Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04880850
Sponsor trial ID:	NN1436-4480
Official title of study:	A 26-week trial comparing the effect and safety of once weekly insulin icodec and once daily insulin glargine 100 units/mL, both in combination with bolus insulin with or without non-insulin anti-diabetic drugs, in subjects with type 2 diabetes on a basal-bolus regimen.
Document date:*	14 April, 2021

* Document date refers to the date on which the document was most recently updated.
Note: The date in the header of Page 2 is the date of compilation of the documents, and not of an update to content.

16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

Protocol title: A 26-week trial comparing the effect and safety of once weekly insulin icodec and once daily insulin glargine 100 units/mL, both in combination with bolus insulin with or without non-insulin anti-diabetic drugs, in subjects with type 2 diabetes on a basal-bolus regimen.

ONWARDS 4

Substance: Insulin icodec

Universal Trial Number: U1111-1247-5269

EudraCT Number: 2020-000474-16

IND Number: 137406

Trial phase: 3a

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	**Date**	**Applicable in country(-ies) and/or site(s)**
Protocol version 4.0	14 April 2021	All countries
Protocol version 3.0	30 November 2020	All countries
Original protocol version 2.0	05 August 2020	All countries

Protocol version 4.0 (14 April 2021*)*

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union[1], because it neither significantly impacts the safety nor physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for preparing protocol, version 4.0:

The protocol has been amended to correct typos and exclude Japan from co-participation in clinical trials evaluating medicinal products for prevention or treatment of COVID-19 disease or postinfectious conditions as per local health authority request.

Section # and name	Description of change	Brief rationale
8.2.2 Physical examinations	"the BMI will be calculated in the eCRF" is corrected to "the BMI should be calculated and recorded in subject's medical records"	Correction
10.6 Appendix 6: Retention of human biosamples	"In case of a systematic hypersensitivity reaction" is corrected to "In case of a systemic hypersensitivity reaction"	Correction of typo
10.8 Appendix 8 Titration guideline	Table for V2 and V3 weekly dose: For "Total daily dose before randomisation (U): 82 " "V2 insulin icodec dose (U)": 960 is corrected to 860	Correction of typo
10.9 Appendix 9: Country/Region-specific requirements	Footnotes related to co-participation in clinical trial for COVID-19 in exclusion criteria 4 and discontinuation criteria 4 are not applicable for Japan.	To meet local Japanese Health Authority (PMDA) request.

Section # and name	Description of change	Brief rationale
10.11 Appendix 11 Protocol amendment history	Amendment history is updated by moving protocol v3.0 history to appendix 11	Due to the new protocol v4.0
11 References	Reference 36 to CTFG guidance is added in Appendix 4. Reference 8 is updated to the latest version 2.0	Reference updates

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Protocol attachment I Global list of key staff and relevant departments and suppliers.

Protocol attachment II Country list of key staff and relevant departments.

1 Protocol summary

1.1 Synopsis

Rationale:

Insulin icodec is a novel long-acting insulin analogue which is developed to safely cover the basal insulin requirements for a full week with a single subcutaneous injection.

The present trial is a 26-week trial designed to investigate effect and safety of once weekly insulin icodec in comparison to once daily insulin glargine 100 units/mL (referred to as insulin glargine in this document), both in combination with a bolus insulin, with or without non-insulin anti-diabetic drugs, in subjects with type 2 diabetes (T2D) on a basal-bolus regimen.

Objectives and endpoints:

Primary objective

The objective of this trial is to demonstrate the effect on glycaemic control of once weekly insulin icodec in combination with insulin aspart, with or without non-insulin anti-diabetic drugs, in subjects with T2D on a basal-bolus regimen. This includes comparing the difference in change from baseline in HbA_{1c} between insulin icodec and insulin glargine after 26 weeks of treatment to a non-inferiority limit of 0.3%.

Estimand

The estimand is the 'treatment policy estimand' defined as the treatment difference between insulin icodec and insulin glargine of the change in HbA_{1c} from baseline to week 26 for all randomised subjects, irrespective of adherence to randomised treatment and changes to anti-diabetic background medication. The following intercurrent events will be handled by the treatment policy strategy: discontinuation of randomised insulin treatment, and withdrawal from the trial (measurements collected after these intercurrent events are used in the primary analysis).

Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline week 0 (V2) to week 26 (V28)	%-point

Overall design:

This is a 26-week randomised, open label, active-controlled, parallel-group, multicentre, multinational, treat-to-target trial with two treatment arms.

Subjects will be randomised (1:1) to receive once weekly insulin icodec or once daily insulin glargine, both in combination with 2-4 times daily injections of insulin aspart.

Key inclusion criteria:

1. Male or female aged above or equal to 18 years at the time of signing informed consent.
2. Diagnosed with T2D ≥ 180 days prior to the day of screening.
3. HbA_{1c} from 7.0-10.0% (53.0-85.8 mmol/mol) both inclusive at screening confirmed by central laboratory analysis.
4. Treated with once daily basal insulin (neutral protamine hagedorn insulin, insulin degludec, insulin detemir, insulin glargine 100 units/mL, or insulin glargine 300 units/mL) and 2-4 daily injections of bolus insulin analog (insulin aspart, faster acting insulin aspart, insulin lispro, insulin glulisine) ≥ 90 days prior to the day of screening with or without any of the following anti-diabetic drugs/regimens with stable doses ≥ 90 days prior to screening:
    - Metformin
    - Sulfonylureas
    - Meglitinides (glinides)
    - DPP-4 inhibitors
    - SGLT2 inhibitors
    - Thiazolidinediones
    - Alpha-glucosidase inhibitors
    - Oral combination products (for the allowed individual oral anti-diabetic drugs)
    - Oral or injectable GLP-1-receptor agonists
5. Body mass index (BMI) ≤ 40.0 kg/m^2.

Key exclusion criteria:

1. Any episodes[a] of diabetic ketoacidosis within 90 days prior to the day of screening.
2. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.
3. Chronic heart failure classified as being in New York Heart Association Class IV at screening.
4. 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).
5. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

[a] as declared by the subject or in the medical records.

Number of subjects:

Approximately 774 subjects will be screened to achieve 580 subjects randomly assigned to trial product.

Treatment groups and duration:

The trial duration is approximately 33 weeks, consisting of a 2-week screening period, followed by a 26-week randomised treatment period and a 5-week follow-up period. All subject will be centrally randomised in a 1:1 manner and assigned to receive once weekly insulin icodec or once daily insulin glargine, both in combination with 2-4 times daily injections of insulin aspart throughout the 26-week treatment period. After end of treatment, subjects will be transferred to a marketed product at the discretion of the investigator.

The following trial products will be supplied by Novo Nordisk for the duration of the trial:

- Insulin icodec 700 units/mL, subcutaneous, solution for injection, 3 mL PDS290 pre-filled pen-injector
- Insulin glargine 100 units/mL, subcutaneous, solution for injection, 3 mL SoloSTAR pre-filled pen-injector
- Insulin aspart 100 units/mL, subcutaneous, solution for injection, 3 mL pre-filled Flexpen

Data monitoring committee: No

1.2 Flowchart

Procedure	*Protocol section*	Screening	Randomisation	Treatment													Follow-up 1	Follow-up 2	Discontinuation follow-up
Visit		V1	V2	V3	V4	V5	V6	V8	V12	V16	V20	V24	V25	V26	V27	V28	V29	V30	V28A
☎ **Weekly Phone Contact number (P) (For details see separate flowchart in 1.3)**							P7	P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23								
Timing of visit (weeks)		≤-2	0	1	2	3	4	6	10	14	18	22	23	24	25	26	28	31	26
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3
Informed consent and demography	10.1 *App. 1*	X																	
Tobacco use	5.3.2	X																	
Eligibility Criteria	5.1 5.2	X	X																
Attend visit fasting	5.3.1		X						X		X					X			
Concomitant illness/medical history	8.2	X	X																
Concomitant medication	6.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	8.2.3	X								X						X			
Physical examination	8.2.2	X														X			
Body measurements	8.2.2	X	X							X						X			X
Eye examination	8.2.5	X														X			

Procedure	***Protocol section***	**Screening**	**Randomisation**	**Treatment**													**Follow-up 1**	**Follow-up 2**	**Discontinuation follow-up**
Visit		V1	V2	V3	V4	V5	V6	V8	V12	V16	V20	V24	V25	V26	V27	V28	V29	V30	V28A
☎ **Weekly Phone Contact number (P) (For details see separate flowchart in 1.3)**							P7	P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23								
Timing of visit (weeks)		≤-2	0	1	2	3	4	6	10	14	18	22	23	24	25	26	28	31	26
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3
ECG	*8.2.4*	X														X			
Pregnancy test	*8.3.5* *10.4* *App.4*		X													X		X	
Laboratory assessments	*10.2* *App.2*	X	X		X			X	X		X					X		X	X
HbA1c		X	X						X		X					X			X
Pop-PK (insulin icodec serum concentration)	*8.5*				X			X	X		X					X		X	
Antibodies (anti-insulin icodec antibodies)	*8.9.1*		X		X			X	X		X					X		X	
4-point SMPG profile	*8.1.1*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event	*8.3* *10.3* *App.3*			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	*8.3* *10.7* *App. 7*			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Training in trial Product, Pen-handling	*6.1*		X	X				X		X		X							

Procedure	***Protocol section***	**Screening**	**Randomisation**	**Treatment**													**Follow-up 1**	**Follow-up 2**	**Discontinuation follow-up**
Visit		V1	V2	V3	V4	V5	V6	V8	V12	V16	V20	V24	V25	V26	V27	V28	V29	V30	V28A
Weekly Phone Contact number (P) (For details see separate flowchart in 1.3)							P7	P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23								
Timing of visit (weeks)		≤-2	0	1	2	3	4	6	10	14	18	22	23	24	25	26	28	31	26
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3
CGM	*8.1.2*		X	X	X	X	X					X	X	X	X	X	X	X	
Drug dispensing	*6*		X					X		X		X							
Hand out and instruct in devices	*6*		X																
End of trial	*4.4*																	X	X

1.3 Flowchart – phone contacts

Phone contacts during the treatment period (P) **Time shown in site visit flow chart**	**Protocol section**	**P7-P23**
Visit window (days)		±3
Concomitant medication	6.5	X
Self-measured plasma glucose	8.1.1	X
Adverse event	*8.3* *10.3* *App.3*	X
Hypoglycaemic episodes	*8.3* *10.7* *App. 7*	X

2 Introduction

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 complications, particularly damage, dysfunction and failure of various tissues – especially the kidney, eye, nerves, heart and blood vessels.[2] Diabetes is generally classified according to aetiological factors, where type 1 diabetes (T1D) and type 2 diabetes (T2D) constitute the vast majority of cases. In the latest edition of the International Diabetes Federation's Diabetes Atlas (2019), the estimated worldwide diabetes prevalence was 463 million, with a prediction that by 2045, the number of people with diabetes will have increased to 700 million.[3]

Insulin icodec (proposed INN) is a novel long-acting insulin analogue which is developed to safely cover the basal insulin requirements for a full week with a single subcutaneous injection. Insulin icodec has a terminal elimination half-life of approximately 196 hours. For subjects with diabetes there is still an unmet medical need for products with the potential to improve clinical outcomes through reduced treatment burden and increased treatment adherence and persistence[4] compared to once or twice daily basal insulin administration. The aim of the development programme for insulin icodec is to improve clinical outcomes for subjects with diabetes by limiting the burden associated with insulin treatment.

2.1 Trial rationale

The present trial is a 26-week trial designed to investigate effect and safety of once weekly insulin icodec in comparison to once daily insulin glargine 100 units/mL (referred to as insulin glargine in this document), both in combination with a bolus insulin, with or without non-insulin anti-diabetic drugs, in subjects with type 2 diabetes (T2D) on a basal-bolus regimen.

The long-acting basal insulin products currently approved for treatment of diabetes are administered once or twice daily. Subjects in need of a basal insulin treatment in combination with bolus insulin have to adhere to a complicated treatment regimen with multiple daily injections. The once weekly treatment regimen for insulin icodec would become a more convenient basal insulin, with significantly fewer injections over time, which could improve treatment adherence[4] as compared to once daily or twice daily basal insulin for subjects with T2D.

The results of the present trial will be important for evaluating the effect and safety parameters in a progressed T2D population specifically on the combined use of insulin icodec and bolus insulin and will be used to support the marketing authorisation approval of insulin icodec. The trial will also generate data for guidance on transfer from once daily basal insulin to once weekly insulin icodec, and data on dosing flexibility.

2.2 Background

Diabetes mellitus

T2D is characterised by insulin resistance, impaired insulin secretion, increased hepatic glucose output due to glucagon dysregulation resulting in chronic hyperglycaemia.[5] The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver.[6] The current treatment cascade follows a stepwise approach comprising lifestyle changes in combination with pharmacological intervention. In many countries, metformin is recommended as initial pharmacological therapy, followed by combination therapy with other oral anti-diabetic drugs, glucagon-like peptide 1 receptor agonists (GLP-1 RA) and/or insulin as the disease progresses.[7] 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.[8] Clinical inertia, often resulting from a resistance to insulin initiation and intensification, is a major contributing factor to subjects with T2D who are not achieving recommended glycaemic targets.[9, 10] Increased convenience is believed to support timely insulin initiation in the treatment for T2D and thereby overcoming the clinical inertia associated with insulin initiation.

Insulin icodec

Insulin icodec is a novel long-acting insulin analogue which is developed to safely cover the basal insulin requirements for a full week with a single subcutaneous injection. Insulin icodec has a terminal elimination half-life of approximately 196 hours. The molecule consists of a peptide backbone and a fatty acid-containing side-chain. The peptide backbone is more resistant towards proteolytical degradation compared to human insulin and the side chain gives a strong binding to albumin. Both features contribute to the long action of insulin icodec.

The development programme for insulin icodec is currently ongoing. Three clinical pharmacology trials, NN1436-4314 [T2D], NN1436-4226 [renal impaired] and NN1436-4422 [T1D] have been completed. No unexpected safety concerns were identified. Two clinical pharmacology trials (NN1436-4462 [T2D] and NN1436-4225 [T1D]) are ongoing.

Three phase 2 trials in subjects with T2D have recently been completed (NN1436-4465, NN1436-4383 and NN1436-4466). Once weekly insulin icodec was shown to provide comparable glucose lowering effects and similar safety profile to insulin glargine in subjects with T2D. Results from these trials were used in the development of the insulin icodec titration guideline, see Appendix 8 (Section 10.8).

