Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04848480
Sponsor trial ID:	NN1436-4625
Official title of study:	Efficacy and Safety of Once Weekly Insulin Icodec Compared to Once Daily Insulin Degludec 100 Units/mL, Both in Combination With Insulin Aspart, in Adults With Type 1 Diabetes. A 26-week, Randomised, Multicentre, Open-label, Active-controlled, Parallel Group, Two Armed, Treat-to-target Trial Investigating the Effect on Glycaemic Control and Safety of Treatment With Once Weekly Insulin Icodec Compared to Once Daily Insulin Degludec, Both in Combination With Insulin Aspart in Adults With Type 1 Diabetes, With a 26-week Extension Investigating Long Term Safety
Document date:	27 June 2022

*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

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Protocol

Efficacy and safety of once weekly insulin icodec compared to once daily insulin degludec 100 units/mL, both in combination with insulin aspart, in adults with type 1 diabetes.

A 26-week, randomised, multicentre, open-label, active-controlled, parallel group, two armed, treat-to-target trial investigating the effect on glycaemic control and safety of treatment with once weekly insulin icodec compared to once daily insulin degludec, both in combination with insulin aspart in adults with type 1 diabetes, with a 26-week extension investigating long term safety.

ONWARDS 6

Substance name: Insulin icodec

Universal Trial Number: U1111-1251-7315

EudraCT Number: 2020-002374-27

IND Number: 137406

Redacted protocol
Includes redaction of personal identifiable information only.

Trial phase: 3a

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

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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	22 February 2021	For Japan only
Protocol version 2.0	07 January 2021	All countries, except Japan
Original protocol version 1.0	20 October 2020	Not submitted

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 Germany 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
2.3.1 Risk assessment	"section 8.9.2." is deleted from the sentence "For further information on injection site reactions, please refer to ~~section 8.9.2 and~~ Appendix 3 (Section 10.3)".	Correction of reference.
5.1 Inclusion criteria	"basal and bolus insulin analogue regimes" is corrected to "basal and bolus insulin analogue regimens"	Correction of typo
10.1.7 Dissemination of clinical trial data	The primary completion date (PCD) is corrected to last subject first treatment (LSFT) + 26 weeks corresponding to visit 28.	Correction of typo, since the primary endpoint will be assessed at week 26 (visit 28).
10.1.9 Source documents	"ePROs" is deleted.	Correction due to no ePROs in this trial.
10.8 Appendix 8 Titration guideline	Table for V2 and V3 weekly dose: For "Total daily dose before randomisation (U): 82 "	Correction of typo

Section # and name	Description of change	Brief rationale
	"V2 insulin icodec dose (U)": 960 is corrected to 860	
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 Germany	To meet local Health Authority request.
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 32 to CTFG guidance is added in appendix 4.	Reference update

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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.

This is a 26-week trial designed to investigate the effect and safety of once weekly insulin icodec compared to once daily insulin degludec 100 units/mL, both in combination with insulin aspart in subjects with type 1 diabetes, with a 26-week extension phase. The first 26 weeks of the trial constitute the main phase, after which the primary analysis is planned. The focus of the 26-week extension phase is to evaluate long-term safety and provide long-term exposure data.

Objectives and endpoints:

Primary objective

To confirm the effect on glycaemic control of once weekly insulin icodec in combination with insulin aspart, in subjects with type 1 diabetes. This includes comparing the difference in change from baseline in HbA_{1c} between once weekly insulin icodec and once daily insulin degludec both in combination with insulin aspart after 26 weeks of treatment to a non-inferiority limit of 0.3%.

Primary endpoint

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

Estimand

The estimand is the 'treatment policy estimand' defined as the treatment difference between insulin icodec and insulin degludec 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).

Overall design:

This is a 26-week randomised, multicentre, multinational, open-label, active controlled, parallel group, two-armed, treat-to-target trial with two treatment arms. Subjects will be randomised (1:1) to receive either insulin icodec or once daily insulin degludec, both in combination with 2-4 daily bolus injections of insulin aspart. Randomisation of subjects will be stratified based on pre-trial basal insulin regimen and by HbA_{1c} (either $<8\%$ or $\geq 8\%$) at screening.

Key inclusion criteria:

1. Male or female aged ≥ 18 years at the time of signing informed consent.
2. Diagnosed with type 1 diabetes mellitus ≥ 1 year prior to the day of screening.

3. Treated with multiple daily insulin injections (basal and bolus insulin analogue regimes) ≥ 1 year prior to the day of screening.
4. HbA_{1c} <10% at screening visit based on analysis from central laboratory.

Key exclusion criteria:

1. Myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.
2. Chronic heart failure classified as New York Heart Association (NYHA) Class IV at screening.
3. 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).
4. 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.

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 59 weeks, consisting of a 2-week screening period, followed by an initial 26-week randomised treatment period, a 26-week extension phase and a 5-week follow-up period. All subjects will be centrally randomised in a 1:1 manner and assigned to receive once weekly insulin icodec or once daily insulin degludec, both in combination with 2-4 times daily injections of insulin aspart throughout the 52-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 degludec 100 units/mL, subcutaneous, solution for injection, 3 mL PDS290 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	Early Discontinuation Follow-up	Early Discontinuation Follow-up
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V12	V16	V20	V24	V25	V26	V27	V28	V30	V34	V38	V42	V46	V50	V51	V52	V53	V54	V55	V56	V28A	V54A
Weekly Phone contact number (P) *(For details see separate flow chart below)*									P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23					P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48 P49									
Timing of visit (weeks)		≤-2	0	1	2	3	4	5	6	10	14	18	22	23	24	25	26	28	32	36	40	44	48	49	50	51	52	54	57	26	52
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Informed consent and demography	App 1 10.1	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			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	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	8.2.3	X									X						X										X				
Physical examination	8.2.2	X															X										X				
Body measurements	8.2.2	X	X								X						X										X			X	X
Clinical outcome assessment: DTSQs	8.1.3		X														X										X				

Procedure	Protocol section	Screening	Randomisation	Treatment																										Follow-up 1	Follow-up 2	Early Discontinuation Follow-up	Early Discontinuation Follow-up
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V12	V16	V20	V24	V25	V26	V27	V28	V30	V34	V38	V42	V46	V50	V51	V52	V53	V54	V55	V56	V28A	V54A
Weekly Phone contact number (P) *(For details see separate flow chart below)*									P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23					P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48 P49									
Timing of visit (weeks)		≤-2	0	1	2	3	4	5	6	10	14	18	22	23	24	25	26	28	32	36	40	44	48	49	50	51	52	54	57	26	52
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Clinical outcome assessment: International Physical Activity Questionnaire	8.1.3		X																													
Eye examination	8.2.5	X															X										X					
ECG	8.2.4	X															X										X					
Pregnancy test	8.3.5 App.4 10.4		X																										X			
Laboratory assessments	App.2 10.2	X	X							X		X					X			X		X					X			X	X	
HbA1c		X	X							X		X					X			X		X					X			X	X	
Antibodies *(anti-insulin icodec antibodies)*	8.9.1		X		X				X	X		X					X			X							X		X			
PK *(insulin icodec serum concentration)*	8.5				X				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	X	X	X	X	X	X	X	X	X	X	X	X			
CGM	8.1.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Procedure	Protocol section	Screening	Randomisation	Treatment																										Follow-up 1	Follow-up 2	Early Discontinuation Follow-up	Early Discontinuation Follow-up
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V12	V16	V20	V24	V25	V26	V27	V28	V30	V34	V38	V42	V46	V50	V51	V52	V53	V54	V55	V56	V28A	V54A
Weekly Phone contact number (P) *(For details see separate flow chart below)*									P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23					P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48 P49									
Timing of visit (weeks)		≤-2	0	1	2	3	4	5	6	10	14	18	22	23	24	25	26	28	32	36	40	44	48	49	50	51	52	54	57	26	52
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Adverse event	8.3 App. 3 10.3			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	8.3 App7 10.7			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Training in trial Product, Pen-handling	6.1		X	X					X		X		X					X		X		X									
Drug dispensing	6.2		X						X		X		X					X		X		X									
Hand out and instruct in devices	6.1.1		X																												
End of Trial	4.4																												X		X

1.3 Flow charts – Phone visits

Phone contacts during treatment period (P) Time shown in site visit flow chart	P9-P49
Visit window (days)	±3
Concomitant medication (6.5)	X
4-point SMPG profile (8.1.1)	X
Adverse events (8.3 Appendix 3)	X
Hypoglycaemic episodes (8.3, Appendix 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 (s.c.) injection. Insulin icodec has a terminal elimination half-life of approximately 196 hours. For patients 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 patients with diabetes by limiting the burden associated with insulin treatment.

2.1 Trial rationale

The present trial is designed to investigate the effect and long-term safety of once weekly insulin icodec in comparison to once daily insulin degludec 100 units/mL (hereafter referred to as insulin degludec) both in combination with insulin aspart in adult subjects with T1D. The effect of insulin icodec is evaluated after the 26-week main phase, followed by a 26-week extension phase with a primary aim to assess long-term safety.

2.2 Background

Diabetes mellitus

T1D is a heterogeneous disorder characterised by T cell-mediated autoimmune destruction of insulin-producing beta cells in the pancreas.[5] The destruction of beta cell function leads to insulin deficiency and the requirement of lifelong administration of exogenous insulin. Results from the DCCT study and the follow-up study (EDIC) have demonstrated the importance of maintaining tight glycaemic control to reduce the risk of long-term complications associated with diabetes.[6] As such, the fundamental principle for insulin treatment of T1D is to mimic normal physiological patterns as closely as possible. The current gold standard of care is based on intensive insulin therapy with multiple daily injections of prandial and basal insulin or continuous subcutaneous insulin infusion.[7, 8]

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

proteolytic 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 phase 2 trials NN1436-4383 [T2D], NN1436-4465 [T2D] and NN1436-4466 [T2D] and four clinical pharmacology trials, NN1436-4314 [T2D], NN1436-4226 [renal impaired], NN1436-4422 [T1D], and NN1436-4225 [T1D]) have been completed. No unexpected safety concerns were identified. One clinical pharmacology trial (NN1436-4462 [T2D] is ongoing.

Data from NN1436-4225 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 (IB)[9] and any updates hereof.

Insulin degludec

For further details on insulin degludec, please refer to the current insulin degludec IB[10], the current EMA summary of product characteristics (SmPC) for insulin degludec (Tresiba®)[11], the U.S. Prescribing Information (US PI)[12], or any locally approved label.

Insulin aspart

For further details on insulin aspart, please refer to the current insulin aspart IB[13], the current EMA summary of product characteristics (SmPC) for insulin aspart (NovoRapid)[14], the U.S. Prescribing Information (US PI) (NovoLog)[15], or any locally approved label.

Trial population

The trial population will consist of subjects with T1D. 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

Main benefits and risks are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of insulin icodec, insulin degludec and insulin aspart may be found in the respective IB, SmPC or US PI.

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.	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. Patients 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. Investigators and subjects will be asked to pay careful attention to injection site reactions. Investigators should ensure careful monitoring and medical evaluation in case of injection site reaction occurrence. For further information on injection site reactions, please refer to Appendix 3 (Section 10.3)
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 NN1436-44422.	Known of 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 and SI-IC. For further information on hypersensitivity reactions, please refer to Sections 8.9.2 and Appendix 3 (Section 10.3.3).

Potential risks: Antibody formation leading to changes in clinical effects	Antibodies to exogenously delivered insulins are common with insulin treatment but are not often clinically significant. In NN1436-4383 clinical trial, 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.	In case lack of clinical effect is observed, rescue actions will be initiated 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 8.9.1 and Appendix 3 (Section 10.3)
Trial treatment (Insulin Degludec & Insulin Aspart)		
For more information regarding the known and expected benefits and risks of insulin degludec, please refer to the insulin degludec IB[10], EMA Summary of Product Characteristics (SmPC)[11] and the US Prescribing Information (PI)[12], or any locally approved label. For more information regarding the known and expected benefits and risks of insulin aspart, please refer to the insulin aspart IB[13], the (NovoRapid) EMA SmPC[14], (NovoLog) US PI[15] or any locally approved label.		
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.

