be reported with geometric mean and coefficient of variation in place of mean and SD. For measurements over time, mean values will be plotted to explore the trajectory over time. 'On-treatment' observed data will be used as the basis for plotting data if not otherwise specified. Mean profile for HbA_{1c} will be plotted by time of treatment discontinuation and treatment in order to investigate discontinuation patterns. Data obtained after treatment discontinuation or initiation of ancillary treatment will be included using different plot symbols. In addition, selected endpoints will be summarised by empirical distribution plots, box plots, and plots of the mean change from baseline over time. For HbA_{1c}, additional summary tables and plots based on 'in-trial' data will also be prepared.

Only endpoints derived after 26 weeks will be analysed statistically. In accordance with guidance[18] endpoints will be assessed at frequent visits and also on subjects who discontinue treatment. If an assessment has been made both at screening and randomisation, and if not otherwise specified, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment also has been made at screening, then the screening value will be used as the baseline value.

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

Presentation of results from a statistical analysis will include the estimated mean treatment effects using least square mean (LSMean) for absolute values, and change from baseline where applicable. The LSMean is either obtained by Rubin's rule weighing together LSMeans from multiple

imputation estimations or obtained directly from estimation of a parameterised statistical model. In addition, estimated mean treatment difference (or ratio) will be presented together with the two-sided 95% confidence interval and corresponding two-sided p-value.

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

- Treatment: Once weekly insulin 287, Once daily IGlar
- DPP4i has 2 levels (yes and no)
- Region has 2 levels (Europe and North America)
- Visit: Planned visits for actual endpoint according to flowchart

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

10.3.1 Primary endpoint

The primary endpoint is change from baseline to week 26 in HbA_{1c}.

Primary estimand

For the primary endpoint, the primary estimand is defined as the "hypothetical" estimand[19].

The treatment difference between once weekly insulin 287 versus once daily IGlar in change from baseline to week 26 in HbA1c for all randomised subjects if all subjects had adhered to treatment and did not initiate ancillary treatment in subjects with T2DM inadequately treated with metformin with or without DPP4i.

The primary estimand will be estimated based on the FAS. This estimand aims to reflect the treatment effect for subjects that are actually able to take the drug during the intended treatment period. With the aim of evaluating proof of concept, this estimand is considered relevant i.e. a de jure estimand addressing efficacy.

Subjects may start ancillary treatment during the trial. Hence, data obtained after occurrence of intercurrent event such as initiation of ancillary treatment and discontinuation of randomised treatment will not be included in the estimation of the primary estimand.

To estimate this estimand, change from baseline in HbA_{1c} after 26 weeks will be analysed with the linear mixed model for repeated measurement (MMRM) method with an unstructured covariance matrix. All post baseline HbA_{1c} measurements obtained on planned visits while the subject continues the randomised treatment will contribute to the analysis. Hence, data obtained after occurrence of the following two intercurrent events such as initiation of ancillary treatment and discontinuation of randomised treatment will not be included in the estimation of the primary estimand. This analysis has the underlying assumption that the missing data mechanism is 'missing at random'. The model will include use of DPP4i (yes/no), region, treatment and visit as fixed factors and baseline HbA_{1c} as covariate. Interactions between visit and all factors and covariates will also be included in the model. The estimated mean treatment difference and the confidence

interval will be presented together with the corresponding two-sided p-value. In the following, this MMRM method will be referred to as the standard MMRM method.

Secondary estimand

The secondary estimand for the primary endpoint is the "treatment policy" estimand.

The secondary estimand is defined as the treatment difference between once weekly insulin 287 versus once daily IGlar in change from baseline to week 26 in HbA1c for all randomised subjects, regardless of the treatment actually received in subjects with T2DM inadequately treated with metformin with or without DPP4i. This estimand aims to reflect the treatment effect for all subjects regardless of treatment adherence, i.e. a de facto estimand addressing effectiveness.

This will be estimated using all HbA_{1c} measurements obtained at week 26, also including measurements from subjects discontinuing their randomised treatment or initiating ancillary treatment. Missing HbA_{1c} measurements at week 26 will be imputed from trial participants who are from the same randomised group, who have discontinued their randomised treatment and have an HbA_{1c} measurement at week 26.