A comprehensive review of results from the non-clinical and clinical studies of insulin icodec can be found in the current edition of the investigator's brochure[11] and any updates hereof.

Insulin glargine

For further details on insulin glargine, please refer to the current EMA summary of product characteristics for insulin glargine (Lantus®)[12], the US prescribing information for insulin glargine (Lantus®)[13], or any locally approved label.

Insulin aspart

For further details on insulin aspart, please refer to the current insulin aspart investigator's brochure[14], the current EMA summary of product characteristics for insulin aspart (NovoRapid®)[15], the US prescribing information for insulin aspart (NovoLog®)[16], or any locally approved label.

Trial population

The trial population will consist of subjects with T2D on a basal-bolus regimen.

Subjects included in the trial will already be on basal insulin analogue treatment with bolus insulin with or without non-insulin anti-diabetic drugs ensuring a trial population representative of a progressed insulin experienced T2D population.

Subjects with T1D are excluded from this trial. Subjects with T1D will be addressed in a dedicated trial.

For more information on the trial population, see Section 4.2, or the inclusion and exclusion criteria, Sections 5.1 and 5.2, respectively.

2.3 Benefit-risk assessment

2.3.1 Risk assessment

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

Identified/Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Trial treatment: insulin icodec		
Identified risk: Hypoglycemia	Hypoglycemia is an anticipated undesirable effect related to the pharmacological mechanism of insulin.	Exclusion criteria in clinical trials with subjects at increased risk of hypoglycaemia: • Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8[17] (Section 5.2), • Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator. Frequent blood glucose 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. The risk of hypoglycaemia is addressed in the SI-IC and IB[11]. Subjects are provided with a guidance on hypoglycaemia awareness and rescue actions.
Identified risk: Injection site reactions	Injection site reactions may occur with all injectable drugs. Injection site reactions were reported in trials NN1436-4422, NN1436-4383, NN1436-4465, NN1436-4466, NN1436-4226. All were mild and resolved during continued treatment with insulin icodec.	Subjects are instructed by the investigators on the most appropriate injection techniques. Recommendations on rotation of the site of injection are included in the trial protocol and SI-IC. Investigators and subjects will be instructed to monitor for injection site reactions at the place of injection for early detection. Investigators should ensure careful monitoring and medical evaluation in case of injection site reaction occurrence. The risk of injection site reactions is described in the IB[11] and the SI-IC. For further information on injection site reactions, please refer to Appendix 3 (Section 10.3.3).

Potential risk: Hypersensitivity	Severe systemic hypersensitivity reactions may potentially occur following injection of therapeutic proteins. No systemic hypersensitivity reactions were observed in trials NN1436-4314, NN1436-4383, NN1436-4465, NN1436-4466, NN1436-4226 and NN1436-4422.	Known or suspected hypersensitivity to trial product(s) or related products is an exclusion criterion in the clinical trial. Subjects and investigators will be instructed in signs and symptoms of hypersensitivity reactions and subjects will be instructed to contact the site immediately in case of signs of systemic hypersensitivity. Blood sampling for assessment of antibodies against insulin icodec, as well as other assessments will be conducted in the case of systemic hypersensitivity reaction. Confirmed anti-insulin icodec antibody positive samples will have an antibody titer value determined and will be further tested for cross-reactivity to endogenous insulin. The risk of hypersensitivity reactions is described in the IB[11] and SI-IC. For further information on hypersensitivity reactions, please refer to Section 8.9.2 and Appendix 3 (Section 10.3.3).
Potential risks: Antibody formation leading to changes in clinical effect	Antibodies to exogenously delivered insulin are common with insulin treatment but are not often clinically significant. In trial NN1436-4383, the proportion of subjects with anti-insulin antibodies was higher with insulin icodec (82.1%) than insulin glargine (35.0%). Maximum level of antibody response was higher against insulin icodec than insulin glargine. No apparent relationship between antibody titres and change in HbA_{1c} or weekly insulin dose was observed.	Blood samples will be taken for analysis of serum antibodies against insulin icodec at pre-first dose time point. Then at appropriate time points during the trial and at the end of trial visit. Confirmed anti-insulin icodec antibody positive samples will have an antibody titer value determined and will be further tested for cross-reactivity to endogenous insulin. There will be a close monitoring of the glycemic control on subject level during the trial. In case lack of clinical effect is observed, rescue medication will be provided if deemed necessary. In the case of systemic hypersensitivity reaction blood sampling for assessment of antibodies against insulin icodec, as well as other assessments will be conducted. For more information, please refer to Section 8.9.2 and Appendix 3 (Section 10.3.3).

Trial procedures		
Potential risk: COVID-19 infection in relation to participation in trial	Subjects may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country.	The risk of COVID-19 transmission in relation to site visits is overall considered to be low, however this may vary between geographical area. To minimize the risk as much as possible, the following measures have been taken: • Cautious subject recruitment planning ensures controlled subject enrolment in countries where the COVID-19 pandemic is evaluated to be sufficiently under control, and at sites where health care resources are evaluated to be adequate. • On-site visits will be well-prepared and as short as possible. Physical contact between subjects and site staff will be limited to the extent possible, and protective measures will be implemented (e.g. use of masks, sanitizers, no aerosol-generating procedures etc. according to the local practice). • A COVID-19 mitigation plan has been developed for this trial which lists the additional actions to consider in case a site or country are locked down and subjects cannot attend on-site visits.
Other		
For more information regarding the known and expected benefits and risk of insulin glargine, please refer to the insulin glargine EMA SmPC[12], the US PI[13], or any locally approved label. For more information regarding the known and expected benefits and risk of insulin aspart, please refer to the insulin aspart IB[14], the EMA SmPC[15], the US PI[16], or any locally approved label.		

2.3.2 Benefit assessment

Insulin icodec is currently in development for treatment of diabetes mellitus. In both clinical and non-clinical trials, insulin icodec has 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. Market research has shown that people with diabetes, put value in reducing the number of insulin injections[18]. Therefore, the treatment

adherence and quality of life are expected to increase by introducing a once weekly basal insulin treatment.

The trial population will consist of subjects with T2D on a basal-bolus regimen. For all subjects participating in this 26-week trial, the anticipated benefits include improved glycaemic control. The titration algorithm in Appendix 8 (Section 10.8), which specifies recommended adjustments of basal insulin dose and bolus insulin dose at different plasma glucose levels, will be used to ensure that subjects receive optimal treatment. Subjects will receive intense medical care by means of contact with the sites weekly.

2.3.3 Overall benefit-risk conclusion

Insulin icodec is efficacious at clinically relevant doses. Titration guidance for phase 3a trials aims to achieve good glycaemic control without increasing the risk of hypoglycaemic events.

No new significant safety information that changes the current benefit–risk profile of insulin icodec emerged from the ongoing and completed clinical trials. The safety profile of insulin icodec remains in line with the cumulative experience.

As an overall assessment, Novo Nordisk evaluates that the benefit–risk balance of insulin icodec remains favourable.

Considering the measures taken to minimise risk to subjects participating in this trial, the potential risks identified in association with insulin icodec are justified by the anticipated benefits that may be afforded to subjects with diabetes mellitus.

More detailed information about the known and expected benefits and risk of insulin icodec can be found in the investigator's brochure[11] and any updates hereof.

3 Objectives and endpoints

3.1 Primary, secondary and exploratory objective and estimand

3.1.1 Primary objective

To demonstrate the effect on glycaemic control of once weekly insulin icodec in combination with insulin aspart, with or without non-insulin anti-diabetic drugs, in subjects with T2D on a basal-bolus regimen. This includes comparing the difference in change from baseline in HbA_{1c} between insulin icodec and insulin glargine after 26 weeks of treatment to a non-inferiority limit of 0.3%.

3.1.2 Secondary objective

To compare safety with once weekly insulin icodec versus once daily insulin glargine, both in combination with insulin aspart, with or without non-insulin anti-diabetic drugs, in subjects with T2D on a basal-bolus regimen.

3.1.3 Estimand

The estimand is the 'treatment policy estimand' defined as the treatment difference between insulin icodec and insulin glargine of the change in HbA_{1c} from baseline to week 26 for all randomised subjects, irrespective of adherence to randomised treatment and changes to anti-diabetic background medication. The following intercurrent events will be handled by the treatment policy strategy: discontinuation of randomised insulin treatment, and withdrawal from the trial (measurements collected after these intercurrent events are used in the primary analysis).

3.2 Primary, secondary and exploratory endpoints

3.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline week 0 (V2) to week 26 (V28)	%-point

3.2.2 Secondary endpoints

3.2.2.1 Confirmatory secondary endpoints

Not applicable for this trial.

3.2.2.2 Supportive secondary endpoints

Secondary efficacy endpoints

Endpoint title	Time frame	Unit
Change in fasting plasma glucose (FPG)	From baseline week 0 (V2) to week 26 (V28)	mmol/L
Time in target-range 3.9–10.0 mmol/L (70-180 mg/dL)*	From week 22 (V24) to week 26 (V28)	% of readings

* using continuous glucose monitoring (CGM) system, Dexcom G6

Secondary safety endpoints

Endpoint title	Time frame	Unit
Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 31 (V30)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 31 (V30)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 31 (V30)	Number of episodes
Time spent < 3.0 mmol/L (54 mg/dL)*	From week 22 (V24) to week 26 (V28)	% of readings
Time spent > 10 mmol/L (180 mg/dL)*	From week 22 (V24) to week 26 (V28)	% of readings
Mean weekly insulin dose	From week 24 (V26) to week 26 (V28)	U
Change in body weight	From baseline week 0 (V2) to week 26 (V28)	kg

* using continuous glucose monitoring (CGM) system, Dexcom G6

3.2.3 Exploratory endpoints

Endpoint title	Time frame	Unit
Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 26 (V28)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 26 (V28)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 26 (V28)	Number of episodes

4 Trial design

4.1 Overall design

This is a 26-week randomised, open label, active-controlled, parallel-group, multicentre, multinational, treat-to-target trial with two treatment arms investigating the effect on glycaemic control and safety of treatment with once weekly insulin icodec compared to once daily insulin

glargine, both in combination with insulin aspart with or without non-insulin anti-diabetic drugs, in subjects with T2D.

The trial duration is approximately 33 weeks, consisting of a 2-week screening period, followed by a 26-week randomised treatment period and a 5-week follow-up period. The overall trial design and visit schedule are outlined in Figure 4-1 and trial flowchart (see Section 1.2), respectively.

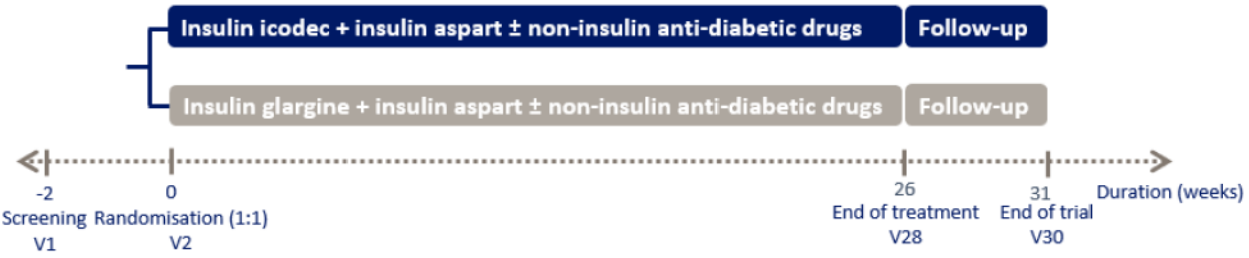

Figure 4-1 Trial design

Subjects will be randomised (1:1) to receive once weekly insulin icodec or once daily insulin glargine, both in combination with 2-4 times daily injections of insulin aspart. The dose and dosing frequency of any pre-trial non-insulin anti-diabetic treatment should not be changed during the trial unless due to safety concerns; except for treatment with sulfonylureas and glinides that must be discontinued at randomisation. During the 26-week treatment period, subjects will have contact with the site weekly either at site visits or by phone. The end of treatment visit (V28) will be one week after the last dose of insulin icodec and on the day of or the day after the last dose of insulin glargine. Two follow-up visits (V29 and V30) will be performed 2 and 5 weeks, respectively, after the end of treatment visit. This will allow for appropriate wash-out of trial drug, following at least 5 half-lives of insulin icodec. After the end of treatment subjects will be transferred to a marketed product at the discretion of the investigator.

To evaluate the effect on glycaemic control, subjects will have continuous glucose monitoring (CGM) profiles collected, as specified in the flowchart (see Section 1.2). The CGM data will be blinded for both subjects and investigators.

Event adjudication will be performed for acute coronary syndrome events (acute myocardial infarction or unstable angina pectoris requiring hospitalisation), cerebrovascular events (stroke or transient ischemic attack), heart failure (requiring hospitalisation or urgent heart failure visit) and all-cause death.

4.2 Scientific rationale for trial design

The trial is designed to investigate the effect on glycaemic control and safety of once weekly insulin icodec versus once daily insulin glargine in combination with 2-4 daily injections of insulin aspart during 26 weeks of treatment.

Currently, basal insulins are dosed once or twice daily. In order to compare to well established and widely used basal insulin analogues with once daily dosing, insulin glargine has been chosen as comparator.

The treatment arms will be open label due to safety concerns. It was not considered feasible to blind the two treatments due to the risk of pen-mix-up in a double-blind, double-dummy trial using three different pens (two basal and one bolus pen).

The treatment duration of 26 weeks is evaluated to be adequate time for assessing effect on glycaemic control and safety. This duration will also allow for up-titrating the basal insulin. The treat-to-target approach has been chosen in order to ensure optimal titration of insulin based on self-measured plasma glucose (SMPG) values with the aim of improving HbA_{1c} in the period.

Titration of insulin icodec and insulin glargine will be based on pre-breakfast SMPG values and follow the principles outlined in the titration guideline, see Appendix 8 (Section 10.8). Said guideline further includes the titration principles of insulin aspart, which is based on pre-prandial and bedtime SMPG values. CGM values will be used during the reporting phase to generate profiles for evaluating the effect on glycaemic control during initiation of trial product, steady state and follow-up. To avoid influence on titration and the glycaemic control the CGM data will be blinded for both study subjects and investigator.

Subjects included in the trial will already be on basal insulin analogue treatment with bolus insulin with or without non-insulin anti-diabetic drugs ensuring a trial population representative of a progressed insulin experienced T2D population. To minimise the risk of hypoglycaemia sulfonylureas and glinides must be discontinued at randomisation.

To safeguard subjects, the inclusion and exclusion criteria defined in this trial will limit the trial population to subjects not suffering from advanced underlying diseases other than T2D and related diseases. This is to avoid compromising the safety of the subjects participating in the trial and to strengthen conclusions regarding the effect and safety of once weekly insulin icodec.