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 or twice daily to provide 24-hour coverage. Market research has shown that

people with diabetes, put value in reducing the number of insulin injections[16]. 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 T1D. For all subjects participating in this 52-week trial, the anticipated benefits include improved glycaemic control. The titration algorithm (Appendix 8, Section 10.8), which specifies recommended adjustments of both basal and bolus insulin dose at different plasma glucose levels, will be used to ensure that subjects receive optimal treatment.

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 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 IB[9] and any updates hereof.

3 Objectives and endpoints

3.1 Primary, secondary and exploratory objectives and estimand

3.1.1 Primary objective

To confirm the effect on glycaemic control of once weekly insulin icodec in combination with insulin aspart, in subjects with T1D. This includes comparing the difference in change from baseline in HbA_{1c} between once weekly insulin icodec and once daily insulin degludec both in combination with insulin aspart after 26 weeks of treatment to a non-inferiority limit of 0.3%.

3.1.2 Secondary objective

To compare the safety and patient reported outcomes of once weekly insulin icodec versus once daily insulin degludec, both in combination with insulin aspart, in subjects with T1D.

Estimand

The estimand is the ‘treatment policy estimand’ defined as the treatment difference between insulin icodec and insulin degludec 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) to week 26	%-point

3.2.2 Secondary endpoints

3.2.2.1 Supportive secondary efficacy endpoints

Endpoint title	Time frame	Unit
Change in fasting plasma glucose (FPG)	From baseline (week 0) to week 26	mmol/L
Time in range 3.9-10.0 mmol/L (70-180 mg/dL)*	From week 22 to week 26	% of readings
Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction	From baseline (week 0) to week 26	Score 0-36 6 items scored on a scale of 0 to 6. The higher the score the greater the satisfaction with treatment
Change in HbA_{1c}	From baseline (week 0) to week 52	%-point

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

3.2.2.2 Secondary safety endpoints

Endpoint title	Time frame	Unit
Number of severe hypoglycaemic episodes (level 3)	From baseline (week 0) to week 26	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) to week 26	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) to week 26	Number of episodes
Number of severe hypoglycaemic episodes (level 3)	From baseline (week 0) to week 57	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) to week 57	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) to week 57	Number of episodes
Number of nocturnal 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) to week 26	Number of episodes
Number of nocturnal 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) to week 57	Number of episodes
Time spent < 3.0 mmol/L (54 mg/dL)*	From week 22 to week 26	% of readings
Time spent > 10 mmol/L (180 mg/dL)*	From week 22 to week 26	% of readings
Mean total weekly insulin dose	From week 24 to week 26	U
Mean total weekly insulin dose	From week 50 to week 52	U
Change in body weight	From baseline (week 0) to week 26	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) to week 52	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) to week 52	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) to week 52	Number of episodes
Number of nocturnal 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) to week 52	Number of episodes

4 Trial design

4.1 Overall design

This is a 26-week, randomised, multicentre, multinational, open-label, active-controlled, parallel group, two-armed, treat-to-target trial investigating the effect on glycaemic control and safety of treatment with once weekly insulin icodec compared to once daily insulin degludec, both in combination with insulin aspart in subjects with T1D, with a 26-week extension phase. The first 26 weeks of the trial constitute the main phase, after which the primary analysis is planned. The focus of the 26-week extension phase is to evaluate long-term safety and provide long-term exposure data.

The trial duration is approximately 59 weeks, consisting of a 2-week screening period, followed by an initial 26-week randomised treatment period, a 26-week extension phase and a 5-week follow-up period. Primary analysis is planned after the initial 26-week main phase.

The overall trial design and visit schedule are outlined in Figure 4-1 and trial flowchart (Section 1.2), respectively.

Subjects will be randomised (1:1) to a treat-to-target basal-bolus insulin regimen with either once weekly insulin icodec or once daily insulin degludec, both in combination with insulin aspart. The randomisation of subjects will be stratified by pre-trial basal insulin regimen (either twice daily/ insulin glargine U300 or once daily) and HbA_{1c} (either <8% or ≥8%) at screening. During the 52-week treatment period, subjects will have weekly contact with the site either at site visits or by phone contacts. The end of treatment visit (V54) will be one week after the last dose of insulin icodec and on the day of or day after the last dose of insulin degludec. The end of trial visit (V56) will be performed 5 weeks after end of treatment visit (V54). 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 (Section 6.7 and Appendix 8, Section 10.8).

Subjects will carry a continuous glucose monitoring (CGM) device for the entire trial duration including the follow-up period. Subjects wearing a personal CGM or flash glucose monitoring (FGM) device prior to entering the trial, will discontinue the use of the personal pre-trial CGM or FGM device and switch to a trial CGM. The trial CGM receiver will be unblinded 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.

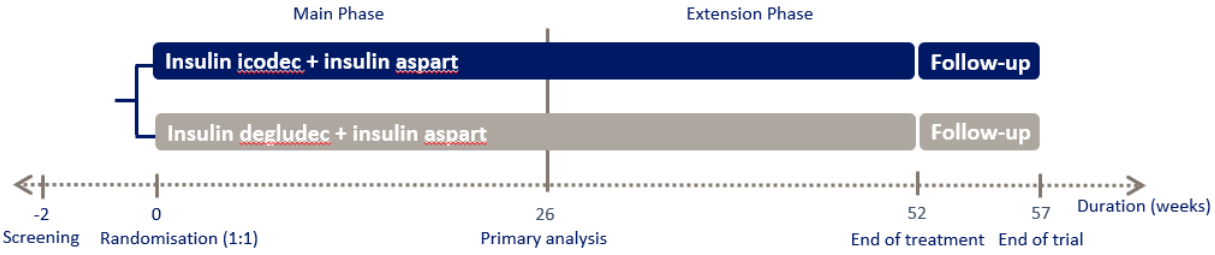


Figure 4-1 Trial design

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 degludec in combination with insulin aspart. A treatment duration of 26 weeks is evaluated as adequate for assessing effect on glycaemic control and safety; the extension of 26 weeks is included to provide long-term insulin icodec exposure for safety evaluation.

Subjects included in the trial will be representative of a broad T1D population that may benefit from insulin titration using a treat-to-target titration algorithm. To safeguard the subjects, the inclusion and exclusion criteria defined in this trial will limit the population to subjects not suffering from advanced underlying diseases other than T1D. 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.

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 degludec has been chosen as comparator.

Treatment in both arms will be open label as it was not considered feasible to blind the two treatments; the dosing regimen is not the same between treatment groups and there is a risk of pen-injector mix-up if a double-blind, double-dummy design was used as it would require the use of three different pen-injectors (two basal and one bolus pen-injector) in both treatment arms.

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}. The initial 26

weeks will allow sufficient time for up-titrating of the basal and bolus insulins and sufficient time in maintenance period for HbA_{1c} analysis.

Titration of insulin icodec, insulin degludec and insulin aspart is outlined in the titration guidelines, Appendix 8, Section 10.8. Titration of insulin icodec and insulin degludec will be based on pre-breakfast SMPG values and adjusted once weekly in connection with the scheduled visits/phone contacts. Titration of insulin aspart will be adjusted once weekly in connection with the scheduled visit/phone contacts based on pre-prandial and bedtime SMPG values as outlined in the titration guidelines or based on carbohydrate counting per investigator's discretion.

CGM will be used both to monitor subjects' glycaemic control and to generate profiles for evaluating the effect on glycaemic control, as per section 3.1.2. CGM data from the receiver will be collected as specified in the flowchart (see Section 1.2). A minimum duration of 4 weeks data collection of CGM for the endpoint assessments has been chosen to accommodate evaluation of hypoglycaemia exposure.[17] CGM values must not be used for hypoglycaemic episode reporting. If a hypoglycaemic episode is captured by the CGM, the subjects should use their BG meter to assess their PG level, and if hypoglycaemia is confirmed, it will be recorded in the eDiary, please refer to Appendix 7 (Section 10.7).

A sufficient assay-sensitivity for the non-inferiority evaluation will be supported 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

Subjects will be switched from pre-trial basal insulin analogues to insulin degludec according to local label, while insulin icodec will be initiated according to the principles outlined in the titration guideline in Appendix 8 (Section 10.8). A loading dose will be applied to avoid glycaemic slip during the first week of treatment. A 50% loading dose will be applied for subjects with an $HbA_{1c} < 8\%$ at screening to reduce the risk of experiencing hypoglycaemic events at the beginning of the trial. While a 100% loading dose will be applied for subjects with an $HbA_{1c} \geq 8\%$ at screening to mitigate the occurrence of hyperglycaemic episodes in subjects entering the trial with poor glycaemic control. Subjects that prior to randomisation received insulin glargine U300 or basal insulin twice daily should receive a 50% loading dose regardless of their HbA_{1c} at screening.

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

The PK and PD properties of insulin icodec following five weeks of once weekly dosing in subjects with T2D (trial NN1436-4314) and T1D (trials NN1436-4225 & NN1436-4422) showed that insulin icodec exposure was well distributed across the dosing interval, with a PK and PD profile suitable for once weekly dosing.

After randomisation, subjects should start once weekly insulin icodec or once daily insulin degludec on the same day as randomisation. Due to the longer half-life of insulin icodec, the last dose of insulin icodec will be administered 51 weeks after randomisation, while once daily insulin degludec injections will continue until 52 weeks after randomisation. The follow up period for both insulin icodec and insulin degludec will be 5 weeks from end of treatment (V54) to end of trial (V56).

Insulin aspart should also be initiated same day as randomisation and should be taken 2-4 times daily with meals throughout the 52 weeks treatment duration. Switch from other rapid-acting insulin analogues should be done unit-to-unit.

Further details on dose adjustment can be found 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.

5.1 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female aged ≥18 years at the time of signing informed consent.
3. Diagnosed with type 1 diabetes mellitus ≥ 1 year prior to the day of screening.
4. Treated with multiple daily insulin injections (basal and bolus insulin analogue regimens) ≥ 1 year prior to the day of screening.
5. HbA_{1c} <10% at screening visit measured by central laboratory.

5.2 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial products 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 T1D which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

6. 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).
7. Myocardial infarction, stroke, hospitalization 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 (NYHA) Class IV at screening.
9. Planned coronary, carotid or peripheral artery revascularisation.
10. Renal impairment with estimated Glomerular Filtration Rate (eGFR) value of <30 ml/min/1.73m^2 at screening measured by central laboratory.
11. Impaired liver function, defined as Alanine Aminotransferase (ALT) ≥2.5 times or Bilirubin >1.5 times upper normal limit at screening measured by central laboratory.
12. Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8.[18]
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. 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.
16. 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.
17. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening.

[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.

5.3 Lifestyle considerations

5.3.1 Meals and dietary restrictions

The subjects should be fasting when attending some of visits (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 fasting visit until blood sampling has 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.

5.4 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. For UK: SAE is also included as minimal information (see Appendix 9, Section 10.9).

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

This section is 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 A/S

Trial product name and strength:	Insulin icodec 700 units/mL *(IMP, test product)*	Insulin degludec, 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. Rotation of injection site within the same area is recommended.	Administer insulin degludec once daily at any time of the day, but preferably at the same time every day throughout the trial. Rotation of injection site within the same area is recommended.
Packaging	3 mL PDS290 pre-filled pen-injector	3 mL PDS290 pre-filled pen-injector

- Insulin icodec and insulin degludec DFU will be provided electronically via the eDiary and available to the subjects throughout the trial.
- A pen differentiation guide will be provided
- At randomisation visit (V2) subjects should administer trial product 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 product

Trial product name:	Insulin aspart 100 units/mL *(NIMP, auxiliary therapy)*
Dosage form	Solution for injection
Route of administration	Subcutaneous
Recommended initial dose	Please refer to Appendix 8 (Section 10.8)
Dosing instructions	Administer insulin aspart with meals, 2-4 times daily
Packaging	3 mL prefilled Flexpen
Provider	Novo Nordisk A/S

- Insulin aspart DFU will be provided electronically via the eDiary and available to the subjects throughout the trial.