This will be done as follows:

- First, one thousand (1000) copies of the dataset will be generated.
- Second, for each dataset copy, and each treatment group, an analysis of variance (ANOVA) model with baseline HbA_{1c} value as a covariate will be fitted to the end of trial value for subjects having discontinued their randomised treatment and have an HbA_{1c} measurement at week 26. The estimated parameters, and their variances, from the model will be used to impute missing values at end of trial in the same treatment group. The factors region and use of DPP4i are not considered in this step assuming the number of subjects to impute from will be low and that may lead the model does not meet the convergence criteria.
- For each of the complete data sets, the change from baseline in HbA_{1c} after 26 weeks will be analysed using an analysis of co-variance model with use of DPP4i (yes/no), region and treatment as fixed factor, and baseline HbA_{1c} as covariate. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated SD using Rubin's rule.

If less than 3 subjects have discontinued their randomised treatment and have an HbA_{1c} measurement at week 26 in any of the treatment groups, then the second step above will be carried out combining the two treatment arms and including treatment as factor in the model.

The estimated mean treatment difference and the confidence interval will be presented together with the corresponding two-sided p-value.

Sensitivity analysis

The following sensitivity analysis of the assumptions about the missing data will be carried out: for the primary estimand, a tipping point like type of analysis will be performed where subjects from

the Insulin 287 arm having no HbA1c measurement at week 26 are assumed to have a worse outcome compared to what was imputed in the primary analysis. This is done by adding a value Δi to the imputed HbA1c values in the Insulin 287 arm before analysing the data. The resulting estimated treatment differences and 95%CIs will be plotted as function of Δi to evaluate the robustness of the primary analysis results.

10.3.2 Secondary endpoints

10.3.3 Confirmatory secondary endpoints

Not applicable for this trial.

10.3.3.1 Supportive secondary endpoints

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

Efficacy endpoints

- Change from baseline to week 26 in fasting plasma glucose
- 9-point profile (individual SMPG values) at week 26
- Change from baseline to week 26 in mean of the 9-point profile, defined as the area under the profile
- Fluctuations of the 9-point profile (defined as the integrated absolute distance from the mean profile value divided by measurement time)
- Change from baseline to week 26 in fasting C-peptide
- Change from baseline to week 26 in body weight
- Weekly dose of insulin 287 and daily dose of IGlar at week 26

FPG, C-peptide and body weight – change from baseline after 26 weeks

Change from baseline in FPG and body weight will be analysed using the standard MMRM method with relevant baseline as the covariate.
Relative change from baseline in C-peptide will be analysed using the standard MMRM method. In this statistical analysis the endpoint will be log-transformed and so will the baseline covariate.

SMPG 9-point profile

The following endpoints will be derived from self-measured plasma glucose,

1. 9-point profile (individual SMPG values)
2. Change from baseline to week 26 in mean of the 9-point profile, defined as the area under the profile

3. Fluctuations of the 9-point profile defined as the integrated absolute distance from the mean profile value divided by measurement time

A linear mixed effect model will be fitted to the 9-point SMPG profile data at week 26. The model will include treatment, region, use of DPP4i, time, the interaction between treatment and time, the interaction between region and time, and the interaction between use of DPP4i and time as fixed factors and subject as random effect. From the model mean profile by treatment and relevant treatment differences will be estimated and explored.

Change from baseline in mean of the 9-point profile, and fluctuation in 9-point profiles after 26 weeks will be analysed separately using the standard MMRM method with relevant baseline as the covariate. Fluctuation in the 9-point profile will be logarithmically transformed before analysed. Baseline fluctuation in the 9-point profile also will be log-transformed in the model.

Insulin dose

Insulin 287 dose and IGlar dose will be summarised by week.

The average insulin 287 dose derived from visit 26 to visit 28 versus average weekly IGlar dose derived from visit 26 to visit 28 will be logarithmically transformed and analysed based on standard MMRM method (except baseline as a covariate).

Safety endpoints

Number of treatment emergent adverse events from baseline to week 31

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

The treatment emergent period represents the period where subjects are considered exposed to trial product. It starts at the first date of exposure to randomised treatment and ends at the last follow-up visit (FU2), thus includes a time period after last dose of randomised treatment corresponding to approximately 5 half-lives of insulin 287. Specifically, it ends at one of the following:

- For subjects completing the trial: Last follow-up visit (FU2)
- For subjects who discontinue: Last follow-up visit (FU2) as defined in section 8.1
- For subjects who discontinue, but do not attend FU2 visit: Last dosing day of randomised treatment + 5 weeks for glargine, and last dosing day of randomised treatment + 6 weeks for insulin 287

A treatment emergent adverse event (TEAE) is defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than the treatment emergent period. If the event has onset date before the first day of exposure on randomised treatment and increases in severity during the treatment period and until the treatment emergent period, then this event should also be considered as a TEAE.