During the 26 weeks long treatment period, the subjects will have weekly contact with the site, either as site visits or phone contacts. The end of trial visit is planned six weeks after the last weekly dose of insulin icodec, allowing enough time for wash-out of trial drug, following at least five half-lives of insulin icodec.

A sufficient assay-sensitivity for the non-inferiority evaluation will be ensured by the treat-to-target trial design, the applied titration target/algorithm together with close titration surveillance and by having focus on adherence and discontinuation.

4.2.1 Subject input into design

Not applicable for this trial.

4.3 Justification for dose

Insulin glargine will be switched from the pre-trial basal insulin analogues according to local label and insulin icodec will be initiated according to the principles outlined in the titration guideline in Appendix 8 (Section 10.8). A 50% loading dose will be applied to avoid glycaemic slip during the first few weeks of treatment. No safety concerns have been identified in subjects with T2D, including vulnerable subjects, using a loading dose when initiating insulin icodec (trial NN1436-4466).

One unit of insulin icodec has similar glucose lowering effect to one unit of insulin glargine, and therefore once weekly dosing corresponds to seven times the daily dose of the once daily comparator.

The PK/PD properties of insulin icodec following five weeks of once weekly dosing in subjects with T2D (trial NN1436-4314) showed that insulin icodec exposure was well distributed across the dosing interval, with a PK profile suitable for once weekly dosing. Insulin icodec was well tolerated in subjects with T2D and no unexpected safety concerns were identified after multiple once weekly dosing in the dose range of 12−24 nmol/kg (2-4 units/kg).

After randomisation, subjects should start once daily insulin glargine or once weekly insulin icodec injections on the same day. Due to the longer half-life of insulin icodec, the last dose of insulin icodec will be administered 25 weeks after randomisation, while the last dose of once daily insulin glargine will be administered 26 weeks after randomisation. The follow-up period for both insulin icodec and insulin glargine will be the 5 weeks from end of treatment (V28) until end of trial (V30).

Insulin aspart should be taken 2-4 times daily with meals throughout the 26 weeks treatment duration. Switch from other short-acting insulin analogues should be done unit-to-unit.

Further details on dose adjustment can be found in the titration guideline in Appendix 8 (Section 10.8).

4.4 End of trial definition

A subject is considered to have completed the trial if he/she has completed all phases of the trial including the last visit.

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

5 Trial population

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

For country-specific requirement to the inclusion and exclusion criteria, please refer to Appendix 9 (Section 10.9) for further information.

5.1 Inclusion criteria

Subjects are eligible to be included in the trial only if all 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.
3. Age above or equal to 18 years at the time of signing informed consent.
4. Diagnosed with T2D ≥ 180 days prior to the day of screening.
5. HbA_{1c} from 7.0-10.0% (53.0-85.8 mmol/mol) both inclusive at screening confirmed by central laboratory analysis.
6. Treated with once daily basal insulin (neutral protamine hagedorn insulin, insulin degludec, insulin detemir, insulin glargine 100 units/mL, or insulin glargine 300 units/mL) and 2-4 daily injections of bolus insulin analog (insulin aspart, faster acting insulin aspart, insulin lispro, faster acting insulin lispro, insulin glulisine) ≥ 90 days prior to the day of screening with or without any of the following anti-diabetic drugs/regimens with stable doses ≥ 90 days prior to screening:
    - Metformin
    - Sulfonylureas
    - Meglitinides (glinides)
    - DPP-4 inhibitors
    - SGLT2 inhibitors
    - Thiazolidinediones
    - Alpha-glucosidase inhibitors
    - Oral combination products (for the allowed individual oral anti-diabetic drugs)
    - Oral or injectable GLP-1 RAs
7. Body mass index (BMI) ≤ 40.0 kg/m^2.

5.2 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 an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice).
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening[a].

5. Any disorder, except for conditions associated with T2D, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.
6. Any episodes[b] of diabetic ketoacidosis within 90 days prior to the day of screening.
7. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.
8. Chronic heart failure classified as being in New York Heart Association Class IV at screening.
9. Planned coronary, carotid or peripheral artery revascularisation.
10. Renal impairment with estimated glomerular filtration rate value of < 30 ml/min/1.73m^2 at screening[19] by central laboratory analysis.
11. Impaired liver function, defined as Alanine Aminotransferase ≥ 2.5 times or Bilirubin >1.5 times upper normal limit at screening by central laboratory analysis.
12. Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8[17] (Section 8.2).
13. Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator.
14. Inadequately treated blood pressure defined as systolic ≥ 180 mmHg or diastolic ≥ 110 mmHg at screening.
15. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days prior to the day of screening.
16. 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).
17. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.
18. Presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in situ prostate cancer) within 5 years prior to the day of screening.
19. Anticipated change in lifestyle affecting glucose control.

[a] Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening.
[b] as declared by the subject or in the medical records.

5.3 Lifestyle considerations

5.3.1 Meals and dietary restrictions

The subjects should be fasting when attending some of the visits, see flowchart (Section 1.2). 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 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 procedures should be re-scheduled.

5.3.2 Caffeine, alcohol and tobacco

Tobacco use is defined as smoking at least one cigarette or equivalent daily.

5.3.3 Physical activity

Not applicable for this trial.

5.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, and eligibility criteria.

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. If the subject has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters, re-sampling is not allowed. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

5.5 Run-in criteria, randomisation criteria and dosing day criteria

Not applicable for this trial.

6 Treatments

6.1 Treatments administered

Investigational medicinal products (IMP)

All investigational medical products (IMPs) are listed in Table 6-1.

Table 6-1 Investigational medicinal product provided by Novo Nordisk

Trial product name:	**Insulin icodec 700 units/mL** *(IMP, test product)*	**Insulin glargine 100 units/mL** *(IMP, reference therapy)*
Dosage form	Solution for injection	Solution for injection
Route of administration	Subcutaneous (into the thigh, upper arm or abdomen)	Subcutaneous (into the thigh, upper arm or abdomen)
Recommended initial dose	Please refer to Appendix 8, Section 10.8	Please refer to Appendix 8, Section 10.8
Dosing instructions	Administer insulin icodec once weekly, on the same day each week, at any time of the day. The day of weekly administration can be changed if necessary, by up to 3 days. A minimum of 4 days between injections should always be ensured. Rotation of injection site is recommended.	Administer insulin glargine once daily, at any time of the day but at the same time every day throughout the trial. Rotation of injection site is recommended.
Packaging	3 mL PDS290 pre-filled pen-injector	3 mL SoloSTAR pre-filled pen-injector

- At randomisation visit (V2) subjects should administer trial drug at site
- Subjects should be instructed to discard the needle after each injection and store the pen-injector without a needle attached.

Non-investigational medicinal products (NIMP)

Table 6-2 Non-investigational medicinal products

Trial product name:	**Insulin aspart 100 units/mL** *(NIMP, auxiliary therapy)*
Dosage form	Solution for injection
Route of administration	Subcutaneous (into the thigh, upper arm or abdomen)
Recommended initial dose	Please refer to Appendix 8, Section 10.8
Dosing instructions	Insulin aspart should be administered with meals 2-4 times daily. Rotation of injection site is recommended
Packaging	3 mL pre-filled Flexpen
Provider	Novo Nordisk

Non-insulin background medication

After randomisation subjects should continue their pre-trial non-insulin anti-diabetic background medication throughout the entire trial except from sulfonylureas and glinides, which must be discontinued at randomisation. The background medication should be maintained at the stable, pre-

trial dose and at the same frequency during the entire treatment period unless due to safety concerns.

In addition, the background medication:

- is considered to be non-investigational medicinal product (NIMP)
- will not be provided by Novo Nordisk and should be purchased or otherwise delivered to subjects in accordance with local health plans
- should be used in accordance with standard of care or local label in the individual country at the discretion of the investigator.

Auxiliary supplies

Auxiliary supplies comprise supplies other than trial products. Auxiliary supplies will be provided in accordance with the trial materials manual, please see Table 6-3.

Table 6-3 Auxiliary supplies

Auxiliary supply	Details
Needles	Needles for pre-filled pen injectors. Only needles provided and approved by Novo Nordisk must be used for administration of trial product.
Blood glucose (BG) meter	At randomisation (V2) subjects must be instructed in how to use the BG meter and the BG meter should be linked to the eDiary as described in the eDiary site guide. Please refer to the [redacted] manufacturer's guide.
Continuous glucose monitoring (CGM) system	At randomisation (V2) subjects must be instructed in handling of the CGM. Please refer to the Dexcom G6® manufacturer's guide provided.
eDiary	Subject Mobile App, HCP Web Portal, & Cloud Service. Please refer to the eDiary site guide.

- Information about the PDS290 pre-filled pen-injector and pre-filled FlexPen can be found in the directions for use provided in the eDiary.
- Information about the SoloSTAR pre-filled pen-injector can be found in the summary of product characteristics.
- A pen differentiation guide will be provided.
- Training in the pen-injectors is the responsibility of the investigator or a delegate and must be repeated during the trial at regular intervals, as specified in the flowchart (see Section 1.2) in order to ensure correct use of the pen-injector.

6.1.1 Medical devices

6.1.1.1 Investigational medical device

Not applicable for this trial.

6.1.1.2 Non-investigational medical devices

Non-investigational medical devices are listed as auxiliary supplies (Table 6-3).

For the countries where BG meter and CGM are not approved, please refer to the Appendix 9 (Section 10.9) country-specific requirements for further information.

6.2 Preparation/handling/storage/accountability

Only subjects randomised to treatment may use trial product and only delegated site staff may supply trial product.

- Acceptable temperature ranges and conditions for storage and handling of each trial product when not in use and when in use are described in the trial material manual and trial product label.
- Each site will be supplied with sufficient trial product for the trial on an ongoing basis. Trial product will be distributed to the sites according to screening and randomisation.
- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that 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 delegated site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the trial material manual.
- The investigator or designee is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- The investigator or designee must instruct the subject in what to return at next visit.
- Each single pen should be accounted.
- 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.
- All returned, un-used, expired or damaged trial products (for technical complaint samples, see Appendix 5 (Section 10.5)) 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 site.

6.3 Measures to minimise bias: Randomisation and blinding

- This is an open label trial; however, the specific treatment for a subject will be assigned using an IWRS. The site will access the IWRS before the start of trial product administration for each subject. Potential bias will be reduced by central randomisation and adjudication.

- All subjects will be centrally screened and randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed/allocated at the trial visits summarised in the flowchart (see Section 1.2).

6.4 Treatment compliance

Drug treatment compliance

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

When subjects self-administer trial product at home, compliance with trial product administration will be assessed by cross checking the following sources and comparing these to the expected use:

- Drug accountability information
- Review of eDiaries including SMPG profiles, insulin dose and hypoglycaemia reporting
- Evaluating glycaemic control and adherence to the visit schedule
- If any suspicion of non-compliance arises the site must enter into a dialogue with the subject, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented in the medical record.

6.5 Concomitant medication

Any medication other than the trial product and anti-diabetic medication that the subject receives from screening (V1) until end of trial visit (V30) must be recorded along with:

- Generic name or trade name
- Indication
- Dates of administration including start and stop date.

Concomitant medication (diabetes)

Any anti-diabetic medication other than the trial product that the subject receives from screening (V1) until end of trial visit (V30) must be recorded in a separate concomitant medication (diabetes) form in the electronic case report form (eCRF).

The following information must be recorded for oral anti-diabetic drugs, GLP-1 RAs, insulin products including pre-trial insulin and post-treatment insulin in the follow-up period:

- Generic name or trade name (for insulin products: only trade name).
- Dates of administration including start and stop date.
- Doses and frequency (e.g. once daily, twice daily).

Until end of treatment (V28) only randomised treatment (trial products and pre-trial non-insulin anti-diabetic background medication except for sulfonylureas and glinides which must be discontinued at randomisation) are allowed, unless due to safety reasons at the discretion of the

investigator. If the investigator chooses to initiate anti-diabetic medication or change dose of pre-trial anti-diabetic background medication prior to end of treatment (V28), this should be registered in the eCRF as change in concomitant medication (diabetes).

Changes in concomitant medication including anti-diabetic medication and other indications must be recorded at each visit. If a change is due to an adverse event, then this must be reported according to Section 8.3.

For information regarding concomitant medication collection including anti-diabetic medication and other indications for subjects who discontinue trial product see Section 7.

6.5.1 Rescue medication or Rescue therapy

Not applicable for this trial.

6.6 Dose modification

Doses are adjusted according to blood/plasma glucose values as described in Appendix 8 (Section 10.8).

6.6.1 Dose escalation trials

Not applicable for this trial.

6.7 Treatment after end of trial

When discontinuing trial products, 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 in Appendix 8 (Section 10.8).

7 Discontinuation of trial treatment and subject discontinuation/withdrawal

Treatment of a 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 (V28) as soon as possible to collect the required data for the analysis of the primary endpoint. Two follow-up visits, V29 and V30, must be performed after discontinuation of the trial product. Visits V29 and V30 must be conducted 3 and 6 weeks respectively after discontinuation of once weekly insulin icodec and 2 and 5 weeks respectively after discontinuation of once daily insulin glargine. It is stressed that the visit window is plus 3 days for both visits V29 and V30.

Further, it is important that discontinued subjects come in for discontinuation follow-up visit V28A, 26 weeks after the randomisation visit. V28A will be the last visit for discontinued subjects.

Subjects who prematurely discontinue trial product should keep and use the eDiary, and return it at the follow-up 2 visit (V30).

The investigator should change subject status in the healthcare professional (HCP) web portal to 'Follow-up' at the end of treatment visit to ensure that the subject should no longer report insulin dose.

Continue to collect, record and report AEs as described in Section 8.3. AEs and anti-diabetic medication should be collected and recorded in the eCRF until the discontinuation follow-up visit (V28A) for discontinued subjects, no other concomitant medication will be collected. Please, refer to Section 6.7 for treatment after end of trial.

In case of any uncertainty regarding the scheduling of the visits after discontinuation or questions to said visits, the investigator should consult Novo Nordisk for further guidance.

Only subjects who withdraw consent will be considered as withdrawn from the trial. Subjects must be educated about the continued scientific importance of their data, even if they discontinue trial product. Further, the site should stay in contact with discontinued subjects by phone and/or site visits to motivate subjects to attend the visits until the discontinuation follow-up visit (V28A). Site contact with discontinued subjects should be documented in the medical record.