Auxiliary supplies

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

Table 6-3 Auxiliary supplies

Auxiliary supply	Details
Needles	Needles for pre-filled pen injector. NovoFine needles no longer than 6 mm will be used for administration of trial product. Only needles approved by Novo Nordisk must be used for administration of trial product.
Blood glucose meter	Roche Accu Check 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 Roche manufacturer's guide provided
Continuous Glucose Monitoring system	Dexcom G6 At randomisation (V2) subjects must be instructed in handling of the CGM. Please refer to the CGM manual for more information.
eDiary	Subject Mobile app, HCP Web Portal & Cloud service Please refer to the eDiary site guide.

6.1.1 Medical devices

6.1.1.1 Investigational medical device

This section is not applicable for this trial

6.1.1.2 Non-investigational medical devices

Non-investigational medical devices including needles for pre-filled pen injector, BG meter and CGM are listed as auxiliary supplies in Table 6-3.

For countries where BG meter and CGM are not approved, please refer to 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 materials manual (TMM).
- Each site will be supplied with sufficient trial products 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 TMM.

- 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 for.
- 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 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. Randomisation will be stratified by pre-trial basal insulin treatment (either twice daily/insulin glargine U300 or once daily) and HbA_{1c} (either <8% or ≥ 8%) at screening. Within each stratum, each subject will be randomly allocated to receive once weekly insulin icodec once daily insulin degludec. Trial product will be dispensed/allocated at the trial visits summarised in the flowchart (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 (V56) 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 (V56) must be recorded in a separate concomitant medication (diabetes) form in the electronic case report form (eCRF).

The following information must be recorded for any anti-diabetic drugs 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 (V54) only randomised treatment are allowed, unless due to safety reasons at the discretion of the investigator. If the investigator chooses to initiate anti-diabetic medication prior to end of treatment (V54), 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.

6.6 Dose modification

Doses are adjusted according to SMPG values as described in Appendix 8 (Section 10.8).

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 and according to local clinical practice. 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 (V54) as soon as possible to collect the required data for the analysis of the primary endpoint. Two follow-up visits, V55 and V56, must be performed after discontinuation of the trial product. Visits V55 and V56 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 degludec. It is stressed that the visit window is plus 3 days for both visits V55 and V56.

Further, it is important that discontinued subjects come in for discontinuation follow-up visit V28A, 26 weeks after the randomisation visit and V54A, 52 weeks after the randomisation visit. V54A 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 V56.

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 8.3.2. AEs and anti-diabetic medication should be collected and recorded in the eCRF until the discontinuation follow-up visit (V54A) 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 (V54A). 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, or to V28 or to V38, or to V46 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.

If a subject is randomised in violation of inclusion and exclusion criteria erroneously, the nature of the specific violation to in- or exclusion criteria will be evaluated carefully both by the principal investigator and Novo Nordisk medical specialist, independently. Subject can be allowed to continue in the trial and receive trial product if the violation is minimal or with no significant clinical relevance, and there are no safety concerns as evaluated by both the investigator and Novo Nordisk medical specialist (not applicable for UK, please see Appendix 9, Section 10.9).

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. Treatment status session must be made in the IWRS when the subject is temporarily discontinued and also when the subject resumes treatment.

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 V54. 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 CRF.

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 or 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 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 (e.g. electronic or paper) 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 eDiaries, PRO instruments, ECG, CGM data, 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.
- 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 (Section 1.2)

8.1.1 Self-measured plasma glucose

Subjects will be provided with a BG 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 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.

Subjects must be instructed in how to transfer the results of the SMPG values daily into the eDiary.

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 (V56) at the following time points: pre-breakfast, pre-lunch, pre-dinner, and at bedtime. The subject should 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 (Section10.8) 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 entire duration of the trial (i.e. from week 0 (V2) to week 57 (V56)).

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

The CGM readings will be open to both the subject and the investigator.

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 CGM 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). The site should ensure the subject can change the sensor at home weekly during trial periods when the subject will not attend site visits.

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. Data upload will occur at each site visit, see flowchart (Section 1.2). Data upload will occur every week from V2 (week 0) to V8 (week 6), from V24 (week 22) to V28 (week 26), and from V50 (week 48) to V54 (week 52). Outside the specified periods, upload will occur every second or forth week in conjunction with site visit, and at the follow-up visits 1 and 2. The upload will be documented by the system directly.

The serial number of the CGM receiver must be recorded in the eCRF at the randomisation visit (V2). In case the CGM receiver is replaced, the new receiver serial number should be entered in the eCRF as well.

8.1.3 Clinical outcome assessments

The patient reported outcome questionnaires are to be completed by the subject without assistance of the site personnel and should preferably be completed after all fasting-related activities are completed, but before any other visit related procedures are conducted. It takes approximately five minutes to complete the questionnaires.

The following patient reported outcome questionnaires will be supplied in linguistically validated versions in all languages relevant for this trial:

- Diabetes Treatment Satisfaction Questionnaire (DTSQs)
  - The questionnaire has been designed to measure satisfaction with diabetes treatment regimens in people with diabetes. The DTSQs questionnaire will be measured at baseline (V2), week 26 (V28), and end of treatment visit (V54).
- International Physical Activity Questionnaire
  - The questionnaire has been designed to measure physical activity. It will be measured at baseline (V2) only. The questionnaire is for all subjects 18-69 years of age.

8.1.4 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 and the laboratory manual.

8.2 Safety assessments

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

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.

Information on hypoglycaemia unawareness will be recorded according to Clarke's questionnaire, question 8. [18] 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 Sections 6.5 and 6.7

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 will be calculated in the eCRF

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 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 visit (V54) 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 laboratory manual and the protocol flowchart (Section 1.2).

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.

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

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.

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 completed in the eCRF. 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 the eCRF, please refer to Appendix 3 (Section 10.3). 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* (stroke or transient ischemic attack)		X
Heart failure (requiring hospitalisation or urgent heart failure visit)		X
Death		X
Hypersensitivity	X	
Injection Site Reaction	X	

*All cerebrovascular events (stroke and transient ischemic attack) are to be reported and sent for adjudication, however the event adjudication committee 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 Appendix 1, 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 at the time points specified in the flowchart. For subjects discontinuing trial product prematurely AEs must be collected from the end of trial visit until the discontinuation follow-up visit (V54A). For AE reporting in UK, please refer to the UK specific requirements in Appendix 9 (Section 10.9).

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 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 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) 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 consult the current version of the insulin icodec investigator's brochure[9].

For more information on overdose for insulin degludec or insulin aspart, consult the relevant IB, EMA SmPC, US PI or locally approved label.

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 (Section1.2) 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 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.

For retention of residual hypersensitivity samples, please refer to Appendix 6, 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 degludec in terms of change from baseline to week 26 in HbA_{1c}.

Formally, let D be the treatment difference 'insulin icodec' minus 'insulin degludec' 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 ≥0.30% against HA: D <0.30%

The non-inferiority margin of 0.3%-point is chosen based on the recommendation of health authority guidance for industry on developing drugs for treatment of diabetes.[19, 20] Furthermore:

- 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 30% of a suitably conservative estimate of insulin degludec´s treatment effect on HbA_{1c} in a placebo-controlled trial in a T1D population; The treatment effect of degludec versus placebo in a T1D population is unknown but in a progressed T2D population of subjects already treated with liraglutide, degludec was shown to be superior to placebo (ETD: -0.92%-point [-1.00; -0.75] 95%CI).

9.2 Sample size determination

The sample size is determined in order to have 90% power for declaring non-inferiority (NI) with a NI margin of 0.3%-point with respect to change in HbA_{1c} for the specified estimand and the full analysis set (primary analysis set). All available data points for the primary endpoint will be used in the primary analysis and this has guided the treatment effect assumptions below.

In studies with insulin degludec 100 units/mL in T1D subjects (NN1250-3583, NN1250-3770, and NN1250-3995) the percent withdrawing from treatment and/or trial during the initial 26 weeks was approximately 9%, 12% and 15%. Considering the increased focus on retention, 10% are expected to experience any of the specified intercurrent events before week 26 in this trial.

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 standard deviation (SD) is assumed to be 1.0%-point based on results from studies with insulin degludec in subjects with T1D (NN1250-3583, NN1250-3770 and NN1250-3995), where the SD was found to be 0.9, 0.9 and 0.93 respectively.

From the above assumptions and requirements, 580 subjects will be randomised to 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 the table below (Table 9-1) displaying power for various alternative treatment differences and standard deviations.

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

SD (%-point)	0.0/0.015	True treatment difference/adjusted treatment difference (%-point) 0.0/0.03	0.0/0.045	0.05/0.08
0.9	97%	95%	93%	84%
1.0	93%	**90%**	87%	75%
1.1	88%	84%	80%	67%

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

9.3 Populations for analyses

The following population*s* are defined:

Population	Description
Randomised	All subjects randomised.
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 one 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.

Baseline assessments are always included in the in-trial observation period.

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 (V56)
- 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.

Main-on-treatment period
The main-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 date of the on-treatment period
- Week 26 (V28).

Baseline assessments are always included in the on-treatment observation periods.

All efficacy endpoints will be summarised and analysed using the full analysis set and the 'in-trial' period. Safety endpoints will be evaluated using both the main-on-treatment and the on-treatment period with descriptive statistics being based on the safety analysis set 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 (FSFV), and it will include a more technical and detailed description of the statistical analyses described in this section.

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 degludec
- Screening HbA_{1c} < 8%: yes, no
- Pre-trial basal insulin treatment: twice daily or insulin glargine U300: yes or no
- Region: Asia, Europe, North America
- The regions will be defined as follows:
  - Asia: India, Japan
  - Europe: Austria, Netherlands, Germany, Turkey, Italy, Russia, Spain, United Kingdom
  - North America: United States, Canada
  -

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.

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 (FAS) 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 having discontinued their randomised treatment prior to the week 26 visit and have a 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 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, screening HbA_{1c} < 8% (yes/no) pre-trial basal insulin treatment and randomised treatment as fixed factors, and baseline HbA_{1c} as covariate.

The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.

Explanatory factors will be coded as follows:

- Treatment: Once weekly insulin icodec, insulin degludec
- Region: Asia, Europe, North America
- Screening HbA_{1c} < 8%: yes, no
- Pre-trial basal insulin treatment: twice daily or insulin glargine U300: yes or no

This analysis has the underlying assumption that subjects with missing data behave similarly as subjects that discontinues 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 degludec 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 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) for both treatment arms will be imputed with baseline value adding a random error term. The random error term is normally distributed with a standard deviation set equal to the estimated residual standard deviation of an ANCOVA analysis on the LAOT values. Specifically, the imputations and analyses will be carried out as follows:

- First, an ANCOVA model with region, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment and randomised treatment as fixed factors, and a baseline value as a covariate will be fitted to the LAOT value.
- Second, the estimated residual standard deviation, *s*, from this model will be used to impute missing values by the baseline value, adding a random normally distributed term with mean 0 and standard deviation *s*. This will be done 1000 times.
- For each of the complete data sets, the endpoint will be analysed using an ANCOVA model with region, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment 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.

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

Missing time in target range 3.9 – 10.0 mmol/L (70-180 mg/dL) (TIR) from week 22 to week 26 will be imputed from trial participants who are from the insulin degludec 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 insulin degludec treatment. Specifically, the imputations and analyses will be carried out as follows:

- First, one thousand (1000) copies of the dataset will be generated for TIR.
- Second, for each dataset copy, an ANCOVA model will be fitted to TIR values for subjects who completed their randomised treatment in the insulin degludec 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, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment and randomised treatment as fixed factors. The estimates and SDs for the 1000 data sets will be pooled to one estimate and associated SD using Rubin's rule.

Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction from baseline week 0 (V2) to week 26 (V28)

The change in DTSQs in total treatment satisfaction from baseline to week 26 will be analysed using the same model as specified for change in FPG, but the corresponding baseline value will be used as a covariate.

Change in HbA_{1c} from baseline week 0 (V2) to week 52 (V54)

The change in HbA_{1c} from baseline to week 52 will be analysed similar to the primary endpoint specified above.

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 26 (V28).
- 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 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 nocturnal 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).

For subjects who discontinued their randomised treatment, the number of episodes in the missing period (time of follow-up 2 visit (V56) to planned end of the main-on-treatment period) will be imputed using a multiple imputation technique, assuming that the event rate pre-follow-up 2 visit (V56) follows the respective treatment groups rate whilst post-follow-up 2 visit (V56) event rate is the rate of the comparator 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, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment and randomised treatment as fixed factors and the logarithm of the main-on-treatment period as offset.
- Second, based on the estimated parameters for the comparator 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.

The following hypoglycaemic endpoints will be analysed separately using the method described above, substituting the main-on-treatment period with the on-treatment period:

- Number of severe hypoglycaemic episodes (level 3), from baseline week 0 (V2) to week 57 (V56).
- 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 57 (V56).
- 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 57 (V56).
- Number of nocturnal 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 57 (V56). Nocturnal hypoglycaemic episodes are hypoglycaemic episodes occurring between 00:01 and 05:59 both inclusive.

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 in a similar manner as 'time in target range 3.9 – 10.0 mmol/L (70-180 mg/dL)' 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 where time spent below or above range will be analysed separately using a negative binomial model on the number of recorded measurements below and above range, respectively, with a log-link function and the logarithm of the total number of

recorded measurements as offset. The model will include randomised treatment and region as factors. Further details will be provided in the SAP.

Mean total weekly insulin dose from week 24 (V26) to week 26 (V28) and mean total weekly insulin dose from week 50 (V52) to week 52 (V54)

Mean weekly insulin dose during the last 2 weeks of treatment (from week 50 to week 52) and during the last 2 weeks in the main part (from week 24 to 26) will be log-transformed and analysed separately using the same statistical model as specified for change in FPG. Pre-trial (baseline) total weekly insulin dose will be log-transformed and included as a covariate in the model.

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.

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 both the main-on-treatment and 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

The trial does not include a formal interim analysis. However, the reporting will be split into a main phase and an extension phase, where the results of the main phase can be reported possibly before LPLV. Subjects will provide consent for the full length of the trial. To preserve trial integrity during the extension phase, dissemination of results from the main phase will, during the extension phase, initially be limited to communication internally and with regulatory authorities.

9.6 Data monitoring committee

This section is not applicable for this trial.

9.7 Reporting of the main part of the trial

A database lock is planned shortly after last subject last visit of the main part of the trial. The results from this main part will thereafter be reported. The complete trial will be reported after database lock of the extension part.

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[21] and applicable ICH Good Clinical Practice (GCP) Guideline[22]
- Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR 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 CTR 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[22], Declaration of Helsinki[21] 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

The site will be offered a communication package for the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the subjects. The written information will be translated and adjusted to local requirements and distributed to 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. The safety committee may recommend unblinding of any data for further analysis, and in this case an internal trial independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

10.1.6.2 Trial safety group

This section is not applicable for this trial.

10.1.6.3 Data monitoring committee

This section is 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 CTR.

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 (ICMJE)[23], the Food and Drug Administration Amendment Act (FDAAA)[24], European Commission Requirements[1, 25, 26] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The primary completion date (PCD) is the last assessment of the primary endpoint, and is for this trial last subject first treatment (LSFT) + 26 weeks corresponding to visit 28. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 28. 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 or designee (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 CRF is revoked or the CRF is temporarily unavailable:

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

- Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.
- Monitors will review the subject's medical records and other source data to ensure consistency and/or identify omissions compared to the CRF.

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 CRF 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 recorded directly into the eCRFs and will be considered source data.

- Data in the service providers' database is considered source data e.g. eDiaries, CGM and laboratory.
- 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 CTR for this trial.

One or two investigators will be appointed by Novo Nordisk to review and sign the CTR (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 CTR is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

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

In all cases, the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. 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.[27]

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 CTR.
- 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 (V1*, V2, V12, V20, V28, V38, V46*, V54, V28A*, V54A*) *HbA_{1c} only	• Fasting plasma glucose (FPG)[1] • HbA_{1c}
NOTE: [1]A FPG result <3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as an AE 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, V38, V54)	• Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Thrombocytes
Biochemistry[1] (V1, V12, V28, V38, V54)	• Alanine Aminotransferase (ALT) • Albumin • Alkaline phosphatase • Aspartate Aminotransferase (AST) • Creatinine • Potassium • Sodium • Bilirubin
Lipids (V2, V12, V28, V38, V54)	• Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • or IRB/IECTriglycerides
Pregnancy Testing (V2, V56)	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test[2]
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation, eGRF 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, V38, V54, V56) • Insulin-icodec serum concentration (V4, V8, V12, V20, V28, V38, V54, V56)
Notes: [1]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Section 10.3 (Hy's Law) and Section 7.1. [2]Local urine testing will be standard unless serum testing is required by local regulation .	

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 unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of an IMP.

Events meeting 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 NOT 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 (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of events for adjudication and AEs requiring additional data collection

Description of events 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. Source data should be in accordance with Section 8.3.

- 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, diarrhoea, 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[28]. 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[29]. 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[30]. 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 or use of wrong device
  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 (e.g. hypoglycaemia or other), 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 NIMP (insulin aspart) 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 brochure and/or product information, for 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.

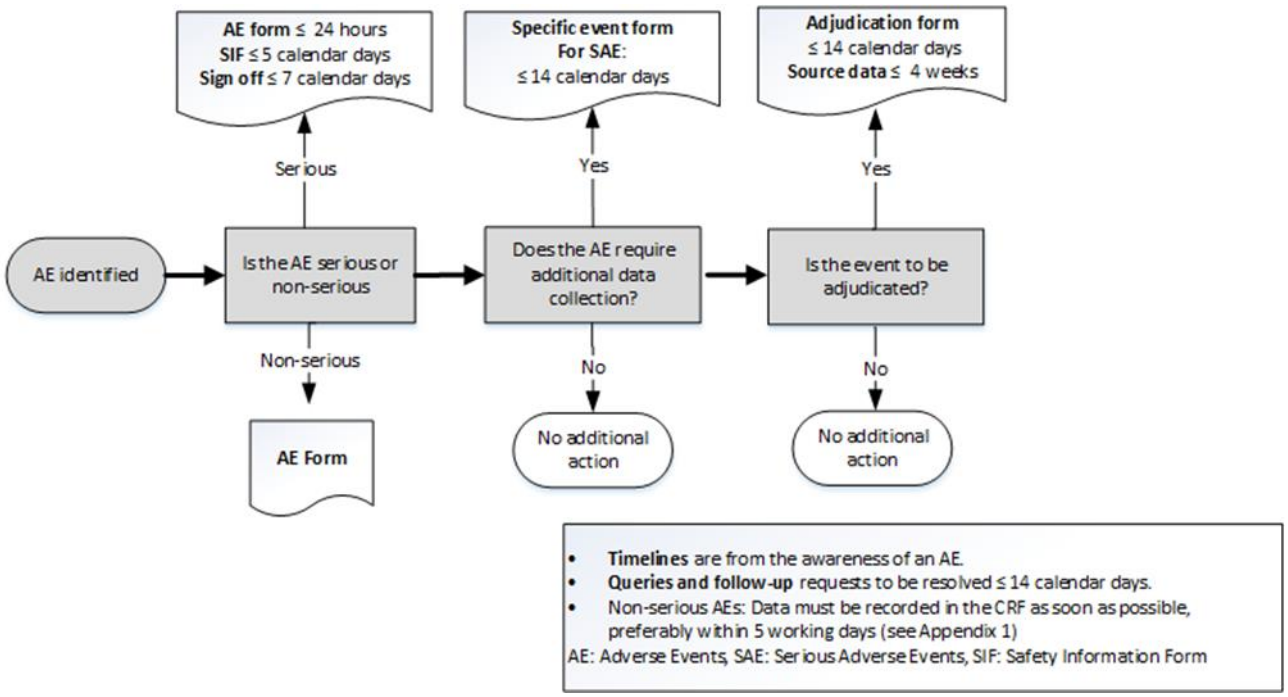
Follow-up of AE and SAE
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity 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, the investigator should provide Novo Nordisk with a copy of 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 below. Source data should be in accordance with Section 8.3. • If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the CRF is unavailable for more than 5 calendar days, then the site will use the safety information form (see box below). • The site will enter the SAE data into the CRF as soon as it becomes available. • 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 the figure below):
  • 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



Source data should be in accordance with Section 8.3

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 Roche 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 (e.g. amenorrhea in adolescents or athletes), 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 effective contraception method.

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 degludec or insulin aspart in seminal fluid is unlikely[31]

Female subjects
Female subjects of childbearing potential are eligible to participate if they agree to use at least an acceptable effective method of contraception consistently and correctly as described in Table 10-3 . As a minimum, contraception should be maintained until treatment discontinuation[32].

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, Section 10.2 and the trial flowchart, Section 1.2).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 a subject's pregnancy (see Figure 10-2).
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate which will be forwarded to Novo Nordisk 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 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 a 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 possibly/probably related to the IMP by the investigator will be reported to Novo Nordisk as described in Section 10.3. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

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

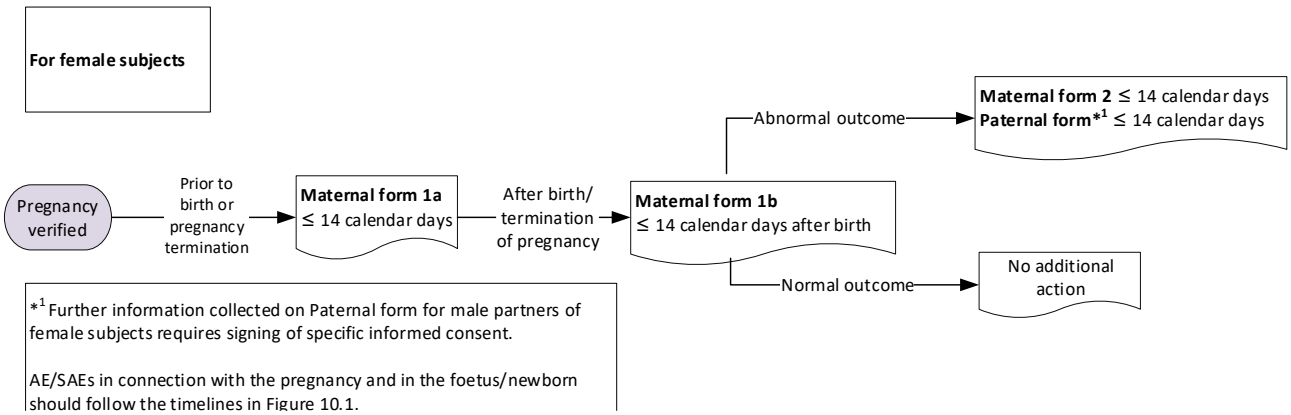


Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy.

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

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.

The investigator must complete the technical complaint form in the CRF within:

- 5 days calendar for all 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[33], ADA[34], ISPAD[35] type 1 diabetes outcomes program[36], ATTD[37]. Severe hypoglycaemia as defined by Seaquist[38] and ISPAD[35].		

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.[38]

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[34]

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[38].

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[38].