TEAEs are summarised descriptively, whereas non-TEAEs are presented in listings. TEAE data will be displayed in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years of exposure (R).

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

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

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

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

Additional summaries will be displayed for SAEs, including events collected after premature treatment discontinuation ("in-trial" summary).

Summary of number of treatment-emergent injection site reactions will be presented as an overview including all AEs, serious AEs, AEs by severity and AEs by relation to treatment and injection site reactions leading to treatment discontinuation or withdrawal. Furthermore summary table of injection site reaction based on system organ class and preferred terms will be made.

Hypoglycaemic episodes

For the definition and classification of hypoglycaemic episodes refer to Appendix 8. Data on treatment-emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one episode (N), the percentage of subjects with at least one episode (%), the number of episodes (E) and the event rate per 100 years of exposure (R).

Repeated SMPG measurements and/or symptoms (see Table 10-2), 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.

Separate summaries will be made according to the level of hypoglycaemia, as recently recommended by the International Hypoglycaemia Study Group (2017 joint ADA/EASD position statement), ADA 'Standards of Medical Care in Diabetes-2018', ISPAD, Type 1 Diabetes Outcomes Program and ATTD congress. For references see Appendix 8.

The classification of hypoglycaemia is outlined in Table 10-2. The summaries are made for all and nocturnal (between 00:01 and 05.59 both inclusive) episodes respectively.

Table 10-2 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

The treatment emergent period represents the period where subjects are considered exposed to trial product. It starts at the first date of exposure to randomised treatment and ends at the last follow-up visit (FU2), thus includes a time period after last dose of randomised treatment corresponding to approximately 5 half-lives of insulin 287. Specifically, it ends at one of the following:

- For subjects completing the trial: Last follow-up visit (FU2)
- For subjects who discontinue: Last follow-up visit (FU2) as defined in section 8.1
- For subjects who discontinue, but do not attend FU2 visit: Last dosing day of randomised treatment + 5 weeks for glargine, and last dosing day of randomised treatment + 6 weeks for insulin 287

Level 1 hypoglycaemic episodes, Level 2 and level 3 combined hypoglycaemic episodes, level 2 hypoglycaemic episodes, and level 3 hypoglycaemic episodes after 26 weeks will be analysed separately by a negative binomial regression model with treatment, region and use of DPP4i (yes/no) as fixed factors and the log of time period (treatment-emergent) for which the hypoglycaemic episodes are considered as an offset.

The above analysis will be repeated for the following time points as below,

1. Number of level 2 and level 3 combined hypoglycaemic episodes from baseline to week 31 (Treatment emergent hypos)
2. Number of level 2 and level 3 combined hypoglycaemic episodes from baseline to week 16 (Titration period)
3. Number of level 2 and level 3 combined hypoglycaemic episodes from week 17 to week 26 (Maintenance period)
4. Number of level 2 hypoglycaemic episodes from baseline to week 31 (Treatment emergent hypos)
5. Number of level 2 hypoglycaemic episodes from baseline to week 16 (Titration period)
6. Number of level 2 hypoglycaemic episodes from week 17 to week 26 (Maintenance period)
7. Number of level 3 hypoglycaemic episodes from baseline to week 31 (Treatment emergent hypos)
8. Number of level 3 hypoglycaemic episodes from baseline to week 16 (Titration period)
9. Number of level 3 hypoglycaemic episodes from week 17 to week 26 (Maintenance period)

The number of nocturnal level 2 and level 3 combined hypoglycaemic episodes and number of level 2 hypoglycaemic episodes, and number of level 3 hypoglycaemic episodes from:

- baseline to 26 weeks
- baseline to week 31
- baseline to week 16 and
- week 17 to week 26

will be analysed similarly.

Antibodies from baseline to 31 weeks

Change in anti-insulin 287 antibodies level, and change in anti-insulin 287 antibody titres will be summarised and tabulated. The correlation between change in values from baseline after 31 weeks of treatment in anti-insulin 287 antibodies level, and anti-insulin 287 antibody titres respectively to insulin dose at 26 weeks of treatment, HbA1c after 26 weeks of treatment and change from baseline after 26 weeks of treatment in HbA1c will be illustrated using scatter plots. The Pearson's correlation coefficient will be tested and displayed in both table and the plots. Number and percentage of subjects positive for cross reactive antibodies will be tabulated by visit.