7.1 Discontinuation of trial treatment

The trial product must be discontinued, if any of the following applies for the subject:

1. Safety concern related to trial product or unacceptable intolerability
2. Pregnancy
3. Intention of becoming pregnant
4. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical trial[a]
5. Lack of efficacy, defined as fulfilment of ALL 4 criteria below:
    a. No reduction in HbA_{1c} measured by central laboratory from randomisation (V2) to V12, or to V20, AND
    b. the pre-breakfast SMPG readings on 3 consecutive days higher than 240 mg/dL (13.3 mmol/L) within the last two weeks period despite appropriate dose adjustments, AND
    c. a confirmatory fasting plasma glucose exceeding 240 mg/dL (13.3 mmol/L) measured by central laboratory. The subject should come in for an unscheduled visit

as soon as possible (within one week), the next scheduled visit should not be awaited, AND

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

[a] Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator discretion without discontinuing trial product.

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

A subject, who does not fulfil the eligibility (inclusion/exclusion) criteria, must not be randomised. Randomisation in violation of any of the eligibility criteria is good clinical practice (GCP) non-compliance and must be reported to the sponsor without delay. This will be handled as an important protocol deviation, and the independent ethics committee/institutional review board (IEC/IRB) and regulatory authorities must be notified according to local requirements.

Subjects that are randomised in violation of inclusion and exclusion criteria can be allowed to continue in the trial and receive trial product if there are no safety concerns as evaluated by the investigator and Novo Nordisk medical specialist.

7.1.1 Temporary discontinuation of trial treatment

The subject should adhere to the treatment to the extent possible, with the exception of any adverse events such as hospitalisation or safety concerns, at the discretion of the investigator. Subjects who have temporarily discontinued trial product are allowed to restart trial product, unless any of the discontinuation criteria specified in Section 7.1 applies.

7.1.2 Rescue criteria

Not applicable for this trial.

7.2 Subject discontinuation/withdrawal from the trial

A subject may withdraw consent at any time at his/her own request. If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to the end of treatment visit (V28). See the flowchart (Section 1.2) for data to be collected.

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

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

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

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 end of trial form in the eCRF.

7.2.1 Replacement of subjects

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

7.3 Lost to follow-up

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

The following actions must be taken if a subject fails to return to the 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 or designee 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'.

8 Trial assessments and procedures

The following sections describe the assessments and procedures, while their timing is summarised in the flowchart (see Section 1.2).

- Informed consent must be obtained before any trial related activity, see Appendix 1 (Section 10.1.3).
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all inclusion criteria and none of the exclusion 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 site staff that can be contacted in case of emergency.

- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- Assessments should be carried out according to the clinic's standard of practice unless specified in the current section. Efforts should be made to limit the bias between the assessments. The suggested order of the assessments at randomisation visit (V2) is as follows:
    - Blood sample collection
    - Other assessments to confirm eligibility
    - Randomisation in IWRS
    - Continuous glucose monitoring fitting and training
    - The investigator should create a subject profile and record administrative information (e.g. subject ID, year of birth and gender and treatment arm in the HCP web portal
    - Subjects should be provided with an eDiary and instructed in how to use it.
    - The BG meter should be connected with the eDiary
    - A fasting SMPG should be measured using the BG meter
    - Dosing of trial product.
- For information regarding the eDiary and HCP web portal please refer to the site guide.
- Please refer to Section 6.4 for drug treatment compliance.
- All data entered in the eDiary is considered source data. The investigator should review all the data for the subjects through the HCP web portal, before or during each visit/phone contact.
- Review of eDiary, ECG, laboratory reports, eye- and physical examinations must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the eDiary is needed, the subject must be questioned, and a conclusion made in the subject's source documents, the eDiary should be updated retrospectively if applicable. Care must be taken not to bias the subject.
- 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; laboratory reports, BG meter, CGM, pictures and ECG recordings.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 (Section 10.2) for further details on laboratory samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart (see Section 1.2).

8.1.1 Self-measured plasma glucose (SMPG)

Subjects will be provided with a blood glucose meter including auxiliaries. 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 should be used for the plasma glucose measurements required in the protocol, as described in the flowchart (see Section 1.2).

A baseline SMPG value, in fasting condition, should be collected using the BG meter at V2.

4-point daily SMPG

Subjects should be instructed to measure their pre-prandial and bedtime SMPGs daily from week 0 (V2) to end of trial (V30) at the following time points: pre-breakfast, pre-lunch, pre-dinner, and at bedtime. The subject shall transfer the measured SMPG values into the eDiary.

Selected titration data (e.g. certain SMPGs and dose data) from the eDiary will be used during the trial for central titration surveillance, to ensure compliance with the titration guideline in Appendix 8 (Section 10.8) and will not be reported in the clinical trial report. All data will be stored by Novo Nordisk (see Appendix 1, Section 10.1).

8.1.2 Continuous glucose monitoring

Subjects will be equipped with a CGM device during the treatment periods from week 0 (V2) to week 4 (V6), and from week 22 (V24) to week 26 (V28) and during the follow-up period from week 26 (V28) to week 31 (V30).

The CGM system used in this trial will be the Dexcom G6®.

The CGM readings will be blinded to both the subject and investigator and will not be used for any insulin dose titration or hypoglycaemic episode reporting.

If a subject withdraws consent during the trial, a site visit should be scheduled in order to remove the CGM sensor and upload the data from the receiver.

CGM fitting and training

The site staff will closely supervise and assist on fitting of the sensor and transmitter on the subject during the site visits. Training in the CGM is the responsibility of the investigator or site staff at the relevant visits. For information on fitting, and changing of the CGM parts, please refer to the manufacturer's manual and subject guide provided.

CGM Sensor Check

The site staff should ensure that the subject has fitted the sensor correctly and that the CGM receiver is working. This will be done in person during the clinic visit, as specified in the flowchart (see Section 1.2). At the end of treatment visit (V28), the site should ensure the subject can change the sensor at home weekly during the follow-up period.

CGM Upload

Data stored on the CGM receiver must be uploaded at the site by the site staff to the CGM software following the instruction provided to the sites. The upload will be documented by the system directly.

The serial number of the CGM receiver must be recorded in the eCRF at the start of each CGM period. In case the CGM receiver is being replaced, the serial number should be updated.

8.1.3 Clinical efficacy laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the flowchart (see Section 1.2) and the laboratory manual.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the flowchart (see Section 1.2).

A **concomitant illness** is any illness that is already present at the time point from which AEs are collected 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 experienced prior to the time point from which AEs are collected. Only relevant medical history as judged by the investigator will be recorded in the eCRF.

In case of an abnormal and clinically significant finding fulfilling the definition of a concomitant illness or medical history, the investigator must record the finding on the Medical History/Concomitant Illness form.

With regard to exclusion criteria 12 (Section 5.2), information on hypoglycaemia unawareness will be recorded according to Clarke's questionnaire, question 8[17]. The investigator must ask the subject in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" Subjects answering 'never, rarely or sometimes' are considered to have impaired awareness of hypoglycaemia, whereas those answering “often or always” are not.

8.2.1 Insulin dose

The prescribed insulin doses will be determined by the investigator in accordance with the titration guideline (see Appendix 8, Section 10.8).

During the trial, starting at randomisation (V2), subjects must be instructed to report date, dose and time of once weekly insulin or once daily insulin, and of bolus insulin in the eDiary. In the follow-up period if the subject switches to a new basal insulin and a new bolus insulin, the subject should also report date, dose and time of the new basal and bolus insulin in the eDiary.

Please refer to Appendix 8 (Section 10.8) for more information.

The investigator must record the following in the eCRF

- First and last date on trial product
- First and last dose of trial product

For dosing of anti-diabetic medication prescribed in the follow-up period please see Section 6.5

8.2.2 Physical examinations

A physical examination will include assessments of:

- Head, ears, eyes, nose, throat, neck
- Cardiovascular system
- Respiratory system
- Gastrointestinal system
- Central and Peripheral Nervous System
- Musculoskeletal system
- Skin.

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

The physical examination will be recorded in the eCRF as either 'normal' or 'abnormal'. If 'abnormal', a comment must be given together with an assessment of clinical significance (yes/no).

Abnormal, clinically significant findings at screening should be recorded as concomitant illness in the eCRF. At the following visits, any new abnormal, clinically significant findings or clinically significant deteriorations from baseline should be reported as an adverse event (see Appendix 3, Section 10.3).

Body measurements (height and weight) will also be measured and recorded. Height will be measured and recorded at screening visit (V1). Weight will be measured and recorded throughout the trial as specified in the flowchart (Section 1.2).

- 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 measured in centimetres (cm) or inches (in) without shoes. Height will be recorded to the nearest whole number.
- From the body weight and height, the BMI should be calculated and recorded in the subject's medical records.

8.2.3 Vital signs

- Pulse rate, as well as systolic and diastolic blood pressure will be assessed.
- Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g. no use of television, mobile phones).
- Blood pressure and pulse rate measurements will be assessed sitting with a completely automated device. Manual techniques must be used only if an automated device is not available.
- Blood pressure and pulse rate at screening (V1), V16 and end of treatment (V28) will consist of 3 systolic and diastolic blood pressure measurements with intervals of at least 1-2 minutes. An additional fourth blood pressure measurement must be performed if the first two readings on systolic or diastolic blood pressure differ by >10 mmHg. Systolic blood pressure will be calculated as the mean of the last 2 systolic blood pressure readings, and diastolic blood pressure as the mean of the last 2 diastolic blood pressure readings. Only the last 2 systolic and last 2 diastolic blood pressure readings must be recorded in the eCRF.
- Pulse rate will be measured in connection to the blood pressure measurements. Record the pulse rate for the last 2 blood pressure measurements in the eCRF. The pulse rate will be calculated as the mean of the last 2 measurements.

8.2.4 Electrocardiograms

- A 12-lead ECG must be performed by the investigator or delegated staff as outlined in the flowchart (Section 1.2).
- The ECG should be preceded by at least 5 minutes of rest for the subject in a supine/sitting position in a quiet setting without distractions (e.g. no use of television, mobile phones).
- The ECG must be interpreted, signed and dated by the investigator to verify that the data has been reviewed.
- The ECG required at screening can be obtained within 2 weeks prior to V2 but at the latest at V2. The results must be interpreted by the investigator prior to randomisation in order to determine the eligibility of the subject.
- The ECG required at the end of treatment visit can be obtained within 2 weeks prior to the end of treatment visit. The results must be available for evaluation at the end of treatment visit.
- Abnormal, clinically significant findings at screening should be recorded as concomitant illness in the eCRF. At the following visits, any new abnormal, clinically significant findings or clinically significant deteriorations from baseline should be reported as an adverse event (see Appendix 3, Section 10.3).

8.2.5 Eye examination

Subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy are not eligible as this indicates retinopathy that has recently progressed to a level that requires intervention or is approaching intervention but has yet to be brought under control.

Results of an eye examination performed by an ophthalmologist or another suitably qualified health care provider (e.g. optometrist) must be available and evaluated by the investigator before randomisation to assess eligibility. The eye examination should be performed as a fundus photography (e.g. 2-field 60 degree or better, colour or red-free) or by slit-lamp biomicroscopy examination (e.g. using a pre-corneal or corneal contact lens examination). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

If the subject had such an eye examination performed within 90 days prior to screening, the investigator may base his/her evaluation upon the results of that examination. The examination must be repeated before randomisation if the subject has experienced worsening of visual function since the last examination. Eye examinations performed prior to randomisation visit (V2) are acceptable if results are available for evaluation before randomisation. 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.

Eye examinations required at the end of treatment (V28) visit can be performed within 2 weeks prior to the visit, if results are available for evaluation at the visit. For discontinued subjects, eye examination can be performed up to 2 weeks after the end of treatment visit. 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 adverse event, please refer to Section 8.3.

8.2.6 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the flowchart (see Section 1.2) and laboratory manual.

8.3 Adverse events and serious adverse events

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

The definition of AEs and SAEs can be found in Appendix 3 (Section 10.3), along with a description of events for adjudication and AEs requiring additional data collection.

Some AEs require additional data collection on a specific event form. This always includes medication, misuse and abuse of IMP. The relevant events are listed in Table 8-1, together with events for adjudication.

Hypoglycaemic episodes

Hypoglycaemic episodes require data collection on a hypoglycaemic episode form in the eDiary. Non-serious hypoglycaemic episodes do not require an AE form to be filled in. If the

hypoglycaemic episode fulfils the criteria for an SAE, then, in addition to the hypoglycaemic episodes form, an AE form and a safety information form must be filled in in the eCRF, please refer to Appendix 3. For more information on hypoglycaemic episodes, please refer to Appendix 7 (Section 10.7).

Table 8-1 AEs requiring additional data collection (serious and non-serious AEs), and events for adjudication

Event type	AE requiring additional data collection	Event for adjudication
Medication error	X	
Misuse and abuse	X	
Acute coronary syndrome (acute myocardial infarction or unstable angina pectoris requiring hospitalisation)		X
Cerebrovascular events[a] (stroke or transient ischemic attack)		X
Heart failure (requiring hospitalisation or urgent heart failure visit)		X
Death		X
Hypersensitivity	X	
Injection Site Reaction	X	

[a] All cerebrovascular events are to be reported and sent for adjudication, however the EAC will only confirm strokes.

A detailed description of the events mentioned in the above table can be found in Appendix 3 (Section 10.3.3).

Events for Adjudication

Event adjudication will be performed in randomised subjects and will be evaluated by an independent external EAC in a blinded manner, please refer to Section 10.1.6.4.

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

- Investigator-reported events for adjudication: investigator selects the appropriate AE category relevant for adjudication (Appendix 3, Section 10.3.3).
- AEs reported with fatal outcome.
- AE search (standardised screening): All AEs not reported with an AE category relevant for adjudication will undergo screening to identify potential events for adjudication. Investigators will be notified of these events in the eCRF.
- EAC-identified events: Unreported events relevant for adjudication identified by the EAC during review of source documents provided for another event for adjudication. Investigators will be notified of these events in the eCRF and has the option to report the EAC-identified event.

For each event relevant for adjudication an event type specific adjudication form should be completed in the eCRF within 14 days.

Copies of source documents should be uploaded to the event adjudication system (EAS) as soon as possible and preferably within 4 weeks. In cases where the EAS is not accessible the investigator should ensure that the relevant source documents are collected and saved locally until the EAS is ready. 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 becomes available for an event sent for adjudication, it is the responsibility of the investigator to ensure the new information is uploaded to the EAS.