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

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 degludec, both in combination with mealtime insulin aspart.

- ***Insulin icodec*** should be taken once weekly on the same day of the week.
  - At randomisation (V2)
    - Subjects that prior to randomisation received insulin glargine U300 or received basal insulin twice daily should receive a dose which consists of total daily basal insulin dose before randomisation x7 + 50% (Table 510-6) regardless of their HbA_{1c} at screening.
    - Subjects with HbA_{1c} <8% (64 mmol/mol) at screening should receive a dose which consists of total daily basal insulin dose before randomisation x7 + 50% (Table 510-6)
    - Subjects with HbA_{1c} ≥ 8% (64 mmol/mol) at screening should receive a dose which consists of total daily basal insulin dose before randomisation x7 + 100% (Table 10-7)

The following weekly dose (V3) for all subjects should be the total daily dose x7. In the following table the weekly V2 and V3 doses for subjects receiving from 10 U to 100 U per day have been calculated. Please note that the displayed values are rounded off to the nearest dose divisible by 10.

Table 510-6 V2 and V3 doses for subjects that prior to randomisation received insulin glargine U300 or received basal insulin twice daily, or subjects with HbA_{1c} <8% (64 mmol/mol) at screening

Total daily dose before randomisation	V2 insulin icodec dose	V3 insulin icodec dose	Total daily dose before randomisation	V2 insulin icodec dose	V3 insulin icodec dose
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			

Table 10-7 V2 and V3 doses for subjects with $HbA_{1c} \geq 8\%$ (64 mmol/mol) at screening

Total daily dose before randomisation	V2 insulin icodec dose	V3 insulin icodec dose	Total daily dose before randomisation	V2 insulin icodec dose	V3 insulin icodec dose
10	140	70	56	780	390
11	150	80	57	800	400

12	170	80	58	810	410
13	180	90	59	830	410
14	200	100	60	840	420
15	210	110	61	850	430
16	220	110	62	870	430
17	240	120	63	880	440
18	250	130	64	900	450
19	270	130	65	910	460
20	280	140	66	920	460
21	300	150	67	940	470
22	310	150	68	950	480
23	320	160	69	970	480
24	340	170	70	980	490
25	350	180	71	990	500
26	360	180	72	1010	500
27	380	190	73	1020	510
28	390	200	74	1040	520
29	410	200	75	1050	530
30	420	210	76	1060	530
31	430	220	77	1080	540
32	450	220	78	1090	550
33	460	230	79	1110	550
34	480	240	80	1120	560
35	490	250	81	1130	570
36	500	250	82	1150	570
37	520	260	83	1160	580
38	530	270	84	1180	590
39	550	270	85	1190	600
40	560	280	86	1200	600
41	570	290	87	1220	610
42	590	290	88	1230	620
43	600	300	89	1250	620
44	620	310	90	1260	630
45	630	320	91	1270	640
46	640	320	92	1290	640
47	660	330	93	1300	650
48	670	340	94	1320	660
49	690	340	95	1330	670
50	700	350	96	1340	670
51	710	360	97	1360	680
52	730	360	98	1370	690
53	740	370	99	1390	690
54	760	380	100	1400	700
55	770	390			

- ***Insulin degludec*** should be taken once daily, at any time of the day but preferably 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 of insulin icodec and insulin degludec 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.

Adjustment of insulin icodec and degludec will be done in accordance with the table below (Table 10-8).

Table 10-8 Adjustment of insulin icodec and insulin degludec

Pre-breakfast SMPG			Icodec adjustment	Degludec adjustment
Value to use	mmol/L	mg/dL	U	U
Lowest of the SMPG values	<4.4	<80	–20	-3
	4.4–7.2	80–130	0	0
	>7.2	>130	+20	+3

Titration of insulin aspart

Titration of insulin aspart can either be adjusted weekly based on pre-prandial and bedtime SMPG values using the algorithm below or based on carbohydrate counting at the investigator's discretion.

Algorithm use:

- In the first 8 weeks after randomisation insulin aspart should be only be adjusted for safety reasons. Thereafter the doses should be considered adjusted weekly by the investigator.
- Dose adjustment will be based on the lowest pre-prandial or bedtime SMPG values measured in the week prior to titration in accordance with Table 10-9.
    - 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 10-9 Insulin aspart

Lowest pre-prandial and bedtime SMPG		Insulin aspart adjustment
mmol/L	mg/dL	U
<4.4	<80	-1
4.4-7.2	80-130	0
>7.2	>130	+1

The subjects can take correction bolus doses in collaboration with the investigator. The investigator should consider using the "100 rule" (for mmol/L) or "1,800 rule" (for mg/dL) to estimate the correction bolus doses.

Carbohydrate counting:

- This method should be reserved to subjects that are willing and able to do so. The subject needs to have prior hands-on experience using this method of determining bolus insulin doses. It is the investigator's responsibility to ensure that the subject is adequately trained. If more training is needed, this should be done in accordance with local practice.
- Insulin aspart should be adjusted daily in accordance with the immediate pre-meal SMPG and carbohydrate content in the meal that the subject is about to eat. To use this method, the investigator needs to determine the insulin-to-carbohydrate ration (I:CHO ratio) and the insulin sensitivity factor (ISF) for each meal and adjust, when needed.
- I:CHO ratio expresses the amount of carbohydrates (in grams) for which IU of bolus insulin that would effectively minimise the postprandial glucose excursion. ISF expresses the expected reduction in plasma glucose concentration, when IU is administered.
- *example:* A subject has pre-prandial plasma glucose of 10.0 mmol/L (180 mg/dL) and intends to eat a meal containing 60 g of carbohydrates. For the given meal the I:CHO ratio has been estimated to 1U:10g and the ISF to be 2.0 mmol/L per 1U (36 mg/dL per 1U) and the target plasma glucose is 7.2 mmol/L (130 mg/dL) in this trial. The bolus dose for this meal can be calculated as follows:
    - To cover the meal carbohydrates: multiply grams of carbohydrates by I:CHO:
    - 60 g x 1U/10 g = 6U
    - To bring the pre-prandial glucose value to target: Subtract the target glucose value from the current pre-prandial glucose value and divide by ISF for this meal:
    - (10.0 mmol/L – 7.2 mmol/L)/2.0 mmol/L/U ~ 1U.
    - Thus, the bolus dose for this meal is 6U + 1U = 7U.

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 measurements and adjust bolus doses if needed. If the missing dose is missed for > 3 days, the subject should await the next planned day of injection. Subjects should perform frequent SMPG measurements to closely monitor their glycaemic control and adjust bolus doses, if needed.

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

It is recommended that the subject is switched from insulin icodec to any available basal insulin at the discretion of the investigator. Regarding the switch from insulin icodec to post-trial basal insulin the following should be considered:

- Calculate the new daily basal insulin dose by dividing the latest insulin icodec dose by 7. For subjects completing the trial the dose taken at V53 will be the latest dose.
- Initiate basal insulin, when pre-breakfast SMPG daily in the follow up-period (after V54) exceeds 10.0 mmol/l (180 mg/dL). It is important that the investigator and the subjects are in close contact to prevent any misunderstanding.
- 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 icodec and insulin degludec or insulin aspart injections
- Ensure transfer of SMPG values with an indication of “pre-breakfast”, “pre-lunch”, “pre-dinner”, “bedtime” or “other” (Section 8.2.1).
- 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 degludec or insulin icodec and insulin aspart doses prescribed at this contact.
- Reasons for deviation from the insulin icodec or insulin degludec 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 Austria:

- **Contraceptive guidance:** A monthly pregnancy test is mandatory for female subjects of childbearing potential.

For Canada

- **Retention of clinical trial documentation:** Part C, Division 5 of the Food and Drug Regulations [C.05.012] requires a 25-year retention period

For Germany

- **Demography:** Subject's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth in CRF.

- **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 Germany.**
- **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 Germany.**

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, Section7.1:** 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 Russia:

- **Trial governance considerations:** The trial should be conducted in compliance with the protocol, Ministry of Healthcare of Russian Federation' order #200H from April, 01, 2016 "Approval of rules of good clinical practice" and legal requirements of the Russian Federation regulating circulation of medicines.

For Spain:

- **Retention of clinical trial documentation:** 25 years according to the new Spanish Royal Decree 1090/2015.

For Turkey

- Blood samples from Turkey will be analysed by a central lab.
    - This trial is a phase 3 trial.

For USA:

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

For Russia where BG meter is not approved at the time of the final protocol version 2.0:

- The BG meter is regarded as investigational devices and will be labelled to indicate for investigational use only. This 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 Roche 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 must be collected by the investigator.

If BG meter is approved during trial conduct, the procedures above are not applicable anymore and technical complaints reporting should follow the standard vigilance procedures.

For UK:

- **Screen failures**: Minimal information includes informed consent date, demography, screen failure details, eligibility criteria, and serious adverse event (SAE).
- **Discontinuation of trial treatment**: Subjects that are randomised in violation of inclusion and exclusion criteria should be discontinued from the trial treatment.
- **Time period and frequency for collecting AE and SAE information**: All AEs and SAEs must be collected from the time of informed consent and until the end of trial visit as specified in the flowchart. For subjects discontinuing trial product prematurely SAEs must be collected from the end of trial visit until the discontinuation follow-up 2 visit (V54A).

For India and Russia where CGM is not approved at the time of the final protocol version 2.0:

- 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

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
CGM	continous glucose monitor
CRF	case report form
CTR	clinical trial report
CRO	contract research organisation
DTSQs	Diabetes Treatment Satisfaction Questionnaire
DFU	directions for use
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FGM	flash glucose monitor
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HbA_{1c}	glycated haemoglobin
HCP	health care professional
HRT	hormone replacement therapy
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgE	immunoglobulin E
IMP	investigational medicinal product
INN	international non-proprietary name
ISPAD	International Society for Pediatric and Adolescent Diabetes
IRB	institutional review board
IWRS	interactive web response system

LDL	low-density lipoprotein
LSLV	last subject last visit
NIMP	non-investigational medical product
PCD	primary completion date
PG	plasma glucose
PRO	patient reported outcomes
SAE	serious adverse event
SAP	statistical analysis plan
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
TMM	trial materials manual
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 (22 February 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 3.0:

The protocol has been amended to exclude Japan from 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.
10.9 Appendix 9: Country/Region-specific requirements	Footnotes related 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.

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Memo

To: NN1436-4625 Clinical Sites

Copy: NN1436-4625 Sponsor Trial Master File (TMF); NN1436-4625 Trial Squad

From: [redacted] ([redacted]) and [redacted] ([redacted])

Date: 09-Dec-2021

Ref: NN1436-4625: Protocol Version 4.0, Flowchart

In the ONWARDS 6/NN1436-4625 Protocol (Version 4.0, 14-Apr-2021), *Section 1.2 Flowchart* an error has been discovered. The error relates to "Hypoglycaemic episodes" for the "Early Discontinuation Follow-up" V28A and V58A:

- For discontinued subjects, hypoglycaemic episodes should ***not*** be collected at V28A and V58A. Therefore, the Flowchart should be as seen below.

Procedure	**Protocol section**	**Screening**	**Randomisation**	**Treatment**																								**Follow-up 1**	**Follow-up 2**	**Early Discontinuation Follow-up**	**Early Discontinuation Follow-up**
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V12	V16	V20	V24	V25	V26	V27	V28	V30	V34	V38	V42	V46	V50	V51	V52	V53	V54	V55	V56	V28A	V54A
Weekly Phone contact number (P) *(For details see separate flow chart below)*									P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23					P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48 P49									
Timing of visit (weeks)		≤-2	0	1	2	3	4	5	6	10	14	18	22	23	24	25	26	28	32	36	40	44	48	49	50	51	52	54	57	26	52
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Adverse event	8.3 App. 3 10.3			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	8.3 App7 10.7			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Training in trial Product, Pen-handling	6.1		X	X					X		X		X					X		X		X									
Drug dispensing	6.2		X						X		X		X					X		X		X									
Hand out and instruct in devices	6.1.1		X																												
End of Trial	4.4																												X		X

Novo Nordisk will not prepare a protocol amendment at the moment, it is important that you are aware of this error when conducting the discontinuation visits. Novo Nordisk does not foresee a risk to study participants of this error.