10.3.3.2 Exploratory endpoints

- Insulin 287 concentrations, evaluated in a population PK analysis
- Time in target-range 3.9-7.8 mmol/L (70–140 mg/dL) measured by flash glucose monitoring (FGM) (Free Style Libre Pro) during the last 2 weeks of treatment (week 25 and 26)

The data accuracy may vary during the first 24 hours after sensor fitting, the FGM data from the 1st day (24h) of each sensor period will be excluded from analysis.

10.3.7 Other analyses

Other efficacy tabulations:

HbA_{1c} responders after 26 weeks (Yes/No)

Dichotomous outcome (responder=yes/non-responder=no) will be defined based on whether a subject has met a specific level of $HbA_{1c} < 7.0\%$ after 26 weeks. Analysis of this responder outcome will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline HbA_{1c} values as covariate.

For subjects who discontinue randomised treatment or start ancillary treatment, missing HbA_{1c} data at 26 weeks are imputed by the MMRM method before applying the specific responder criteria.

HbA_{1c} responders with minimal weight gain after 26 weeks

Responder for HbA_{1c} with minimal weight gain after 26 weeks of treatment will be defined as:

- $HbA_{1c} < 7.0\%$ and change from baseline in body weight ≤ 3 %

Analysis of this responder outcome will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline HbA_{1c} and baseline body weight values as covariates.

For subjects who discontinue randomised treatment or start ancillary treatment, missing HbA_{1c} and body weight data at 26 weeks are imputed by the MMRM method before applying the specific responder criteria.

HbA_{1c} responders without treatment-emergent clinically significant hypoglycaemic episodes and without treatment-emergent severe hypoglycaemic episodes after 26 weeks

Responder for HbA_{1c} without treatment-emergent clinically significant hypoglycaemic episodes and without treatment-emergent severe hypoglycaemic episodes after 26 weeks of treatment will be defined as:

- $HbA_{1c} < 7.0\%$ and without treatment-emergent clinically significant hypoglycaemic episodes and without treatment-emergent severe hypoglycaemic episodes during the last 12 weeks of treatment

Analysis of this outcome will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline HbA_{1c} values as covariates, where subjects with less than 12 weeks of treatment conservatively will be set to being non-responder.

For subjects who discontinue randomised treatment or start ancillary treatment, missing HbA_{1c} data at 26 weeks are imputed based on the MMRM method before applying the specific responder criteria.

HbA_{1c} responders without treatment-emergent severe hypoglycaemic episodes after 26 weeks

Responder for HbA_{1c} without treatment-emergent severe hypoglycaemic episodes after 26 weeks of treatment will be defined as:

- HbA_{1c} < 7.0% and without treatment-emergent severe hypoglycaemic episodes during the last 12 weeks of treatment

Analysis of this endpoint will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline HbA_{1c} values as covariates, where subjects with less than 12 weeks of treatment conservatively will be set to being non-responder.

For subjects who discontinue randomised treatment or start ancillary treatment, missing HbA_{1c} data at 26 weeks are imputed based on the MMRM method before applying the specific responder criteria.

HbA_{1c} responders without treatment-emergent clinically significant hypoglycaemic episodes and with minimal weight gain after 26 weeks

Responder for HbA_{1c} without treatment-emergent clinically significant hypoglycaemic episodes and with minimal weight gain after 26 weeks of treatment will be defined as:

- HbA_{1c} < 7.0% without treatment-emergent clinically significant hypoglycaemic episodes during the last 12 weeks of treatment, and change from baseline in body weight ≤ 3 %

Analysis of this responder outcome will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline HbA_{1c} and body weight values as covariates, where subjects with less than 12 weeks of treatment will conservatively be set to being non-responder.

For subjects who discontinue randomised treatment or start ancillary treatment, missing HbA_{1c} and body weight data at 26 weeks are imputed by the MMRM method before applying the specific responder criteria.

HbA_{1c} responders without treatment-emergent severe hypoglycaemic episodes and with minimal weight gain after 26 weeks

Responder for HbA_{1c} without treatment-emergent severe hypoglycaemic episodes and with minimal weight gain after 26 weeks of treatment will be defined as:

- HbA_{1c} < 7.0% without treatment-emergent severe hypoglycaemic episodes during the last 12 weeks of treatment, and change from baseline in body weight ≤ 3 %

Analysis of this responder outcome will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline HbA_{1c} and body weight values as covariates, where subjects with less than 12 weeks of treatment will conservatively be set to being non-responder.