An event adjudication site manual will be provided to each site detailing which source documents are relevant and how these should be provided to the adjudication supplier. The anonymization and labelling requirements are also described in the event adjudication site manual.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs must be collected from the randomisation visit and until the end of trial visit as specified in the flowchart (see Section 1.2). For subjects discontinuing trial product prematurely AEs must be collected until the discontinuation follow-up visit (V28A).

Medical occurrences that take place or have onset prior to the time point from which AEs are collected will be recorded as concomitant illness/medical history. AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3). All SAEs must be recorded and reported to Novo Nordisk within 24 hours, and 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 trial product or related to trial participation, the investigator must promptly notify Novo Nordisk.

8.3.2 Method of detecting AEs and SAEs

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 3 (Section 10.3).

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.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs should be followed until final outcome of the event or the subject is lost to follow-up as described in Section 7.3. Further information on follow-up and final outcome of events is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk or designee 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. This also includes suspected unexpected serious adverse reactions (SUSAR).

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.

8.3.5 Pregnancy

Details of pregnancies in female subjects will be collected from first exposure to trial product and until the new-born infant is one month of age.

If a female subject becomes pregnant, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

8.3.6 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to Section 8.3.

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

Not applicable for this trial.

8.3.8 Adverse event of special interest[a]

Not applicable for this trial.

[a] Adverse events of special interest are, as per Novo Nordisk definitions and processes, required to have expedited reporting by the investigators. Only adverse events fulfilling the seriousness criteria are considered for expedited reporting in this trial.

8.3.9 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form.

Instructions for reporting technical complaints can be found in Appendix 5 (Section 10.5).

In order for Novo Nordisk to perform a complete investigation of reported SAEs, Novo Nordisk might ask the investigator to complete a technical complaint form.

8.4 Treatment of overdose

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.3 and Appendix 3 (Section 10.3.3) for further details.

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

A specific overdose for insulin icodec 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 subcutaneously by a trained person, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the subject dose 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 the insulin icodec investigator's brochure[11] or the insulin glargine EMA summary of product characteristics[12], US prescribing information[13], or any locally approved label; or insulin aspart investigator's brochure[14].

8.5 Pharmacokinetics

Blood samples will be used to evaluate the pharmacokinetics (PK) of insulin icodec. PK samples will be collected at the visits outlined in the flowchart (Section 1.2) for subjects randomised to insulin icodec. The date and exact clock time for blood sampling must be recorded.

Bioanalysis of insulin icodec samples will be performed at a special laboratory using a validated luminescent oxygen channelling immunoassay. The exact method will be described in a bioanalytical report.

Residual PK samples may be used for exploratory metabolite analysis. Potential metabolite analysis will be reported separately from the clinical trial report.

Genetic analyses will not be performed on these plasma/serum/whole blood samples. Subject confidentiality will be maintained.

Procedures for sampling, handling, storage, labelling and shipments of the specimens must be performed in accordance with the laboratory manual. A randomisation list will be provided to the special laboratory. Samples from randomised subjects will be analysed for insulin icodec concentration.

Subjects should be instructed to report dosing information in the eDiary as per Section 8.2.1.

8.6 Pharmacodynamics

Not applicable for this trial.

8.7 Genetics

Not applicable for this trial.

8.8 Biomarkers

Not applicable for this trial.

8.9 Immunogenicity assessments

8.9.1 Anti-drug antibodies

Anti-drug antibody samples will be collected according to the flowchart (Section 1.2) for subjects randomised to insulin icodec. All samples must be drawn prior to trial product administration if trial product administration is planned on the sampling day. Assessment of antibodies against insulin icodec (anti-drug antibodies) in serum will be performed at a Novo Nordisk appointed laboratory. For details on blood sampling, serum preparation and storage, please refer to the laboratory manual.

Analysis for anti-drug antibody will be done as listed in flowchart with a binding anti-drug antibody assay. Positive samples will be further characterised for titre, and cross-reactivity to endogenous human insulin.

Detailed description of the assay methods will be included in an analytical report. Antibody assays will be validated according to international guidelines and recommendations.

At the end of the trial, the following data will be electronically transferred to the Novo Nordisk database: Anti-insulin icodec binding antibodies (pos/neg) and titre of anti-drug antibody positive samples, and anti-insulin icodec binding antibodies cross-reacting with endogenous human insulin status (pos/neg).

The investigator will not be able to review the results of antibody measurements in relation to AEs as the samples are often analysed after last subject last visit. Results from the binding anti-drug antibody analyses from visits randomisation (V2), V4, V8, V12, V20, end of treatment (V28) and end of trial (V30) will be available after the completion of the trial.

8.9.2 Hypersensitivity

Subjects and investigators will be instructed to detect signs and symptoms of systemic hypersensitivity.

For subjects randomised to insulin icodec: In the event of a systemic hypersensitivity (not locally at the injection site), 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 the hypersensitivity reaction)
- Total immunoglobulin E (IgE) antibodies
- Anti-insulin icodec IgE antibodies
- Anti-insulin icodec binding antibodies
- Anti-human insulin IgE antibodies.

The blood sampling should be repeated 2-4 weeks following onset of the systemic hypersensitivity reaction. If possible, the tests should also be performed on samples drawn prior to first administration of trial drug.

For details related to blood sampling, plasma preparation and storage, please refer to the laboratory manual.

Analysis will be performed by Novo Nordisk or a Novo Nordisk appointed special laboratory (please refer to Attachment I). The results will be reported in a separate report and attached to the clinical trial report.

If the reaction is classified as a SAE, the results from the hypersensitivity tests will also be reported to Novo Nordisk Safety Operations for inclusion in the ARGUS database and included in the narratives of the clinical trial report.

For retention of residual hypersensitivity samples, please refer to Section 10.6.

Digital pictures

The investigator or the subject must take digital pictures of the affected area at time of identification, using any device available (mobile phone, camera etc.) 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 must be stored as part of source documentation at site.

8.10 Health economics

Not applicable for this trial.

9 Statistical considerations

9.1 Statistical hypotheses

The primary hypothesis to be tested is that insulin icodec is non-inferior to insulin glargine in terms of change from baseline to week 26 in HbA_{1c}.

Formally, let D be the treatment difference 'insulin icodec' minus 'insulin glargine' of the change in HbA_{1c} from baseline to week 26. The null-hypothesis will be tested against the alternative hypothesis of non-inferiority as given by

$$H0: D \geq 0.30\% \text{ against } HA: D < 0.30\%$$

The non-inferiority margin of 0.3%-point is chosen based on the recommendation in the FDA guidance for industry on developing drugs for treatment of diabetes.[20] Also, this margin is considered to provide sufficient assay sensitivity based on the below considerations:

- The margin does not represent an unacceptable loss of efficacy with insulin icodec relative to treatment with a basal insulin analogue.
- It represents less than 50% of a suitably conservative estimate of insulin glargine´s treatment effect on HbA_{1c} in a placebo-controlled trial in a basal-bolus insulin treated population; The treatment effect of glargine versus placebo in a basal-bolus insulin treated population is unknown but glargine was shown to be superior to placebo in insulin naïve subjects (estimated treatment difference: -0.85%-point $[-1.04; -0.66]_{95\%CI}$).[21] In a more progressed T2D population of subjects already treated with liraglutide, degludec was shown to be superior to placebo (estimated treatment difference: -0.92%-point $[-1.00; -0.75]_{95\%CI}$)

and other basal insulins have previously been shown to yield similar reductions in HbA_{1c} compared to insulin glargine.[22]

9.2 Sample size determination

The sample size is determined in order to have 90% power for declaring non-inferiority with a non-inferiority margin of 0.3%-point with respect to change in HbA_{1c} for the specified estimand and the full analysis set (primary analysis set).

Based on a recent study with basal-bolus treatment (NN9068-4185) the percent experiencing an intercurrent event as specified above is expected to be 10% per 6 months in a basal-bolus study in subjects with T2D.

It is assumed that there is no difference in HbA_{1c} between the treatment arms for subjects completing randomised treatment and a treatment difference of 0.3%-point in favour of the comparator for subjects either discontinuing treatment prematurely or withdrawing from trial. Thus, with 10% expected to experience any of the specified intercurrent events before week 26, this leads to an assumption of a mean treatment difference of 0.03%-point for the specified estimand in the overall population.

The SD is assumed to be 1.0%-point based on results from studies with insulin glargine 100 units/mL in subjects treated with basal insulin (NN1250-3582).

From the above assumptions and requirements, 580 subjects will be randomised trial product. This will ensure sufficient power (90%) of confirming non-inferiority.

With an expected screening failure rate of 25%, approximately 774 subjects will be screened to achieve 580 subjects randomly assigned to trial product.

This sample size appears to be reasonable also under deviations from the assumed treatment difference as illustrated in Table 9-1 displaying power for various alternative treatment differences and SDs.

Table 9-1 Power for various treatment differences and standard deviations.

SD (%-point)	0.015	**Treatment difference** (%-point) 0.03	0.045
0.9	97%	95%	93%
1.0	93%	90%	87%
1.1	88%	84%	80%

SD: Power is computed for 1:1 randomisation and 580 subjects randomised.

9.3 Populations for analyses

The following populations are defined:

Population	**Description**
Randomised	All subjects randomised
Full analysis set	Full analysis set: All subjects randomised. Subjects will be analysed according to the randomised treatment.
Safety analysis set	All subjects randomly assigned to trial treatment and who take at least 1 dose of trial product. Subjects are analysed according to the treatment they actually received.

In exceptional cases, subjects or observations may be eliminated from the full analysis set. In such case the reasons for their exclusion will be documented before unblinding. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

The following periods will be considered for the data collected:

In-trial period

The in-trial period starts at randomisation and ends at the date of:

- The last direct subject-site contact.
- Withdrawal for subjects who withdraw their informed consent.
- The last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up (i.e. possibly an unscheduled phone visit).
- Death for subjects who die before any of the above.

For subjects not randomised but exposed to trial product the in-trial period starts at the date of first dose of trial product. The end date is as defined as above.

On-treatment period

The on-treatment period starts at the date of first dose of trial product as recorded on the eCRF, and ends at the first date of any of the following:

- The end of trial visit (V30).
- The last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin (corresponding to 5 weeks after the end of the dosing interval for both treatment arms).
- The end-date for the in-trial observation period.

The on-treatment period represents the time period in which a subject is considered exposed to trial product.

All efficacy endpoints will be summarised and analysed using the full analysis set and the 'in-trial' period. Safety endpoints will be evaluated using the on-treatment period with descriptive statistics being based on the safety analysis set (SAS) and statistical analyses being based on the full analysis set unless otherwise specified.

9.4 Statistical analyses

The statistical analysis plan (SAP) will be finalised prior to first subject first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1 General considerations

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

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

- Treatment: Once weekly insulin icodec, insulin glargine.
- Region: Asia, Europe, North America, South America.

The regions will be defined as follows:

- Asia: India, Japan.
- Europe: Belgium, Netherlands, Italy, Romania, Russia.
- North America: United States.
- South America: Mexico.

The last available assessment made prior to the first dose will be used as the baseline value.

All endpoints based on CGM measurements will be derived the following way. The percentage of time spent in a given glycaemic range will be calculated as 100 times the number of recorded

measurements in the given glycaemic range, divided by the total number of recorded measurements. Following international consensus criteria it will be required that at least 70% of the planned CGM measurements during the last four weeks of treatment are available for endpoint data to be included in the analysis.[23]

9.4.2 Primary endpoint

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

The 'treatment policy' estimand, will be estimated based on the full analysis set using all HbA_{1c} measurements obtained at the week 26 visit, especially including measurements from subjects discontinuing their randomised treatment. Missing HbA_{1c} at the week 26 visit (regardless of treatment completion status) will be imputed from trial participants, who have discontinued their randomised treatment prior to the week 26 visit and have a measurement at the week 26 visit in the following way:

- First, one thousand (1000) copies of the dataset will be generated for HbA_{1c}.
- Second, for subjects who discontinued their randomised treatment prior to the week 26 visit and have an HbA_{1c} visit measurement at the week 26 visit, the change in HbA_{1c} from last available planned on-treatment (LAOT) value to the week 26 visit will be analysed for each dataset copy using an analysis of covariance (ANCOVA) model with randomised treatment as fixed factor and LAOT value and the time point (study day) of this assessment as covariates. The estimated parameters, and their variances, from the model will be used to impute missing HbA_{1c} values for the change from LAOT to the week 26 visit and subsequently the missing HbA_{1c} value at the week 26 visit.
- For each of the complete data sets, the primary endpoint will be analysed using an ANCOVA model with region and randomised treatment as fixed factors, and baseline HbA_{1c} as a covariate. The estimates and SDs for the 1000 data sets will be pooled to one estimate and associated SD using Rubin's rule.[24]

This analysis has the underlying assumption that subjects with missing data behave similarly as subjects that discontinue randomised treatment.

The following sensitivity analysis evaluating the robustness of the assumptions about the missing data will be carried out:
For the primary endpoint, a two-dimensional tipping point analysis will be performed where subjects having imputed HbA_{1c} measurement at the week 26 visit are assumed to have a worse outcome in the insulin icodec arm and a better outcome in the insulin glargine arm compared to what was imputed in the primary analysis. This is done by adding or subtracting values Δi to the imputed HbA_{1c} values before analysing the data. The value of Δi will be varied independently in the two treatment arms. The non-inferiority margin of 0.3% will be among the Δi values investigated. The plausibility of the values of Δi where the conclusion of the primary analysis change will be evaluated to assess the robustness of the primary analysis result.

9.4.3 Secondary endpoints

9.4.3.1 Confirmatory secondary endpoint

Not applicable for this trial.

9.4.3.2 Supportive secondary endpoints

Supportive secondary endpoints will be evaluated in the framework of the primary estimand.

Efficacy endpoints

Change in fasting plasma glucose (FPG) from baseline week 0 (V2) to week 26 (V28)

Missing FPG values at the week 26 visit (regardless of treatment completion status) will be imputed from trial participants who are from the insulin glargine group, and who have completed and adhered to their randomised insulin treatment - i.e., data will be imputed based on the assumption that subjects with missing endpoint data will behave like subjects completing the insulin glargine treatment. Specifically, the imputations and analyses will be carried out as follows:

- First, one thousand (1000) copies of the dataset will be generated for FPG.
- Second, for each dataset copy, an analysis of covariance (ANCOVA) model with a baseline value as a covariate will be fitted to FPG values for subjects who completed their randomised treatment in the insulin glargine group. The estimated mean, and variances, from the model will be used to impute missing values in both treatment groups.
- For each of the complete data sets, the endpoint will be analysed using an ANCOVA model with region and randomised treatment as fixed factors, and a baseline value as a covariate. The estimates and SDs for the 1000 data sets will be pooled to one estimate and associated SD using Rubin's rule.[24]

Time in target range 3.9-10.0 mmol/L (70-180 mg/dL) from week 22 (V24) to week 26 (V28)

Time in target range 3.9-10.0 mmol/L (70-180 mg/dL) from week 22 to week 26 will be analysed using the same model as specified for change in FPG, but without using the baseline value as a covariate.