Please keep this communication with the protocol (V4.0) at all times.

Thank you for your cooperation.

Novo Nordisk A/S

Vandtårnsvej 108-110
DK-2860 Søborg
Denmark

Telephone:
+45 4444 8888
Direct dial:
[redacted]

E-mail:
[redacted]
Internet:
www.novonordisk.com

Ref: (only relevant to UK) NN1436-4625: Protocol Version 4.0, Appendix 9

In the ONWARDS 6/NN1436-4625 Protocol (Version 4.0, 14-Apr-2021), *Appendix 9: Country-specific requirements*; *For UK* an error has been discovered. The error relates to "Time period and frequency for collecting AE and SAE information" for UK:

- Time period and frequency for collecting AE and SAE information: All AEs and SAEs must be collected from the time of informed consent and until the end of trial visit as specified in the flowchart. For subjects discontinuing trial product prematurely ~~SAEs~~ AEs must be collected from the end of trial visit until the discontinuation follow-up 2 visit (V54A).

Novo Nordisk will not prepare a protocol amendment at the moment, it is important that investigators in UK are aware of this error. Novo Nordisk does not foresee a risk to study participants of this error.

Please keep this communication with the protocol (V4.0) at all times.

Thank you for your cooperation.

Protocol

Efficacy and safety of once weekly insulin icodec compared to once daily insulin degludec 100 units/mL, both in combination with insulin aspart, in adults with type 1 diabetes.

A 26-week, randomised, multicentre, open-label, active-controlled, parallel group, two armed, treat-to-target trial investigating the effect on glycaemic control and safety of treatment with once weekly insulin icodec compared to once daily insulin degludec, both in combination with insulin aspart in adults with type 1 diabetes, with a 26-week extension investigating long term safety.

ONWARDS 6

Substance name: Insulin icodec

Universal Trial Number: U1111-1251-7315

EudraCT Number: 2020-002374-27

IND Number: 137406

Trial phase: 3a

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

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	**Date**	**Applicable in country(-ies) and/or site(s)**
Protocol version 5.0	27 June 2022	For Japan only
Protocol version 4.0	14 April 2021	All countries
Protocol version 3.0	22 February 2021	For Japan only
Protocol version 2.0	07 January 2021	All countries, except Japan
Original protocol version 1.0	20 October 2020	Not submitted

Protocol version 5.0 (27 June 2022)

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 5.0:

The protocol has been amended to specify Drug(s) used in the clinical trial except for IMP(s) as per local regulatory requirement.

Section # and name	Description of change	Brief rationale
10.11 Appendix 11 Protocol amendment history	Amendment history is updated by moving protocol v4.0 history to appendix 11	Due to the new protocol v5.0
10.9 Appendix 9: Country/Region-specific requirements	Definition of Drug(s) used in the clinical trial except for IMP(s) is added for Japan.	To meet new Japanese regulatory requirement.

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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.

This is a 26-week trial designed to investigate the effect and safety of once weekly insulin icodec compared to once daily insulin degludec 100 units/mL, both in combination with insulin aspart in subjects with type 1 diabetes, with a 26-week extension phase. The first 26 weeks of the trial constitute the main phase, after which the primary analysis is planned. The focus of the 26-week extension phase is to evaluate long-term safety and provide long-term exposure data.

Objectives and endpoints:

Primary objective

To confirm the effect on glycaemic control of once weekly insulin icodec in combination with insulin aspart, in subjects with type 1 diabetes. This includes comparing the difference in change from baseline in HbA_{1c} between once weekly insulin icodec and once daily insulin degludec both in combination with insulin aspart after 26 weeks of treatment to a non-inferiority limit of 0.3%.

Primary endpoint

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

Estimand

The estimand is the 'treatment policy estimand' defined as the treatment difference between insulin icodec and insulin degludec 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).

Overall design:

This is a 26-week randomised, multicentre, multinational, open-label, active controlled, parallel group, two-armed, treat-to-target trial with two treatment arms. Subjects will be randomised (1:1) to receive either insulin icodec or once daily insulin degludec, both in combination with 2-4 daily bolus injections of insulin aspart. Randomisation of subjects will be stratified based on pre-trial basal insulin regimen and by HbA_{1c} (either $<8\%$ or $\geq 8\%$) at screening.

Key inclusion criteria:

1. Male or female aged ≥ 18 years at the time of signing informed consent.
2. Diagnosed with type 1 diabetes mellitus ≥ 1 year prior to the day of screening.
3. Treated with multiple daily insulin injections (basal and bolus insulin analogue regimes) ≥ 1 year prior to the day of screening.
4. HbA_{1c} <10% at screening visit based on analysis from central laboratory.

Key exclusion criteria:

1. Myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.
2. Chronic heart failure classified as New York Heart Association (NYHA) Class IV at screening.
3. 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).
4. 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.

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 59 weeks, consisting of a 2-week screening period, followed by an initial 26-week randomised treatment period, a 26-week extension phase and a 5-week follow-up period. All subjects will be centrally randomised in a 1:1 manner and assigned to receive once weekly insulin icodec or once daily insulin degludec, both in combination with 2-4 times daily injections of insulin aspart throughout the 52-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 degludec 100 units/mL, subcutaneous, solution for injection, 3 mL PDS290 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	Early Discontinuation Follow-up	Early Discontinuation Follow-up
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V12	V16	V20	V24	V25	V26	V27	V28	V30	V34	V38	V42	V46	V50	V51	V52	V53	V54	V55	V56	V28A	V54A
Weekly Phone contact number (P) *(For details see separate flow chart below)*									P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23					P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48 P49									
Timing of visit (weeks)		≤-2	0	1	2	3	4	5	6	10	14	18	22	23	24	25	26	28	32	36	40	44	48	49	50	51	52	54	57	26	52
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Informed consent and demography	App 1 10.1	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			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	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	8.2.3	X									X						X										X				
Physical examination	8.2.2	X															X										X				
Body measurements	8.2.2	X	X								X						X										X			X	X
Clinical outcome assessment: DTSQs	8.1.3		X														X										X				

Procedure	Protocol section	Screening	Randomisation	Treatment																										Follow-up 1	Follow-up 2	Early Discontinuation Follow-up	Early Discontinuation Follow-up
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V12	V16	V20	V24	V25	V26	V27	V28	V30	V34	V38	V42	V46	V50	V51	V52	V53	V54	V55	V56	V28A	V54A
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Timing of visit (weeks)		≤-2	0	1	2	3	4	5	6	10	14	18	22	23	24	25	26	28	32	36	40	44	48	49	50	51	52	54	57	26	52
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Clinical outcome assessment: International Physical Activity Questionnaire	8.1.3		X																													
Eye examination	8.2.5	X															X										X					
ECG	8.2.4	X															X										X					
Pregnancy test	8.3.5 App.4 10.4		X																										X			
Laboratory assessments	App.2 10.2	X	X							X		X					X			X		X					X			X	X	
HbA1c		X	X							X		X					X			X		X					X			X	X	
Antibodies *(anti-insulin icodec antibodies)*	8.9.1		X		X				X	X		X					X			X							X		X			
PK *(insulin icodec serum concentration)*	8.5				X				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	X	X	X	X	X	X	X	X	X	X	X	X			
CGM	8.1.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Procedure	**Protocol section**	**Screening**	**Randomisation**	**Treatment**																										**Follow-up 1**	**Follow-up 2**	**Early Discontinuation Follow-up**	**Early Discontinuation Follow-up**
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V12	V16	V20	V24	V25	V26	V27	V28	V30	V34	V38	V42	V46	V50	V51	V52	V53	V54	V55	V56	V28A	V54A
Weekly Phone contact number (P) *(For details see separate flow chart below)*									P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23					P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48 P49								
Timing of visit (weeks)		≤-2	0	1	2	3	4	5	6	10	14	18	22	23	24	25	26	28	32	36	40	44	48	49	50	51	52	54	57	26	52
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3	±3
Adverse event	8.3 App. 3 10.3			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	8.3 App7 10.7			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Training in trial Product, Pen-handling	6.1		X	X					X		X		X					X		X		X									
Drug dispensing	6.2		X						X		X		X					X		X		X									
Hand out and instruct in devices	6.1.1		X																												
End of Trial	4.4																												X		X

1.3 Flow charts – Phone visits

Phone contacts during treatment period (P) Time shown in site visit flow chart	P9-P49
Visit window (days)	±3
Concomitant medication (6.5)	X
4-point SMPG profile (8.1.1)	X
Adverse events (8.3 Appendix 3)	X
Hypoglycaemic episodes (8.3, Appendix 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 (s.c.) injection. Insulin icodec has a terminal elimination half-life of approximately 196 hours. For patients 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 patients with diabetes by limiting the burden associated with insulin treatment.

2.1 Trial rationale

The present trial is designed to investigate the effect and long-term safety of once weekly insulin icodec in comparison to once daily insulin degludec 100 units/mL (hereafter referred to as insulin degludec) both in combination with insulin aspart in adult subjects with T1D. The effect of insulin icodec is evaluated after the 26-week main phase, followed by a 26-week extension phase with a primary aim to assess long-term safety.

2.2 Background

Diabetes mellitus

T1D is a heterogeneous disorder characterised by T cell-mediated autoimmune destruction of insulin-producing beta cells in the pancreas.[5] The destruction of beta cell function leads to insulin deficiency and the requirement of lifelong administration of exogenous insulin. Results from the DCCT study and the follow-up study (EDIC) have demonstrated the importance of maintaining tight glycaemic control to reduce the risk of long-term complications associated with diabetes.[6] As such, the fundamental principle for insulin treatment of T1D is to mimic normal physiological patterns as closely as possible. The current gold standard of care is based on intensive insulin therapy with multiple daily injections of prandial and basal insulin or continuous subcutaneous insulin infusion.[7, 8]

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

proteolytic 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 phase 2 trials NN1436-4383 [T2D], NN1436-4465 [T2D] and NN1436-4466 [T2D] and four clinical pharmacology trials, NN1436-4314 [T2D], NN1436-4226 [renal impaired], NN1436-4422 [T1D], and NN1436-4225 [T1D]) have been completed. No unexpected safety concerns were identified. One clinical pharmacology trial (NN1436-4462 [T2D] is ongoing.

Data from NN1436-4225 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 (IB)[9] and any updates hereof.

Insulin degludec

For further details on insulin degludec, please refer to the current insulin degludec IB[10], the current EMA summary of product characteristics (SmPC) for insulin degludec (Tresiba®)[11], the U.S. Prescribing Information (US PI)[12], or any locally approved label.

Insulin aspart

For further details on insulin aspart, please refer to the current insulin aspart IB[13], the current EMA summary of product characteristics (SmPC) for insulin aspart (NovoRapid)[14], the U.S. Prescribing Information (US PI) (NovoLog)[15], or any locally approved label.

Trial population

The trial population will consist of subjects with T1D. 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

Main benefits and risks are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of insulin icodec, insulin degludec and insulin aspart may be found in the respective IB, SmPC or US PI.

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.	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. Patients 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. Investigators and subjects will be asked to pay careful attention to injection site reactions. Investigators should ensure careful monitoring and medical evaluation in case of injection site reaction occurrence. For further information on injection site reactions, please refer to Appendix 3 (Section 10.3)
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 NN1436-44422.	Known of 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 and SI-IC. For further information on hypersensitivity reactions, please refer to Sections 8.9.2 and Appendix 3 (Section 10.3.3).