For subjects who discontinue randomised treatment or start ancillary treatment, missing HbA_{1c} and body weight data at 26 weeks are imputed by the MMRM method before applying the specific responder criteria.

Similar analyses as defined above will be carried out for responder targets replacing HbA_{1c} <7.0% with HbA_{1c} ≤6.5%.

FPG responder to treatment target after 26 weeks (Yes/No)

Dichotomous outcome (responder=yes/non-responder=no) will be defined based on whether a subject has met a specific target level of FPG ≤ 7.2 mmol/L (130 mg/dL) after 26 weeks. Analysis of this responder endpoint will be based on a logistic regression model with treatment, region and use of DPP4i as fixed factors and baseline FPG values as covariate.

For subjects who discontinue randomised treatment or start ancillary treatment, missing FPG data at 26 weeks are imputed by the MMRM method before applying the specific responder criteria.

Similar analyses as defined above will be carried out for responder targets replacing <7.2 mmol/L (130 mg/dL) with ≤ 6 mmol/L (108 mg/dL).

Other safety tabulations:

Antibodies from baseline to 31 weeks

Number and percentage of subjects positive for anti-insulin 287 and anti-insulin glargine antibodies will be tabulated by visit. Anti-insulin glargine antibodies (both in %B/T and titres) will be summarised and tabulated. The correlation between change in titre values from baseline after 26 weeks of treatment in anti-insulin glargine, to insulin dose after 26 weeks of treatment, HbA1c after 26 weeks of treatment and change from baseline after 26 weeks of treatment in HbA1c will be illustrated using scatter plots. Also the Pearson's correlation coefficient will be tested and displayed in both table and the plots.

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

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

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

Laboratory assessment (Biochemistry and Haematology) - change from baseline after 26 weeks

All laboratory parameters will be summarised descriptively including:

- Summaries by visit
- Shift tables from baseline to after 26 weeks
- Proportion of subjects with measurements outside reference range by treatment and week
- Box plots by time since randomisation
- Listings of individual values outside reference ranges (abnormal values)

Lipids and vital signs

Lipids and vital signs will be summarised by treatment.

Other exploratory tabulations:

Time in target-range measured by FGM, Libre Pro will be analysed using the standard MMRM method except baseline as a covariate for the following time in range,

- Time in range 3.9–6.0 mmol/L (70-108 mg/dL)
- Time in range 3.9–10.0 mmol/L (70-180 mg/dL)
- Time spent < 3.0 mmol/L (54 mg/dL)
- Time spent < 3.9 mmol/L (70 mg/dL)
- Time spent > 10.0 mmol/L (180 mg/dL)
- Time spent > 13.9 mmol/L (250 mg/dL)

Within subject variability as measured by CV%
The logarithm transformed FGM values will be analysed as repeated measures in a linear mixed model with treatment, use of DPP4i and region as fixed factors and subject as random factor. The model will assume independent within- and between-subject errors with variances depending on treatment. Within subject variability as measured by CV% for a treatment can be calculated from the corresponding residual variance σ^2 as $\% = \sqrt{(exp(\sigma^2) - 1)}$. The confidence interval for the CV ratio between treatments will be calculated using the delta method.

For population PK analysis refer section 10.4.

10.4 Pharmacokinetic and/or pharmacodynamic modelling

Insulin 287 serum concentration data will be used for a population PK analysis. The objective of the population PK analysis is to evaluate the effects of pre-specified covariates on serum concentrations of insulin 287.

The population PK analysis will be performed by Quantitative Clinical Pharmacology, Novo Nordisk A/S. A more technical and detailed elaboration of the population PK analysis will be given in a modelling analysis plan (MAP), which will be prepared before Database Lock (DBL). In brief, a previously developed PK model for insulin 287 will be applied. The absorption rate constant (Ka) in the model will be fixed, and the apparent clearance (CL/F) and the apparent volume of distribution (V/F) will be re-estimated. The covariates of interest will be incorporated into the PK model using criteria which will be specified in the MAP.

The population PK analysis will be reported in a separate modelling report, which will not be a part of the clinical trial report. The individual insulin 287 serum concentration data will be tabulated in the bioanalytical report (BAR).