Safety endpoints

Hypoglycaemic episodes

The following hypoglycaemic endpoints will be analysed separately using the method described below:

- Number of severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 31 (V30).
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) from baseline week 0 (V2) to week 31 (V30).

- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 31 (V30).

For subjects who discontinued their randomised treatment the number of episodes in the missing period (time of follow-up 2 visit (V30) to planned end of the on-treatment period) will be imputed using a multiple imputation technique, assuming that the event rate pre follow-up 2 visit (V30) follows the respective treatment groups rate whilst post follow-up 2 visit (V30) event rate is the rate of the insulin glargine group. The imputation will be done as follows:

- First, a Bayes negative binomial model with log-link function will be fitted to the event rate data to obtain the posterior distribution of model parameters. The model will include region and randomised treatment as fixed factors and the logarithm of the on-treatment period as offset.
- Second, based on the estimated parameters for the insulin glargine group in this model, the number of episodes in the missing period will be imputed for subjects who discontinued their randomised treatment. Multiple copies (1000 copies) of a complete data set will be generated by sampling from the estimated distribution.
- For each of the complete data sets, the number of episodes will be analysed using a negative binomial model with log-link, fixed factors and offset as described in step 1. The estimates and SDs for the 1000 data sets will be pooled to one estimate and associated SD using Rubin's rule.[24]

For the definition and classification of hypoglycaemic episodes refer to Appendix 7 (Section 10.7).

Time spent < 3.0 mmol/L (54 mg/dL) and time spent > 10 mmol/L (180 mg/dL) from week 22 (V24) to week 26 (V28)

Time spent < 3.0 mmol/L (54 mg/dL) (below range) and time spent > 10 mmol/L (180 mg/dL) (above range) from week 22 to week 26 will be analysed separately using the same model as specified for change in FPG, but without using the baseline value as a covariate. This model will be used if deemed appropriate, i.e. if data can be considered normally distributed. However, if a large number of subjects have 0% time spent, then an alternative analysis will be performed either considering the endpoint as a dichotomous endpoint or by applying a censored analysis of the log-transformed values. Further details will be provided in the SAP.

Mean weekly insulin dose from week 24 (V26) to week 26 (V28)

Mean weekly insulin dose during the last 2 weeks of treatment (from week 24 to week 26), defined as the sum of the mean weekly basal and the mean weekly bolus dose, will be log-transformed and analysed using the same model as specified for change in FPG, but with using the log-transformed weekly insulin dose at screening as a covariate.

Change in body weight from baseline week 0 (V2) to week 26 (V28)

Change in body weight from week 0 to week 26 will be analysed using the same statistical model as specified for the primary endpoint, but with the corresponding baseline value as a covariate.

For details on analyses of additional supportive secondary endpoints, please refer to the SAP.

9.4.4 Exploratory endpoints

For details on analyses of exploratory endpoints, please refer to the SAP.

9.4.5 Other safety analyses

All safety analyses will be made on the safety analysis set. The standard safety assessments (SAEs, AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively based on the on-treatment period; including any notable changes of clinical interest in laboratory parameters. In addition, SAEs will be reported descriptively based on the in-trial period.

9.4.6 Other analyses

For other analyses, please refer to the SAP.

9.4.6.1 Pharmacokinetic modelling

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

The population PK analysis will be performed by Quantitative Clinical Pharmacology, Novo Nordisk. A more technical and detailed elaboration of the population PK analysis will be given in a modelling analysis plan, which will be prepared before database lock. In brief, a previously developed PK model for insulin icodec 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 modelling analysis plan.

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

9.5 Interim analyses

Not applicable for this trial.

9.6 Data monitoring committee

Not applicable for this trial.

9.7 Reporting of the main part of the trial

Not applicable for this trial.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and trial oversight considerations

10.1.1 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[25] and applicable ICH good clinical practice (GCP) Guideline[26].
- 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 site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
    - providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
    - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
    - ensuring submission of the clinical trial report synopsis to the IRB/IEC
    - reporting any potential serious breaches to the sponsor immediately after discovery

10.1.2 Financial disclosure

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

10.1.3 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 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 must be informed about their privacy rights.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[26], Declaration of Helsinki[25] and the IRB/IEC or 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 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.

10.1.4 Information to subjects during trial

Novo Nordisk offers a communication package for the subject during the conduct of the trial. The communication package contains written information which will be translated and adjusted to local requirements and distributed to the subject at the discretion of the investigator. The subject may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further, the subject may receive 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.

10.1.5 Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the subject are transferred to Novo Nordisk.
- 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 about his/her privacy rights, including 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.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee.

10.1.6.2 Trial safety group

Not applicable for this trial.

10.1.6.3 Data monitoring committee

Not applicable for this trial.

10.1.6.4 Event adjudication committee

An independent external EAC is established to perform ongoing blinded adjudication of selected AEs and deaths (see Table 8-1).

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 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 trial conduct, trial protocol or amendments. The assessments made by both the event adjudication committee and the investigator will be evaluated and included in the clinical trial report.

10.1.7 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[27], the Food and Drug Administration Amendment Act (FDAAA)[28], European Commission Requirements[1, 29, 30] and other relevant recommendations or regulations. If a subject request 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 + 26 weeks corresponding to visit V28. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit V28. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

- 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 (eCRFs) unless transmitted electronically to Novo Nordisk (e.g. laboratory and eDiary data) or when applicable on paper CRF. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The following will be provided as paper CRFs:
    - Pregnancy forms

- The following will be provided as paper CRFs to be used when access to the eCRF is revoked or the eCRF is temporarily unavailable:
    - Adverse event forms
    - Safety information forms
    - Technical complaint forms (also to be used to report complaints on trial product not yet allocated to a subject)

- 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.

10.1.8.2 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 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 eCRF 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 sites.
- Monitors will review the subject's medical records and other source data to ensure consistency and/or identify omissions compared to the eCRF.

10.1.8.3 Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without delay and the implications of the deviation must be reviewed and discussed.

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

10.1.9 Source documents

All data entered in the eCRF must be verifiable in source documentation, except for the following data that has been transferred directly into the database and will be considered source data:

- For e.g. eDiary, data in the service providers' database is considered source data.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data reported on the paper CRF or entered in the eCRF 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 site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems 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 site. 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.

10.1.11 Trial and site closure

Novo Nordisk reserves the right to close the 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.

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

The investigator may initiate 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 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.

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

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

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

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

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

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

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

10.1.13 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.

10.1.14 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 or two investigators will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators.

10.1.14.1 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.

10.1.14.2 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.[31]

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 site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

10.1.14.3 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.

10.1.14.4 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.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10-1 and Table 10-2 will be performed by the central laboratory.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow-up on AEs, this must be done at a local laboratory.
- The central lab will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their lab SOPs. These data will not be transferred to the trial database. The investigator should review such values for AEs and report these according to this protocol.
- The investigator must review all laboratory results for concomitant illnesses and AEs.
- Laboratory samples will be destroyed no later than at finalisation of the clinical trial report, except the following:
  - For haematology samples (differential count) where the test result is not normal, then a part of the sample may be kept for up to two years or according to local regulations.
  - Human biosamples for retention will be stored as described in Appendix 6 (Section 10.6).

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism (V2, V12, V20, V28)	• Fasting plasma glucose (FPG)[1] • HbA_{1c} (also at V1 and V28A)
NOTE: [1]An 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 3, Section 10.3). A FPG result >16.7 mmol/L (300 mg/dL) should not be reported as a hyperglycaemic episode but as an AE at the discretion of the investigator (Appendix 3, Section 10.3).	

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology (V1, V12, V28)	• Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Thrombocytes • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils
Biochemistry[1] (V1, V12, V28)	• Alanine Aminotransferase • Albumin • Alkaline phosphatase • Aspartate Aminotransferase • Creatinine • Potassium • Sodium • Total bilirubin
Lipids (V2, V12, V28)	• Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides • Free fatty acids
Pregnancy Testing (V2, V28, V30)	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation, eGFR is for screening purposes only. • In case of systemic hypersensitivity (Section 8.9.2): Tryptase (optimal 0.5-2 hours post the hypersensitivity reaction), total IgE antibodies, anti-insulin icodec IgE antibodies, anti-insulin icodec binding antibodies, anti-human insulin IgE antibodies. • Anti-insulin icodec antibodies (V2, V4, V8, V12, V20, V28, V30). • Insulin-icodec serum concentration (V4, V8, V12, V20, V28, V30).
Notes: [1]Details of required actions for increased liver parameters are given in Section 10.3.2 (Hy's Law). [2]Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.	

10.3 Appendix 3: Adverse events: Definitions and procedures for recording, evaluation, follow-up, and reporting

10.3.1 Definition of AE

AE definition
An AE is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP. An AE can therefore be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of an IMP.

Events <u>meeting</u> the AE definition
• Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected. • Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected. • Exacerbation/worsening of a chronic or intermittent 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 IMP 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 <u>NOT</u> meeting the AE definition
• Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or other trial procedures performed before exposure to IMP. • Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history. • Medical or surgical procedures (e.g. endoscopy, appendectomy). The condition that leads to the procedure is the AE. • Medical or surgical procedures not preceded by an AE or worsening of a known condition.

10.3.2 Definition of an SAE

An SAE is an AE that fulfils at least one of the following criteria:
a. Results in death
b. 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.
c. 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 seriousness 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 (e.g. elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE. Note: • Hospitalisations for administrative, trial related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. • Hospital admissions for medical or surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.
d. Results in persistent or significant 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.
e. Is a congenital anomaly/birth defect
f. 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 IMP • Risk of liver injury defined as alanine aminotransferase or aspartate aminotransferase >3 x UNL and total bilirubin >2 x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of event(s) for adjudication and AEs requiring additional data collection

Description of event(s) for adjudication-and AEs requiring additional data collection (on specific event form)

Events for adjudication
An event for adjudication is a selected AE or death evaluated by an independent external EAC in a blinded manner, please refer to Table 8-1 Appendix 1 (Section 10.1.6.4) and Figure 10-1.

- Death
  - All cause death
- Acute coronary syndrome
  - All types of acute myocardial infarction and unstable angina pectoris requiring hospitalisation
- Cerebrovascular event (stroke or transient ischemic attack)
  - Episode of focal or global neurological dysfunction that could be caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or ischemia, with or without infarction
- Heart failure (requiring hospitalisation or urgent heart failure visit)
  - New episode or worsening of existing heart failure leading to an urgent, unscheduled hospital admission or clinic/office/emergency department visit

Adverse events requiring additional data collection
AEs requiring additional data collection on a specific event form.

Injection site reaction
If an event of injection site reaction is observed, additional information must be obtained if available on a separate form.

Hypersensitivity

Systemic hypersensitivity can be manifested as isolated symptoms such as urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), or as anaphylaxis or anaphylactic shock.

Anaphylaxis is an acute, potentially lethal, multisystem syndrome resulting from the sudden release of mast cell- and basophil-derived mediators into the circulation[32]. It most often results from immunologic reactions to foods, medications, and insect stings, although it can also be induced through nonimmunologic mechanisms by any agent capable of producing a sudden, systemic degranulation of mast cells or basophils[33]. Characteristic symptoms and signs, occurring minutes to a few hours after exposure to potential triggering agents or events may include: flushing, urticaria, angioedema, hoarseness, throat tightness, stridor, wheezing, coughing, shortness of breath, abdominal pain, vomiting, and/or hypotension, dizziness or collapse.

Local hypersensitivity reactions, including rash, redness, pruritus and oedema, may occur at the site of investigational drug injection.

Drug hypersensitivity reactions (DHRs) are the adverse effects of pharmaceutical formulations (including active drugs and excipients) that clinically resemble allergy[34]. They can be allergic and non-allergic.

If a hypersensitivity event is suspected, the subjects must contact the site staff as soon as possible for further guidance. All events must be reported, and in case of systemic hypersensitivity, additional information must be provided on a separate form.

Medication error

A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the subject, such as:

- administration of wrong drug.
  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- wrong route of administration, such as intramuscular instead of subcutaneous
- accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.
- missed doses or drug pauses are not to be reported as a medication error.

Misuse and abuse

- Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g. overdose to maximise effect)
- Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm)

Medication error, misuse and abuse must always be reported as an AE (e.g. accidental overdose, intentional overdose or other) on a separate AE form, and a medication error, misuse and abuse form must be completed. In case of a medication error and/or misuse and abuse resulting in a clinical consequence, this must be reported on an additional AE form.

10.3.4 Recording and follow-up of AE and/or SAE

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.
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
- 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 "AE and SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication or NIMP: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as or NIMP or concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

The investigator will assess severity 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: An AE that is assessed as severe should not be confused with a SAE. Both AEs and SAEs can be assessed as severe.

Assessment of causality

- The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE.
- Relationship between an AE/SAE and the relevant IMP(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 IMP.

- Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
- The investigator should use the Investigator's Brochures for insulin icodec and insulin aspart, and the summary of product characteristics for non-Novo Nordisk marketed 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 update the causality assessment in the CRF.
- 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 when first documented
- **Recovering/resolving:** The condition is improving, and the subject is expected to recover from the event. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- Note: For SAEs, this term is only applicable if the subject has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae:** The subject has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the subject has not improved, and the symptoms are unchanged, or the outcome is not known.
  Note: This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **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. If a subject dies during participation in the trial or during a recognised follow-up period, Novo Nordisk may request a copy of the autopsy report including histopathology. New or updated information will be recorded in the CRF.

10.3.5 Reporting of SAEs

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 Figure 10-1. • 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 paper safety information form (see box below). • The site will enter the SAE data into the CRF as soon as it becomes available. • After the trial is completed, the trial database will be locked, and 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.