Potential risks: Antibody formation leading to changes in clinical effects	Antibodies to exogenously delivered insulins are common with insulin treatment but are not often clinically significant. In NN1436-4383 clinical trial, 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.	In case lack of clinical effect is observed, rescue actions will be initiated 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 8.9.1 and Appendix 3 (Section 10.3)
Trial treatment (Insulin Degludec & Insulin Aspart)		
For more information regarding the known and expected benefits and risks of insulin degludec, please refer to the insulin degludec IB[10], EMA Summary of Product Characteristics (SmPC)[11] and the US Prescribing Information (PI)[12], or any locally approved label. For more information regarding the known and expected benefits and risks of insulin aspart, please refer to the insulin aspart IB[13], the (NovoRapid) EMA SmPC[14], (NovoLog) US PI[15] or any locally approved label.		
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.

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 or twice daily to provide 24-hour coverage. Market research has shown that

people with diabetes, put value in reducing the number of insulin injections[16]. 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 T1D. For all subjects participating in this 52-week trial, the anticipated benefits include improved glycaemic control. The titration algorithm (Appendix 8, Section 10.8), which specifies recommended adjustments of both basal and bolus insulin dose at different plasma glucose levels, will be used to ensure that subjects receive optimal treatment.

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 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 IB[9] and any updates hereof.

3 Objectives and endpoints

3.1 Primary, secondary and exploratory objectives and estimand

3.1.1 Primary objective

To confirm the effect on glycaemic control of once weekly insulin icodec in combination with insulin aspart, in subjects with T1D. This includes comparing the difference in change from baseline in HbA_{1c} between once weekly insulin icodec and once daily insulin degludec both in combination with insulin aspart after 26 weeks of treatment to a non-inferiority limit of 0.3%.

3.1.2 Secondary objective

To compare the safety and patient reported outcomes of once weekly insulin icodec versus once daily insulin degludec, both in combination with insulin aspart, in subjects with T1D.

Estimand

The estimand is the ‘treatment policy estimand’ defined as the treatment difference between insulin icodec and insulin degludec 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) to week 26	%-point

3.2.2 Secondary endpoints

3.2.2.1 Supportive secondary efficacy endpoints

Endpoint title	Time frame	Unit
Change in fasting plasma glucose (FPG)	From baseline (week 0) to week 26	mmol/L
Time in range 3.9-10.0 mmol/L (70-180 mg/dL)*	From week 22 to week 26	% of readings
Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction	From baseline (week 0) to week 26	Score 0-36 6 items scored on a scale of 0 to 6. The higher the score the greater the satisfaction with treatment
Change in HbA_{1c}	From baseline (week 0) to week 52	%-point

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

3.2.2.2 Secondary safety endpoints

Endpoint title	Time frame	Unit
Number of severe hypoglycaemic episodes (level 3)	From baseline (week 0) to week 26	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) to week 26	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) to week 26	Number of episodes
Number of severe hypoglycaemic episodes (level 3)	From baseline (week 0) to week 57	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) to week 57	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) to week 57	Number of episodes
Number of nocturnal 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) to week 26	Number of episodes
Number of nocturnal 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) to week 57	Number of episodes
Time spent < 3.0 mmol/L (54 mg/dL)*	From week 22 to week 26	% of readings
Time spent > 10 mmol/L (180 mg/dL)*	From week 22 to week 26	% of readings
Mean total weekly insulin dose	From week 24 to week 26	U
Mean total weekly insulin dose	From week 50 to week 52	U
Change in body weight	From baseline (week 0) to week 26	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) to week 52	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) to week 52	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) to week 52	Number of episodes
Number of nocturnal 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) to week 52	Number of episodes

4 Trial design

4.1 Overall design

This is a 26-week, randomised, multicentre, multinational, open-label, active-controlled, parallel group, two-armed, treat-to-target trial investigating the effect on glycaemic control and safety of treatment with once weekly insulin icodec compared to once daily insulin degludec, both in combination with insulin aspart in subjects with T1D, with a 26-week extension phase. The first 26 weeks of the trial constitute the main phase, after which the primary analysis is planned. The focus of the 26-week extension phase is to evaluate long-term safety and provide long-term exposure data.

The trial duration is approximately 59 weeks, consisting of a 2-week screening period, followed by an initial 26-week randomised treatment period, a 26-week extension phase and a 5-week follow-up period. Primary analysis is planned after the initial 26-week main phase.

The overall trial design and visit schedule are outlined in Figure 4-1 and trial flowchart (Section 1.2), respectively.

Subjects will be randomised (1:1) to a treat-to-target basal-bolus insulin regimen with either once weekly insulin icodec or once daily insulin degludec, both in combination with insulin aspart. The randomisation of subjects will be stratified by pre-trial basal insulin regimen (either twice daily/ insulin glargine U300 or once daily) and HbA_{1c} (either <8% or ≥8%) at screening. During the 52-week treatment period, subjects will have weekly contact with the site either at site visits or by phone contacts. The end of treatment visit (V54) will be one week after the last dose of insulin icodec and on the day of or day after the last dose of insulin degludec. The end of trial visit (V56) will be performed 5 weeks after end of treatment visit (V54). 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 (Section 6.7 and Appendix 8, Section 10.8).

Subjects will carry a continuous glucose monitoring (CGM) device for the entire trial duration including the follow-up period. Subjects wearing a personal CGM or flash glucose monitoring (FGM) device prior to entering the trial, will discontinue the use of the personal pre-trial CGM or FGM device and switch to a trial CGM. The trial CGM receiver will be unblinded 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.

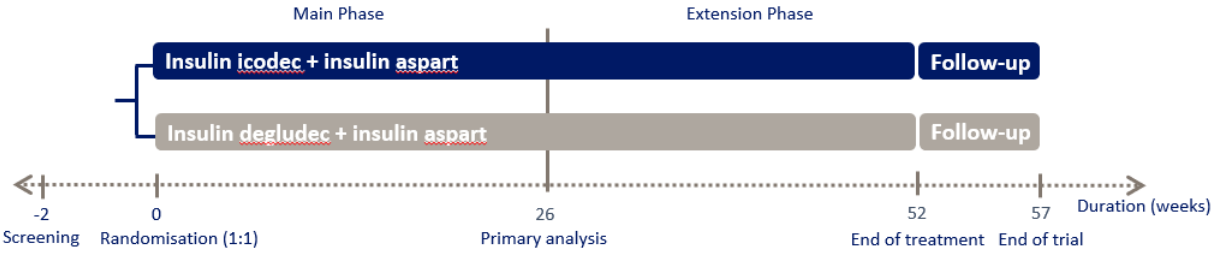


Figure 4-1 Trial design

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 degludec in combination with insulin aspart. A treatment duration of 26 weeks is evaluated as adequate for assessing effect on glycaemic control and safety; the extension of 26 weeks is included to provide long-term insulin icodec exposure for safety evaluation.

Subjects included in the trial will be representative of a broad T1D population that may benefit from insulin titration using a treat-to-target titration algorithm. To safeguard the subjects, the inclusion and exclusion criteria defined in this trial will limit the population to subjects not suffering from advanced underlying diseases other than T1D. 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.

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 degludec has been chosen as comparator.

Treatment in both arms will be open label as it was not considered feasible to blind the two treatments; the dosing regimen is not the same between treatment groups and there is a risk of pen-injector mix-up if a double-blind, double-dummy design was used as it would require the use of three different pen-injectors (two basal and one bolus pen-injector) in both treatment arms.

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}. The initial 26

weeks will allow sufficient time for up-titrating of the basal and bolus insulins and sufficient time in maintenance period for HbA_{1c} analysis.

Titration of insulin icodec, insulin degludec and insulin aspart is outlined in the titration guidelines, Appendix 8, Section 10.8. Titration of insulin icodec and insulin degludec will be based on pre-breakfast SMPG values and adjusted once weekly in connection with the scheduled visits/phone contacts. Titration of insulin aspart will be adjusted once weekly in connection with the scheduled visit/phone contacts based on pre-prandial and bedtime SMPG values as outlined in the titration guidelines or based on carbohydrate counting per investigator's discretion.

CGM will be used both to monitor subjects' glycaemic control and to generate profiles for evaluating the effect on glycaemic control, as per section 3.1.2. CGM data from the receiver will be collected as specified in the flowchart (see Section 1.2). A minimum duration of 4 weeks data collection of CGM for the endpoint assessments has been chosen to accommodate evaluation of hypoglycaemia exposure.[17] CGM values must not be used for hypoglycaemic episode reporting. If a hypoglycaemic episode is captured by the CGM, the subjects should use their BG meter to assess their PG level, and if hypoglycaemia is confirmed, it will be recorded in the eDiary, please refer to Appendix 7 (Section 10.7).

A sufficient assay-sensitivity for the non-inferiority evaluation will be supported 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

Subjects will be switched from pre-trial basal insulin analogues to insulin degludec according to local label, while insulin icodec will be initiated according to the principles outlined in the titration guideline in Appendix 8 (Section 10.8). A loading dose will be applied to avoid glycaemic slip during the first week of treatment. A 50% loading dose will be applied for subjects with an $HbA_{1c} < 8\%$ at screening to reduce the risk of experiencing hypoglycaemic events at the beginning of the trial. While a 100% loading dose will be applied for subjects with an $HbA_{1c} \geq 8\%$ at screening to mitigate the occurrence of hyperglycaemic episodes in subjects entering the trial with poor glycaemic control. Subjects that prior to randomisation received insulin glargine U300 or basal insulin twice daily should receive a 50% loading dose regardless of their HbA_{1c} at screening.

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

The PK and PD properties of insulin icodec following five weeks of once weekly dosing in subjects with T2D (trial NN1436-4314) and T1D (trials NN1436-4225 & NN1436-4422) showed that insulin icodec exposure was well distributed across the dosing interval, with a PK and PD profile suitable for once weekly dosing.

After randomisation, subjects should start once weekly insulin icodec or once daily insulin degludec on the same day as randomisation. Due to the longer half-life of insulin icodec, the last dose of insulin icodec will be administered 51 weeks after randomisation, while once daily insulin degludec injections will continue until 52 weeks after randomisation. The follow up period for both insulin icodec and insulin degludec will be 5 weeks from end of treatment (V54) to end of trial (V56).

Insulin aspart should also be initiated same day as randomisation and should be taken 2-4 times daily with meals throughout the 52 weeks treatment duration. Switch from other rapid-acting insulin analogues should be done unit-to-unit.

Further details on dose adjustment can be found 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.

5.1 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female aged ≥18 years at the time of signing informed consent.
3. Diagnosed with type 1 diabetes mellitus ≥ 1 year prior to the day of screening.
4. Treated with multiple daily insulin injections (basal and bolus insulin analogue regimens) ≥ 1 year prior to the day of screening.
5. HbA_{1c} <10% at screening visit measured by central laboratory.

5.2 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial products 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 T1D which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

6. 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).
7. Myocardial infarction, stroke, hospitalization 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 (NYHA) Class IV at screening.
9. Planned coronary, carotid or peripheral artery revascularisation.
10. Renal impairment with estimated Glomerular Filtration Rate (eGFR) value of <30 ml/min/1.73m^2 at screening measured by central laboratory.
11. Impaired liver function, defined as Alanine Aminotransferase (ALT) ≥2.5 times or Bilirubin >1.5 times upper normal limit at screening measured by central laboratory.
12. Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8.[18]
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. 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.
16. 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.
17. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days prior to the day of screening.

[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.

5.3 Lifestyle considerations

5.3.1 Meals and dietary restrictions

The subjects should be fasting when attending some of visits (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 fasting visit until blood sampling has 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.

5.4 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. For UK: SAE is also included as minimal information (see Appendix 9, Section 10.9).