11 References

1. Polonsky WH, Fisher L, Hessler D, Bruhn D, Best JH. Patient perspectives on once-weekly medications for diabetes. Diabetes Obesity & Metabolism. 2011;13(2):144-9.
2. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1). Adoption by CHMP. 14 May 2012.
3. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, Draft Guidance. February 2008.
4. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S55-S64.
5. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-53, Erratum 1999; 354: 602.
6. American Diabetes Association. Abridged for Primary Care Providers. Clin Diabetes. 2018;36(1):14-37.
7. Novo Nordisk A/S. Investigator's Brochure, NNC0148-0287 (insulin 287), NN1436, (edition 4). 2016.
8. Sanofi-Aventis Groupe. Lantus® (insulin glargine), EU Summary of Product Characteristics (SmPC). 01 Mar 2017.
9. Food and Drug Administration. Lantus - U.S. Label information. 2015.
10. Local SmPC for metformin, current version. 2008 2008.
11. American Diabetes Association. 8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S73-S85.
12. Hauber AB, Johnson FR, Sauriol L, Lescrauwaet B. Risking health to avoid injections: preferences of Canadians with type 2 diabetes. Diabetes Care. 2005;28(9):2243-5.
13. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 1) (EMA/838713/2011 Rev 1). 15 Apr 2014.
14. the European Economic Community. Medical Device Directive 93/42, Annex I. 1993.
15. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM). Guidance for Industry. Bioanalytical Method Validation. 2001.
16. European Medicines Agency (EMA) CfMPfHUC. Guideline on Bioanalytical Method Validation. EMEA/CHMP/19221/2009. 21 July 2011. 7/21/2011 2011.
17. Little RJA, Rubin DB. Statistical analysis with missing data: New York: John Wiley & Sons. 1987.
18. National Academy of Sciences (NAS). The Prevention and Treatment of Missing Data in Clinical Trials. Washington D.C.: The National Academies Press. 2010.
19. Mallinckrodt CH, Lin Q, Lipkovich I, Molenberghs G. A structured approach to choosing estimands and estimators in longitudinal clinical trials. Pharm Stat. 2012;11(6):456-61.
20. World Medical Association. Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. 1 Oct 2013.

21. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R2), Current Step 4 version. 09 Nov 2016.
22. International Organization for Standardization. ISO 14155:2011, Clinical investigation of medical devices for human subjects - Good clinical practice. 01 Feb 2011.
23. Hicks KA, Hung HMJ, Mahaffey KW, Mehran R, Nissen SE, Stockbridge NL, et al. Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials (Draft). 20 Aug 2014.
24. International Committee of Medicinal Journal Editors. Uniform Requirements for Manuscripts submitted to Biomedical Journals.: N Engl J Med; 1997 1997. p. 309-15.
25. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals; current version available at www.icmje.org.
26. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351(12):1250-1.
27. U.S. Food and Drug Administration. Food and Drug Administration Amendments Act of 2007 as amended by the Final Rule "Clinical Trials Registration and Results Information Submission". 21 September 2016.
28. The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, article 11. Official Journal of the European Communities. 01 May 2001.
29. The European Parliament and the Council of the European Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. 30 April 2004.
30. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2017;40(1):155-7.
31. Jones TW, Group IHGW. Defining relevant hypoglycemia measures in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2017.
32. Agiostratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, et al. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care. 2017;40(12):1622-30.
33. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017;40(12):1631-40.

34. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95.
35. U.S. Department of Health and Human Services FaDA, ; Center for Drug Evaluation and Research (CDER),; Center for Biologics Evaluation and Research (CBER),; Center for Devices and Radiological Health (CDRH),. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009.
36. Stull DE, Leidy NK, Parasuraman B, Chassany O. Optimal recall periods for patient-reported outcomes: challenges and potential solutions. Curr Med Res Opin. 2009;25(4):929-42.