AE and SAE reporting via paper CRF

• Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk in accordance with Section 10.1.5.
• For SAEs, 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 timelines (as illustrated in Figure 10-1):
  • AE form within 24 hours
  • Safety information form within 5 calendar days
  • Both forms must be signed within 7 calendar days after first knowledge by the investigator.
• The specific event form for AEs requiring additional data collection within 14 calendar days

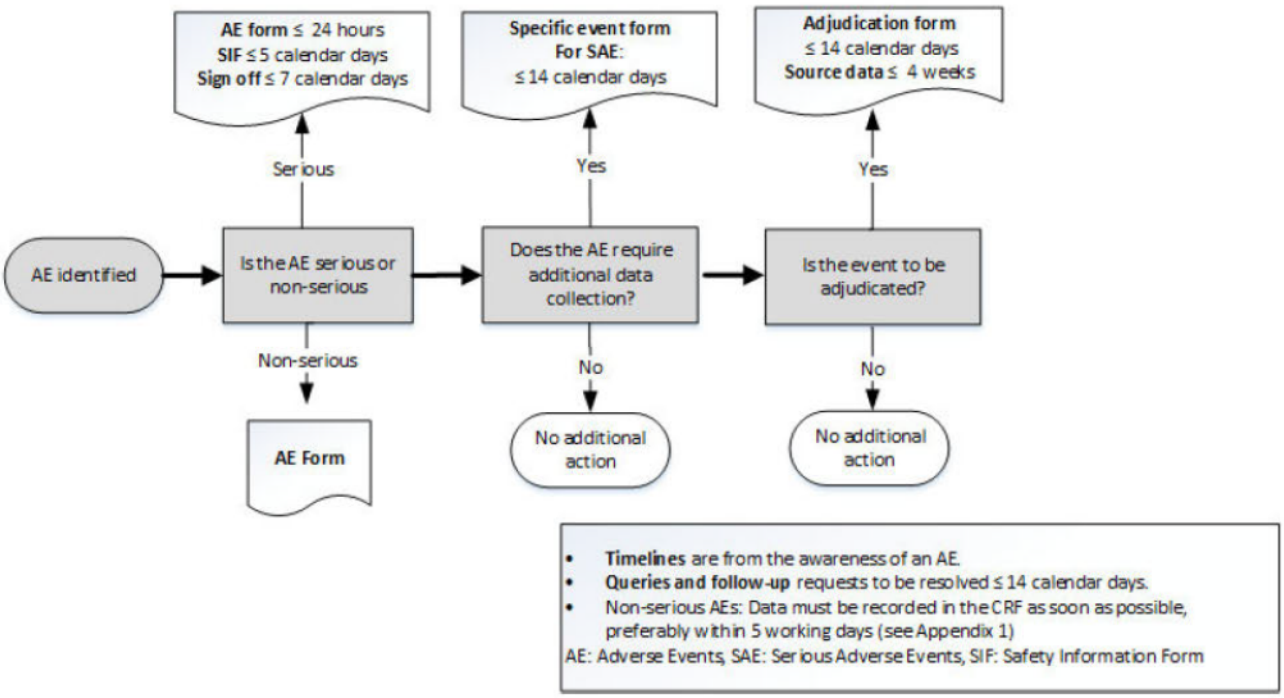

Figure 10-1 Decision tree for determining the event type and the respective forms to complete with associated timelines

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] Accu check and Dexcom G6: All complaints (including AEs) should be reported directly to the manufacturer.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. If fertility is unclear and a menstrual cycle cannot be confirmed before first dose of trial treatment, additional evaluation should be considered.

Females in the following categories are not considered WOCBP

1. Premenarcheal
2. Females with one or more of the following:
   - Documented total hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

Females with permanent infertility due to an alternate medical cause other than the above (e.g. Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining trial enrolment.

3. Postmenopausal female:

- A postmenopausal state is defined as amenorrhoea for 12 months without an alternative medical cause.
- Females ≥ 50 years of age can be considered postmenopausal (irrespective of treatment with a hormonal contraception or hormone replacement therapy (HRT)) if they have both:
  - Amenorrhoea and
  - Documentation of 2 high follicle stimulating hormone (FSH) measurements in the postmenopausal range and one of these was observed ≥1 year prior to screening.
- Females ≥ 60 years of age can be considered postmenopausal.

Females on HRT and whose menopausal status is in doubt are considered of childbearing potential and will be required to use at least an acceptable effective contraception methods as described in Table 10-3.

Note: Documentation regarding categories 1-3 can come from the site staff's review of subject's medical records, medical examination or medical history interview.

Contraception guidance

Male subjects
No contraception measures are required as the risk of teratogenicity/fetotoxicity caused by transfer of insulin icodec or insulin glargine or insulin aspart in seminal fluid is unlikely[35].

Female subjects
Female subjects of childbearing potential are eligible to participate if they agree to use at least an acceptable effective methods of contraception consistently and correctly as described in Table 10-3. As a minimum, contraception should be maintained until treatment discontinuation[36].

Table 10-3 Acceptable contraceptive methods

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:
ACCEPTABLE METHODS[b]
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide[c] • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).
NOTES a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical trials. b) Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy testing

- Additional pregnancy testing should be performed during the treatment period, if required locally. Please refer to the Appendix 9 (Section 10.9).
- WOCBP should only be included after a negative highly sensitive urine pregnancy test (refer to Appendix 2 (Section 10.2) and the trial flowchart (Section 1.2).
- As a minimum, pregnancy test should be performed at the end of relevant systemic exposure (refer to Appendix 2 and the trial flowchart).
- Pregnancy testing should be performed whenever a menstruation 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 subject's pregnancy (see Figure 10-2).
- Subject will be followed to determine the outcome of the pregnancy. The investigators will collect follow-up information on subject and neonate which will be forwarded to Novo Nordisk within 14 calendar days. 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 the foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding "gestational", "pregnancy related" or similar term when reporting the AE/SAE.
- 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.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possible/probably related to the IMP by the investigator will be reported to Novo Nordisk as described in Appendix 3 (Section 10.3) . While the investigator is not obligated to actively seek this information in former subjects, he/she may learn of an SAE through spontaneous reporting.

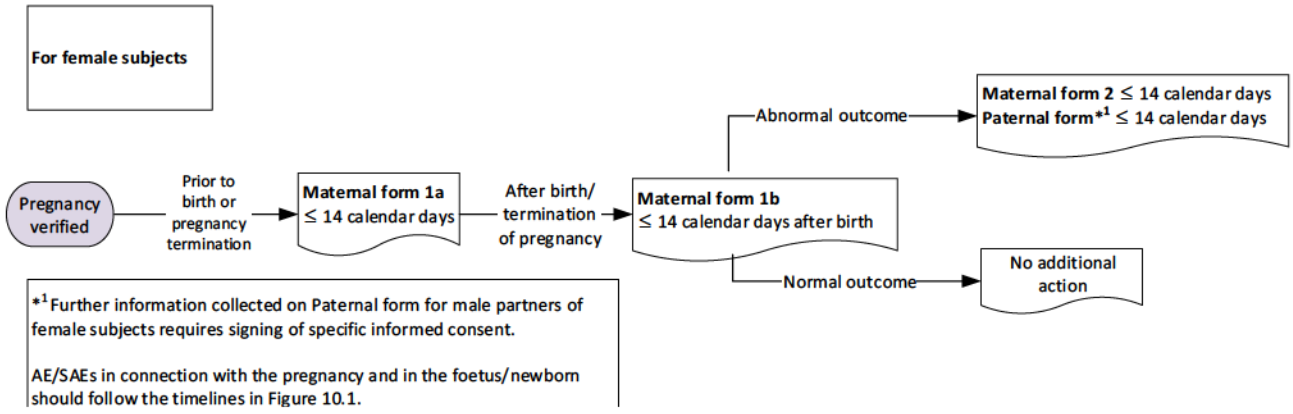

Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy.

Any female subject who becomes pregnant while participating in the trial will discontinue IMP.

10.5 Appendix 5: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

10.5.1 Definition of technical complaint

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 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 site until the time of the last usage of the product must be collected for products predefined on the technical complaint form.

10.5.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk
Contact details for Customer Complaint Center, please 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: • 24 hours if related to an SAE • 5 days calendar for all other technical complaints If the CRF is unavailable, or when reporting a technical complaint on a trial product that is not yet allocated to subject, the information must be provided on a paper form 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 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.

10.5.3 Reporting of technical complaints

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.

10.6 Appendix 6: Retention of human biosamples

Hypersensitivity reaction samples

In case of a systemic hypersensitivity reaction, the additional blood samples taken in relation to the reaction (Section 8.9.2) may be retained to follow-up on the hypersensitivity reaction. If deemed relevant by Novo Nordisk, relevant exploratory tests may be performed, e.g. histamine release (basophil activation). If measured, such data will be reported in a separate report.

The samples will be stored at Novo Nordisk or a Novo Nordisk designated referral central bio-repository. The samples might be transferred to other countries, if not prohibited by local regulations. Only Novo Nordisk staff and bio-repository personnel will have access to the stored samples. The samples may be shipped to a contract research organisation (CRO) for analysis.

The samples will be anonymised (identified only by a unique sample ID, visit number, trial identification number and sampling date). Confidentiality and personal data protection will be ensured during storage after the end of trial and no direct identification of the subject will be stored together with the samples.

Potential further analyses of the samples will not have any consequences for the subject and their relatives. Subjects can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

The samples will be stored 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

Antibody samples may be retained for further characterisation of antibody responses towards drug, if required by health authorities or for safety reasons. The samples may also be used for further development of anti-insulin antibody assays, or for exploratory investigation of antibodies.

The antibody samples will be stored 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.

Metabolism samples (PK samples)

Samples for metabolism analysis may be retained for later analysis of metabolites if needed. If samples are selected for metabolite analysis, they will be stored at Novo Nordisk 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.

10.7 Appendix 7: Hypoglycaemic episodes

Table 10-4 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	[1]Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery
Notes: The Novo Nordisk terms are adapted from IHSG[37], ADA[38], ISPAD[39], type 1 diabetes outcomes program[40], ATTD[23]. Severe hypoglycaemia as defined by Seaquist[41] and ISPAD[39].		

Severe hypoglycaemia

[1]Severe hypoglycaemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration[41].

In case of recurrent severe hypoglycaemia, the treatment of the subject is the responsibility of the investigator and the titration guidelines can be overruled at his/her discretion[38].

Nocturnal hypoglycaemia

Nocturnal hypoglycaemic episodes: episodes occurring between 00:01 and 05:59 both inclusive.

Reporting of hypoglycaemic episodes in the eDiary

Plasma glucose (PG) should always be measured by the trial BG meter and hypoglycaemic episodes should be recorded in the eDiary.

The following should be reported in the eDiary as hypoglycaemic events:

- PG values < 3.9 mmol/L (70 mg/dL)

- Severe hypoglycaemic episodes without confirmed PG values

The investigator should ensure correct reporting of the hypoglycaemic episode. Confirmation of the hypoglycaemic episode review must be documented in the web portal. In case a subject is not able to fill in the eDiary (e.g. in case of hospitalisation) at time of episode, the subject can report the episode in the eDiary retrospectively.

If the hypoglycaemic episode fulfils the criteria for an SAE then in addition to the above patient reported data, an eCRF AE form and a safety information form must also be filled in. One AE form and safety information form can cover several hypoglycaemic values, if the subject has not recovered between them and has reported them as one episode in the eDiary.

Upon onset of a hypoglycaemic episode the subject is recommended to measure PG every 15 minutes until the PG value is ≥ 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines[41].

Repeated low PG measurements can be reported by the subject as one hypoglycaemic episode until a succeeding PG value is ≥ 3.9 mmol/L (70 mg/dL). In case of several low PG values within the hypoglycaemic episode, the lowest value is the one that will be reported as the PG value for the hypoglycaemic episode, but the start time of the episode will remain as the time for the first low PG value. The remaining values will be kept as source data.

If the severity of a hypoglycaemic episode changes, only one hypoglycaemic episode will 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 the subjects to answer "Yes", if the episode was an event that required 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[41].

eDiary review

At each contact the investigator should review the eDiary data for correct reporting of PG values and hypoglycaemic episodes. In case of incomplete or incorrect data in the eDiary, the subject must be questioned whether there have been any severe hypoglycaemic episodes since the last visit. The subject shall update the reported data in the eDiary accordingly.

Re-training of subjects

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

10.8 Appendix 8: 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 icodec or insulin glargine. Both in combination with bolus insulin aspart.

- ***Insulin icodec*** should be taken once weekly on the same day of the week. All patients should receive a loading dose at randomisation (V2), which consist of total daily basal insulin dose before randomisation x 7 + 50% of their total daily basal insulin dose x 7. The following weekly dose (V3) should be the total daily dose x 7. In the following table the weekly V2 and V3 doses for patients receiving from 10U to 100U per day have been calculated. Please, note that the displayed values are round off to the nearest dose dividable by 10.

Total daily dose before randomisation (U)	V2 insulin icodec dose (U)	V3 insulin icodec dose (U)	Total daily dose before randomisation (U)	V2 insulin icodec dose (U)	V3 insulin icodec dose (U)
10	110	70	56	590	390
11	120	80	57	600	400
12	130	80	58	610	410
13	140	90	59	620	410
14	150	100	60	630	420
15	160	110	61	640	430
16	170	110	62	650	430
17	180	120	63	660	440
18	190	130	64	670	450
19	200	130	65	682	460
20	210	140	66	690	460
21	220	150	67	700	470
22	230	150	68	710	480
23	240	160	69	720	480
24	250	170	70	740	490
25	260	180	71	750	500

26	270	180	72	760	500
27	280	190	73	770	510
28	290	200	74	780	520
29	300	200	75	790	530
30	320	210	76	800	530
31	330	220	77	810	540
32	340	220	78	820	550
33	350	230	79	830	550
34	360	240	80	840	560
35	370	250	81	850	570
36	380	250	82	860	570
37	390	260	83	870	580
38	400	270	84	880	590
39	410	270	85	890	600
40	420	280	86	900	600
41	430	290	87	910	610
42	440	290	88	920	620
43	450	300	89	930	620
44	460	310	90	950	630
45	470	320	91	960	640
46	480	320	92	970	640
47	490	330	93	980	650
48	500	340	94	990	660
49	510	340	95	1000	670
50	530	350	96	1010	670
51	540	360	97	1020	680
52	550	360	98	1030	690
53	560	370	99	1040	690
54	570	380	100	1050	700
55	580	390			

- ***Insulin glargine*** should be taken once daily, at anytime of the day but at the same time every day. Switching from previous basal insulin should be in accordance with local label.
- ***Insulin aspart*** should be taken with main meals 2-4 times per day. Switch from previous bolus insulin should be done unit-to-unit per meal.
- The treat-to-target approach will be applied to both treatment arms to optimise glycaemic control throughout the trial.
- There are no maximum or minimum insulin doses.