12 Appendices

Appendix 1 Abbreviations and Trademarks

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
CRF	case report form
CTR	clinical trial report
DFU	directions for use
DPP-4i	dipeptidyl peptidase-4 inhibitor
DRE	disease related event
DUN	dispensing unit number
EAC	event adjudication committee
EAS	event adjudication system
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FGM	flash glucose monitoring
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HbA_{1c}	glycated haemoglobin
ICH	International Council for Harmonisation
IEC	independent ethics committee

IGlar	insulin glargine
IMP	investigational medicinal product
IRB	institutional review board
ITT	Intention to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LDL	low-density lipoprotein
MACE	major adverse cardiovascular event
NIMP	Non-investigational medical product
OAD	oral antidiabetic drug
PCD	primary completion date
PD	pharmacodynamic
PG	plasma glucose
PK	pharmacokinetic
SAE	serious adverse event
SD	standard deviation
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T½	half- life
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
TMM	trial materials manual
ULN	upper limit of normal
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 addit ional 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.
- PK samples will be destroyed at finalisation of the clinical trial report.
- Antibody samples and samples to assess systemic hypersensitivity reactions 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} • Fasting C-peptide
NOTES : [1] 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 (LDL) 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 • Anti-insulin 287 antibodies • Anti-insulin glargine antibodies • Pharmacokinetics • 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 : [1]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 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[20], applicable ICH Good Clinical Practice (GCP) Guideline[21] and ISO 14155[22]
- 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 (CTR) synopsis to the IRB/IEC.

2) Financial disclosure

Investigators and subinvestigators 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 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[21], Declaration of Helsinki[20] 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 which will remain the same throughout the trial. Each site is assigned a 3-digit number and all subject numbers will start with the site 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 FDA requirements[23].

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[24].

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[25].

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 publication(s) by investigator(s)
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)[26], the Food and Drug Administration Amendment Act (FDAAA)[27], European Commission Requirements[28, 29,] 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 (PCD) is the last assessment of the primary endpoint, and is for this trial Last Subject First Treatment (LSFT) + 26 weeks corresponding to Visit 28. If the last subject is withdrawn early, the PCD is considered the date when the last subject randomised in the trial would have completed end of treatment Visit 28. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

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 FGM Libre Pro data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- 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). 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 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 mu st 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.
- 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 perio d. 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 subinvestigator 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) for Poland, please see Appendix 10 for details.

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.

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):

Medication error:

A medication error concerning trial products is defined as:

- Administration of wrong drug

Note: Use of wrong DUN is not considered a medication error unless it results in a confirmed administration of wrong drug.

- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Accidental administration of a lower or higher dose than intended. Accidental administration of a lower or higher dose than intended. i.e. dose which may lead to significant health consequences, as judged by the Investigator, irrespective of whether the SAE criteria are fulfilled or not; however, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

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	• Ischaemic stroke • Haemorrhagic stroke • Undetermined stroke

	cord, or retinal vascular injury as a result of haemorrhage or infarction	
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 a sequelae meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the subject has not improved and the symptoms are unchanged or the outcome is not known.
- **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with 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.

Reporting of AEs for Non-Novo Nordisk medical devices provided by Novo Nordisk for use in the trial

Reporting of AEs on: [redacted] FreeStyle Libre Pro device and supplies or BG meter device and related auxiliaries

All technical complaints on [redacted] FreeStyle Libre Pro and supplies or BG-meter, strips, lancets and control solutions must be reported directly to the supplier/manufacturer using the supplier reporting form within the timelines defined from supplier/manufacturer.

Contact details are provided in Attachment I to the protocol

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

1. Premenarcheal
2. 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.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high Follicle Stimulating Hormone (FSH) 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 FSH 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 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 [b] • 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 (IUD) • Intrauterine hormone-releasing System (IUS) • 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 Center, 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 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 antibo dy 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[30], ADA-2018 [4], ISPAD[31], Type 1 diabetes outcomes program[32], ATTD[33]. Severe hypoglycaemia as defined by Seaquist[34].		

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[34].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.[34]

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 the diary for low SMPG values not reported as hypoglycaemic episodes. The subject must be questioned whether any of the low values were severe, i.e. whether the subject 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.[35] [36]

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 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 + insulin glargine-placebo or insulin 287-placebo + insulin glargine.

Insulin 287 and insulin 287-placebo should be taken once weekly at the same day of the week. The starting dose will be 70U.

Insulin glargine and insulin glargine-placebo will be taken once daily anytime of the day preferably the same time every day. The starting dose will be 10U.

The treat-to-target approach will be applied in both treatments to optimise titration and glycaemic control throughout the trial.

There are no maximum or minimum doses.

Dose adjustment of trial products during the trial

Titration of insulin glargine and insulin glargine-placebo

After randomisation insulin glargine and insulin glargine-placebo doses will be adjusted once weekly by the investigator in connection with the scheduled visits/phone contacts as described below. Titrated dosed should be maintained until new titration or review is performed by the Investigator.