Dose adjustment of trial products during the trial

After randomisation the investigator should adjust the trial products once weekly in connection with the scheduled visits/phone contacts as described below:

- The dose adjustment will be based on the three pre-breakfast SMPG values measured on two days prior to titration and on the day of the contact.
- If one or more pre-breakfast SMPG values are missing, the dose adjustment should be performed on the remaining SMPG value(s).
- The prescribed dose should be determined by the investigator and recorded in the HCP web portal.

Titration of insulin glargine

Adjustment of insulin glargine will be done in accordance with Table 10-5.

Table 10-5 Insulin glargine

Pre-breakfast SMPG			Dose adjustment
Value to use	mmol/L	mg/dL	U
Lowest of the SMPG values	<4.4	<80	–3
Mean of the SMPG values	4.4–7.2	80–130	0
	>7.2	>130	+3

Titration of insulin icodec

Adjustment of insulin icodec will be done in accordance with Table 10-6.

Table 10-6 Insulin icodec

Pre-breakfast SMPG			Dose adjustment
Value to use	mmol/L	mg/dL	U
Lowest of the SMPG values	<4.4	<80	–20
Mean of the SMPG values	4.4–7.2	80–130	0
	>7.2	>130	+20

Titration of insulin aspart

In the first 8 weeks after randomisation insulin aspart should only be adjusted for safety reasons. Thereafter the doses should be considered adjusted twice weekly at intervals of 3-4 days, either as self-titration or assisted by the investigator.

Dose adjustment will be based on the pre-prandial or bedtime SMPG values measured on the three days prior to titration in accordance with Table 10-7.

- Breakfast dose will be adjusted based on the pre-lunch SMPG values.

- Lunch dose will be adjusted based on the pre-dinner SMPG values.
- Dinner dose will be adjusted based on the bedtime SMPG values.

If the patient eats more than four times a day the fourth dose will be adjusted in agreement with the investigator.

Table 10-7 Insulin aspart

Target pre-prandial and bedtime SMPG		Rule	Dose adjustment
mmol/L	mg/dL		U
4.4-7.2	80-130	≥1 SMPG below target	-1
		No SMPG below target 0-1 SMPG above target	0
		No SMPG below target ≥2 SMPGs above target	+1

Deviations from the algorithm

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

Missing insulin icodec dose guidance

If an insulin icodec dose is missed for ≤ 3 days after the planned dosing day, subjects should inject the planned dose as soon as possible and perform control SMPG measurement. If the missing dose is missed for > 3 days, the subject should await the next planned day-of-injection.

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

If it is decided that the individual subject should continue basal insulin after end of treatment, it is recommended that the subject is switched from insulin icodec to any available basal insulin at the discretion of the investigator. The investigator should instruct the subject in how to switch at the end of treatment visit (V28).

Regarding the switch from insulin icodec to post-trial basal insulin the following should be considered:

- Calculate the new daily basal insulin dose dividing the latest insulin icodec dose by 7.
- Initiate the new daily basal insulin **two weeks** after the last injection of insulin icodec.

- Continue to measure pre-breakfast SMPG daily in the follow up period. If pre-breakfast SMPG exceeds 10.0 mmol/L (180 mg/dL), it should be considered to initiate the daily basal insulin dose earlier than two weeks after the last dose of insulin icodec.
- Consider titrating the basal insulin once or twice weekly according to the pre-breakfast SMPG values and the local label of the chosen insulin.

Data collection

The subject should be instructed to report the following in the eDiary:

- Date, dose and time of insulin aspart and insulin glargine or insulin icodec injections.
- Ensure transfer of SMPG values with an indication of "pre-breakfast", "pre-lunch", "pre-dinner", "bedtime" or "other" (see Section 8.1.1).
- Hypoglycaemic episodes as described in Appendix 7 (Section 10.7).

While using the HCP web portal for titration the following will be entered by investigator:

- Insulin glargine or insulin icodec and insulin aspart doses prescribed at this contact.
- Reasons for deviation from the insulin glargine or insulin icodec titration algorithms, if applicable.

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 deviations from the titration algorithm will be followed up.

It is important that data regarding dose titration is entered into the eDiary and the HCP web portal. Timely registration is crucial in order to take appropriate actions 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.

10.9 Appendix 9: Country-specific requirements

For Belgium:

- **Contraceptive guidance**: Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly; such as implants, injectables, combined oral contraceptives, some intrauterine devices, true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) or vasectomised partner.

- **Indemnity statement:** "Law concerning experiments on the human person of 07 May 2004 - Article 29: §1. Even if without fault, the sponsor is liable for the damage which the subject and/or his rightful claimants sustain and which shows either a direct or an indirect connection with the trial.

For Italy:

- **Additional exclusion criteria:** 20. Known severe diabetic autonomic neuropathy as judged by the investigator.

For Japan:

- **Inclusion criteria 3**: age ≥ 20 years at the time of signing informed consent

- Preparation/Handling/Storage/Accountability: The head of the trial site or the trial product storage manager assigned by the head of the trial site (a pharmacist in principle) is responsible for control and accountability of the trial products.

- **Trial governance consideration:** A seal is accepted as signature.

- **Exclusion criteria 4:** the footnote, "Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed if the last dose of the investigational medicinal product has been received more than 30 days before screening", **is not applicable for Japan.**
- **Discontinuation criteria 4, Section 7.1:** the footnote, "Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or postinfectious conditions is allowed at the investigator discretion without discontinuing trial product", **is not applicable for Japan.**

For Mexico:

- **Withdrawal from the trial:** should the subject, his/her family members, parents or legal representative decide to withdraw the consent from the trial, the subject will be entitled to receive appropriate, free of charge medical care and/or trial drug during the follow-up period of the protocol when it will be established with certainty that no untoward medical consequences of the subject´s participation in the research occurred.

- **Trial governance considerations**: In the case of Mexico, the following responsibilities will be included for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility: a) Investigation follow-up; b) Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the Subject; c) Timely compliance of the terms in which the authorization of a research for health in human beings had been issued; d) To present in a timely manner the information required by the Health Authority.

- **Indemnity statement:** a) 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, including those applicable provisions on the Mexican United States. If the subject feels that something goes wrong during the course of this trial, the subject should contact the trial staff in the first instance.

- b) If during their participation in the trial the subject experiences a disease or injury that, according to the trial doctor and the sponsor, is directly caused by the study medication and/or a study procedure that otherwise would not have been part of his/her regular medical care, the subject will receive from the institution or medical care establishment and free of charge, the appropriate medical treatment as required. In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by the trial sponsor in accordance with the terms provided by all applicable regulations; even if the subject discontinues his/her participation in the study by his own will or by a decision from the investigator.

- c) By signing the informed consent, the subject will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the trial; any additional expense resulting from the subject's participation in the trial will be covered by the trial sponsor.

For Russia:

- **Trial governance considerations:** The trial should be conducted in compliance with the protocol, Ministry of Healthcare of Russian Federation' order #200н from April, 01, 2016

"Approval of rules of good clinical practice" and legal requirements of the Russian Federation regulating circulation of medicines.

- The BG meter and CGM are not approved at the time of the final protocol version 1.0, therefore are regarded as investigational devices and will be labelled to indicate for investigational use only.
  The BG meter has been selected in order to have automatic transfer of SMPG data to the eDiary and thereby increase the accuracy of SMPG values. It is expected that the better accuracy in SMPG data will facilitate an improvement in the insulin titration efforts during the trial.
  Technical complaints on the BG meter, strips, lancets or control solutions, including technical complaints related to AEs and SAEs, must be reported to [redacted] on a special technical complaint paper form.

  The CGM has been selected in order to provide the best data accuracy and to be consistent in the global clinical programme. Technical complaints on the CGM must be reported to [redacted] on a special technical complaint paper form.

  Timelines for reporting, from the trial site obtaining knowledge of the technical complaint:
    - Technical complaint assessed as related to a SAE within 24 hours
    - All other technical complaints within 5 calendar days

  AEs and SAEs related to the technical complaint must be reported both on the special technical complaint paper form and in the eCRF. In addition they must be reported in accordance with the standard protocol requirements for AE and SAE reporting as described in Section 8.3.

  At the end of the trial the BG meter and CGM must be collected by the investigator.
  If the CGM or BGM is approved in Russia during the trial conduct, the procedures above are not applicable any more and technical complaints reporting should follow the standard vigilance procedures.

For USA:

- **Financial disclosure**: Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

For India and Mexico where CGM is not approved at the time of the final protocol version 1.0:

- The CGM is regarded as an investigational device and will be labelled to indicate for investigational use only.

The CGM has been selected in order to provide the best data accuracy and to be consistent in the global clinical programme. Technical complaints on the CGM must be reported to [redacted] on a special technical complaint paper form.
Timelines for reporting, from the trial site obtaining knowledge of the technical complaint:

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

AEs and SAEs related to the technical complaint must be reported both on the special technical complaint paper form and in the eCRF. In addition they must be reported in accordance with the standard protocol requirements for AE and SAE reporting as described in Section 8.3.
At the end of the trial CGM must be collected by the investigator.

If the CGM is approved in any of the countries during the trial conduct, the procedures above are not applicable any more in the said country and technical complaints reporting should follow the standard vigilance procedures.

10.10 Appendix 10: Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
BG	blood glucose
CGM	continuous glucose monitoring
CI	confidence interval
CRF	case report form
DPP-4	dipeptidyl peptidase-4
DUN	dispensing unit number
EAC	event adjudication committee
EAS	event adjudication system
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicinal Agency
FDA	U.S. Food and Drug Administration
FDAAA	U.S. Food and Drug Administration Amendments Act
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GLP-1 RA	glucagon-like peptide 1 receptor agonists
HbA_{1c}	glycated haemoglobin
HCP	healthcare professional
HRT	hormone replacement therapy
IB	investigator's brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgE	immunoglobulin E
IMP	investigational medicinal product
INN	international nonproprietary name
IRB	institutional review board
IWRS	interactive web response system
LAOT-WOB	last available planned on-treatment without initiation of more than 2 weeks bolus insulin treatment

NIMP	non-investigational medical product
PCD	primary completion date
PD	pharmacodynamic
PI	prescribing information
PK	pharmacokinetics
PG	plasma glucose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI-IC	subject information-informed consent
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
V	visit
WOCBP	woman of child bearing potential

10.11 Appendix 11: Protocol amendment history

The Protocol amendment summary of changes table for the current protocol version is located directly before the table of contents.

Protocol version 3.0 (30 November 2020*)*

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union[1], because it neither significantly impacts the safety nor physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for preparing protocol, version 3.0:

The protocol has been amended to allow subjects to co-participate in clinical trials evaluating medicinal products for prevention or treatment of COVID-19 disease or postinfectious conditions.

Section # and name	Description of change	Brief rationale
Protocol amendment summary of changes table	New section added.	Disclose version history.
1.2 Flowchart	"(insulin icodec serum concentration)" and "(anti-insulin icodec antibodies)" have been added.	To make it clear that PK and antibody testing are only conducted in the insulin icodec arm.
1.2 Flowchart	Deleted randomisation visit "X" for hypo-reporting.	Correction of error (hypo-reporting should follow AE reporting).
2.3.1 Risk assessment	Added a further COVID-19 related mitigation strategy.	To provide guidance in case of COVID-19 related lock down of a site or country.
5 Trial population	Added a reference to Appendix 9 (Section 10.9).	To stress that country-specific requirements to the eligibility criteria are described in appendix 9.
5.2 Exclusion criteria	A clarifying footnote has been added to exclusion criteria 4.	To allow subjects to co-participate in clinical trials evaluating medicinal products for prevention or treatment of COVID-19 disease or postinfectious conditions.
7.1 Discontinuation of trial treatment	A clarifying footnote has been added to discontinuation criteria 4.	To allow subjects to co-participate in clinical trials evaluating medicinal products for prevention or treatment of COVID-19 disease or postinfectious conditions without discontinuing trial product.

Section # and name	Description of change	Brief rationale
7.1 Discontinuation of trial treatment 7.2 Subject discontinuation/withdrawal from the trial	Updated wording to "treatment status session".	Correction of error.
8.2 Safety assessments	Deleted a sentence describing a disease specific form in the eCRF.	The eCRF for medical history has changed to include the diagnosis of diabetes, thus the information is not applicable anymore.
8.2.2 Physical examinations	Correcting wrong cross-reference.	Correction of typo.
8.2.4 Electrocardiograms	Correcting wrong cross-reference.	Correction of typo.
8.3 Adverse events (AEs) and serious adverse events (SAE)	Footnote to table 8-1 inserted.	To clarify that investigators should collect all cerebrovascular events even though the EAC will only be confirming stroke.
8.3.1 Time period and frequency for collecting AE and SAE information	Rephrasing a sentence in the first paragraph.	Correction of an error and clarification.
8.3.8 Adverse event of special interest	A clarifying footnote has been added.	To clarify Novo Nordisk definitions and processes about AE of special interest.
8.4 Treatment of overdose	Cross-reference specified.	Improve reader-friendliness.
8.5 Pharmacokinetics	"for subjects randomised to insulin icodec" has been added.	To make it clear that PK testing is only conducted in the insulin icodec arm.
8.5 Pharmacokinetics	Rephrasing to: The date and exact clock time for blood sampling must be recorded.	The date and exact clock time of the sampling must be recorded in the lab requisition form, not in the eCRF.
8.9.1 Anti-drug antibodies	"for subjects randomised to insulin icodec" has been added.	To make it clear that anti-drug antibodies testing is only conducted in the insulin icodec arm.
8.9.2 Hypersensitivity	The sentence "For the subjects randomised to insulin icodec" has been added in the first paragraph.	To clarify that the additional blood sampling is only taken in the insulin icodec arm.
9.4.3.2 Supportive secondary endpoints: *Mean weekly insulin dose from week 24 (V26) to week 26 (V28)*	Added the sentence: "defined as the sum of the weekly basal and weekly bolus dose".	To clarify how the endpoint is defined.
10.1.8.2 Monitoring	Deleted "HCP web portal" and "eDiaries".	Monitors are not requested to perform source data verification in the HCP web portal.
10.9 Appendix 9: Country/Region-specific requirements	Added an Italian specific exclusion criteria.	Added exclusion criteria as requested by Italian Health Authority in ONWARDS 1 trial.

Section # and name	Description of change	Brief rationale
10.9 Appendix 9: Country/Region-specific requirements	Deleted USA specific eye examination requirement.	USA will follow the global requirements for eye examination in section 8.2.5.
10.11 Appendix 11: Protocol amendment history	New appendix added.	Log amendments and version history.

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~~CONFIDENTIAL~~

16.1.01 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

If applicable, Protocol Attachment II is also located in the Trial Master File.

Content: Global key staff and Country key staff.