The dose adjustment will be based on the three pre-breakfast SMPG values measured on two days prior to titration and on the day of the contact.

If one or more SMPG values are missing, the dose adjustment should be performed on the remaining SMPG value(s). The insulin dose adjustment should aim to reach an SMPG of 3.9–6.0 mmol/L (70–108 mg/dL).

If there are no hypoglycaemic values in the pre-breakfast SMPGs value(s) the dose is adjusted according to Table 12-4. If there are hypoglycaemic values the dose is adjusted according to Table 12-5

Table 12-4 Insulin glargine and insulin glargine-placebo increase

Mean pre-breakfast SMPG		Dose adjustment
mmol/L	mg/dL	U
3.9 – 6.0	70 – 108	No adjustment
6.1 – 7.0	109 – 126	+ 2
> 7.0	> 126	+ 4

Table 12-5 Insulin glargine and insulin glargine-placebo reduction

Lowest pre-breakfast SMPG		Dose adjustment
mmol/L	mg/dL	U
3.0 – 3.8	54 – 69	- 2
< 3.0	< 54	- 4

Titration of insulin 287 and insulin 287-placebo

The dose adjustment will be based on the three fasting SMPG values measured on two days prior to titration and on the day of the contact.

If one or more SMPG values are missing, the dose adjustment should be performed on the remaining SMPG value(s). The insulin dose adjustment should aim to reach a SMPG of 3.9–6.0 mmol/L (70–108 mg/dL).

If there are no hypoglycaemic values in the fasting SMPGs value(s) the dose is adjusted according to Table 12-6. If there are hypoglycaemic values the dose is adjusted according to Table 12-7

Table 12-6 Insulin 287 and insulin 287-placebo increase

Mean pre-breakfast SMPG		Dose adjustment
mmol/L	mg/dL	U
3.9 – 6.0	70 – 108	No adjustment
6.1 – 7.0	109 – 126	+ 14
> 7.0	> 126	+ 28

Table 12-7 Insulin 287 and insulin 287-placebo reduction

Lowest pre-breakfast SMPG		Dose adjustment
mmol/L	mg/dL	U
3.0 – 3.8	54 – 69	- 14
< 3.0	< 54	- 28

Deviations from the algorithm

It is recommended that the algorithm is followed. The prescribed daily dose must always correspond to the prescribed weekly dose divided by 7. 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 eCRF by the investigator as applicable.

Missing dose guidance:

The dosing window 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 measurement. If the missing dose is observed from day 5 to day 7 (which is the next p lanned dosing day), subject should inject 50% of the missed dose rounded down to the closest possible dose which can be divided with 7. 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 dosing should still be taken. Additional SMPG measurement should be performed to control BG.

Dose recommendation from V28 (end of treatment) and during follow up

If it is decided that the individual subject should continue on insulin from V28 it is recommended that the subject is switched 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 daily insulin glargine/insulin glargine-placebo dose
- Calculate 50% of the latest weekly insulin 287/insulin 287-placebo dose divided by 7
- Initiate the new daily basal insulin based on the lowest of the two calculated doses above
- Consider titrating the basal insulin once or twice weekly in accordance with Table 12-4 and Table 12-5 during the follow up period

Data collection

The following data should be entered into the diary by the subject and reviewed by the investigator prior to the contact:

- Per protocol pre-breakfast SMPG values measured since last visit/telephone contact

- Insulin glargine/insulin glargine-placebo and insulin 287/insulin 287-placebo doses taken prior to the visit/phone contact

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

- Insulin glargine/insulin glargine-placebo and insulin 287/insulin 287-placebo 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 dose titration is entered into the diary and into the eCRF. 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 Greece: Adequate contraceptive measures are defined as combined hormonal contraception (containing oestrogen and progesterone), which suppress ovulation (oral, intravaginal, percutaneous), progesterone-only hormonal contraception which suppress ovulation (oral, injectable, implantable), intrauterine device, hormone-releasing intrauterine system, bilateral tubal occlusion, partner with vasectomy, sexual abstinence.

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

For Slovakia: It is necessary that the trial sponsor covers all costs for treatment of the disease studied. It is necessary to cover the whole diabetes medication payment, including metformin and DPP4i.

Log of 4383 protocols

Please note that *text in italics* is only here to provide a full overview.

Date	Versions	Submitted	Comments
25-Jun-2018	1.0	Yes	First version on the CTA *nD object ID:* [redacted]

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