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

This section is 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 A/S

Trial product name and strength:	Insulin icodec 700 units/mL *(IMP, test product)*	Insulin degludec, 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. Rotation of injection site within the same area is recommended.	Administer insulin degludec once daily at any time of the day, but preferably at the same time every day throughout the trial. Rotation of injection site within the same area is recommended.
Packaging	3 mL PDS290 pre-filled pen-injector	3 mL PDS290 pre-filled pen-injector

- Insulin icodec and insulin degludec DFU will be provided electronically via the eDiary and available to the subjects throughout the trial.
- A pen differentiation guide will be provided
- At randomisation visit (V2) subjects should administer trial product 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 product

Trial product name:	Insulin aspart 100 units/mL *(NIMP, auxiliary therapy)*
Dosage form	Solution for injection
Route of administration	Subcutaneous
Recommended initial dose	Please refer to Appendix 8 (Section 10.8)
Dosing instructions	Administer insulin aspart with meals, 2-4 times daily
Packaging	3 mL prefilled Flexpen
Provider	Novo Nordisk A/S

- Insulin aspart DFU will be provided electronically via the eDiary and available to the subjects throughout the trial.

Auxiliary supplies

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

Table 6-3 Auxiliary supplies

Auxiliary supply	Details
Needles	Needles for pre-filled pen injector. NovoFine needles no longer than 6 mm will be used for administration of trial product. Only needles approved by Novo Nordisk must be used for administration of trial product.
Blood glucose meter	Roche Accu Check 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 Roche manufacturer's guide provided
Continuous Glucose Monitoring system	Dexcom G6 At randomisation (V2) subjects must be instructed in handling of the CGM. Please refer to the CGM manual for more information.
eDiary	Subject Mobile app, HCP Web Portal & Cloud service Please refer to the eDiary site guide.

6.1.1 Medical devices

6.1.1.1 Investigational medical device

This section is not applicable for this trial

6.1.1.2 Non-investigational medical devices

Non-investigational medical devices including needles for pre-filled pen injector, BG meter and CGM are listed as auxiliary supplies in Table 6-3.

For countries where BG meter and CGM are not approved, please refer to 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 materials manual (TMM).
- Each site will be supplied with sufficient trial products 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 TMM.

- 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 for.
- 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 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. Randomisation will be stratified by pre-trial basal insulin treatment (either twice daily/insulin glargine U300 or once daily) and HbA_{1c} (either <8% or ≥ 8%) at screening. Within each stratum, each subject will be randomly allocated to receive once weekly insulin icodec once daily insulin degludec. Trial product will be dispensed/allocated at the trial visits summarised in the flowchart (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 (V56) 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 (V56) must be recorded in a separate concomitant medication (diabetes) form in the electronic case report form (eCRF).

The following information must be recorded for any anti-diabetic drugs 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 (V54) only randomised treatment are allowed, unless due to safety reasons at the discretion of the investigator. If the investigator chooses to initiate anti-diabetic medication prior to end of treatment (V54), 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.

6.6 Dose modification

Doses are adjusted according to SMPG values as described in Appendix 8 (Section 10.8).

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 and according to local clinical practice. 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 (V54) as soon as possible to collect the required data for the analysis of the primary endpoint.

Two follow-up visits, V55 and V56, must be performed after discontinuation of the trial product. Visits V55 and V56 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 degludec. It is stressed that the visit window is plus 3 days for both visits V55 and V56.

Further, it is important that discontinued subjects come in for discontinuation follow-up visit V28A, 26 weeks after the randomisation visit and V54A, 52 weeks after the randomisation visit. V54A 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 V56.

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 8.3.2. AEs and anti-diabetic medication should be collected and recorded in the eCRF until the discontinuation follow-up visit (V54A) 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 (V54A). 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, or to V28 or to V38, or to V46 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.

If a subject is randomised in violation of inclusion and exclusion criteria erroneously, the nature of the specific violation to in- or exclusion criteria will be evaluated carefully both by the principal investigator and Novo Nordisk medical specialist, independently. Subject can be allowed to continue in the trial and receive trial product if the violation is minimal or with no significant clinical relevance, and there are no safety concerns as evaluated by both the investigator and Novo Nordisk medical specialist (not applicable for UK, please see Appendix 9, Section 10.9).

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. Treatment status session must be made in the IWRS when the subject is temporarily discontinued and also when the subject resumes treatment.

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 V54. 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 CRF.

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 or 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 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 (e.g. electronic or paper) 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 eDiaries, PRO instruments, ECG, CGM data, 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.
- 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 (Section 1.2)

8.1.1 Self-measured plasma glucose

Subjects will be provided with a BG 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 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.

Subjects must be instructed in how to transfer the results of the SMPG values daily into the eDiary.

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 (V56) at the following time points: pre-breakfast, pre-lunch, pre-dinner, and at bedtime. The subject should 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 entire duration of the trial (i.e. from week 0 (V2) to week 57 (V56)).

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

The CGM readings will be open to both the subject and the investigator.

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 CGM 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). The site should ensure the subject can change the sensor at home weekly during trial periods when the subject will not attend site visits.

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. Data upload will occur at each site visit, see flowchart (Section 1.2). Data upload will occur every week from V2 (week 0) to V8 (week 6), from V24 (week 22) to V28 (week 26), and from V50 (week 48) to V54 (week 52). Outside the specified periods, upload will occur every second or forth week in conjunction with site visit, and at the follow-up visits 1 and 2. The upload will be documented by the system directly.

The serial number of the CGM receiver must be recorded in the eCRF at the randomisation visit (V2). In case the CGM receiver is replaced, the new receiver serial number should be entered in the eCRF as well.

8.1.3 Clinical outcome assessments

The patient reported outcome questionnaires are to be completed by the subject without assistance of the site personnel and should preferably be completed after all fasting-related activities are completed, but before any other visit related procedures are conducted. It takes approximately five minutes to complete the questionnaires.

The following patient reported outcome questionnaires will be supplied in linguistically validated versions in all languages relevant for this trial:

- Diabetes Treatment Satisfaction Questionnaire (DTSQs)

- The questionnaire has been designed to measure satisfaction with diabetes treatment regimens in people with diabetes. The DTSQs questionnaire will be measured at baseline (V2), week 26 (V28), and end of treatment visit (V54).

- International Physical Activity Questionnaire
  - The questionnaire has been designed to measure physical activity. It will be measured at baseline (V2) only. The questionnaire is for all subjects 18-69 years of age.

8.1.4 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 and the laboratory manual.

8.2 Safety assessments

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

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.

Information on hypoglycaemia unawareness will be recorded according to Clarke's questionnaire, question 8. [18] 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 Sections 6.5 and 6.7

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 will be calculated in the eCRF

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 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 visit (V54) 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 laboratory manual and the protocol flowchart (Section 1.2).

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.

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

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.

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 completed in the eCRF. 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 the eCRF, please refer to Appendix 3 (Section 10.3). 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* (stroke or transient ischemic attack)		X
Heart failure (requiring hospitalisation or urgent heart failure visit)		X
Death		X
Hypersensitivity	X	
Injection Site Reaction	X	

*All cerebrovascular events (stroke and transient ischemic attack) are to be reported and sent for adjudication, however the event adjudication committee 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 Appendix 1, 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 at the time points specified in the flowchart. For subjects discontinuing trial product prematurely AEs must be collected from the end of trial visit until the discontinuation follow-up visit (V54A). For AE reporting in UK, please refer to the UK specific requirements in Appendix 9 (Section 10.9).

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 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 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) 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 consult the current version of the insulin icodec investigator's brochure[9].

For more information on overdose for insulin degludec or insulin aspart, consult the relevant IB, EMA SmPC, US PI or locally approved label.

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 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.

For retention of residual hypersensitivity samples, please refer to Appendix 6, 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 degludec in terms of change from baseline to week 26 in HbA_{1c}.

Formally, let D be the treatment difference 'insulin icodec' minus 'insulin degludec' 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 ≥0.30% against HA: D <0.30%

The non-inferiority margin of 0.3%-point is chosen based on the recommendation of health authority guidance for industry on developing drugs for treatment of diabetes.[19, 20] Furthermore:

- 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 30% of a suitably conservative estimate of insulin degludec´s treatment effect on HbA_{1c} in a placebo-controlled trial in a T1D population; The treatment effect of degludec versus placebo in a T1D population is unknown but in a progressed T2D population of subjects already treated with liraglutide, degludec was shown to be superior to placebo (ETD: -0.92%-point [-1.00; -0.75] 95%CI).

9.2 Sample size determination

The sample size is determined in order to have 90% power for declaring non-inferiority (NI) with a NI margin of 0.3%-point with respect to change in HbA_{1c} for the specified estimand and the full analysis set (primary analysis set). All available data points for the primary endpoint will be used in the primary analysis and this has guided the treatment effect assumptions below.

In studies with insulin degludec 100 units/mL in T1D subjects (NN1250-3583, NN1250-3770, and NN1250-3995) the percent withdrawing from treatment and/or trial during the initial 26 weeks was approximately 9%, 12% and 15%. Considering the increased focus on retention, 10% are expected to experience any of the specified intercurrent events before week 26 in this trial.

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 standard deviation (SD) is assumed to be 1.0%-point based on results from studies with insulin degludec in subjects with T1D (NN1250-3583, NN1250-3770 and NN1250-3995), where the SD was found to be 0.9, 0.9 and 0.93 respectively.

From the above assumptions and requirements, 580 subjects will be randomised to 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 the table below (Table 9-1) displaying power for various alternative treatment differences and standard deviations.

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

SD (%-point)	0.0/0.015	True treatment difference/adjusted treatment difference (%-point) 0.0/0.03	0.0/0.045	0.05/0.08
0.9	97%	95%	93%	84%
1.0	93%	**90%**	87%	75%
1.1	88%	84%	80%	67%

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

9.3 Populations for analyses

The following population*s* are defined:

Population	Description
Randomised	All subjects randomised.
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 one 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.

Baseline assessments are always included in the in-trial observation period.

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 (V56)
- 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.

Main-on-treatment period

The main-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 date of the on-treatment period
- Week 26 (V28).

Baseline assessments are always included in the on-treatment observation periods.

All efficacy endpoints will be summarised and analysed using the full analysis set and the 'in-trial' period. Safety endpoints will be evaluated using both the main-on-treatment and the on-treatment period with descriptive statistics being based on the safety analysis set 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 (FSFV), and it will include a more technical and detailed description of the statistical analyses described in this section.

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 degludec
- Screening HbA_{1c} < 8%: yes, no
- Pre-trial basal insulin treatment: twice daily or insulin glargine U300: yes or no
- Region: Asia, Europe, North America
- The regions will be defined as follows:
  - Asia: India, Japan
  - Europe: Austria, Netherlands, Germany, Turkey, Italy, Russia, Spain, United Kingdom
  - North America: United States, Canada
  -

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.

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 (FAS) 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 having discontinued their randomised treatment prior to the week 26 visit and have a 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 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, screening HbA_{1c} < 8% (yes/no) pre-trial basal insulin treatment and randomised treatment as fixed factors, and baseline HbA_{1c} as covariate. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.

Explanatory factors will be coded as follows:

- Treatment: Once weekly insulin icodec, insulin degludec
- Region: Asia, Europe, North America
- Screening HbA_{1c} < 8%: yes, no
- Pre-trial basal insulin treatment: twice daily or insulin glargine U300: yes or no

This analysis has the underlying assumption that subjects with missing data behave similarly as subjects that discontinues 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 degludec 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 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) for both treatment arms will be imputed with baseline value adding a random error term. The random error term is normally distributed with a standard deviation set equal to the estimated residual standard deviation of an ANCOVA analysis on the LAOT values. Specifically, the imputations and analyses will be carried out as follows:

- First, an ANCOVA model with region, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment and randomised treatment as fixed factors, and a baseline value as a covariate will be fitted to the LAOT value.
- Second, the estimated residual standard deviation, *s*, from this model will be used to impute missing values by the baseline value, adding a random normally distributed term with mean 0 and standard deviation *s*. This will be done 1000 times.

- For each of the complete data sets, the endpoint will be analysed using an ANCOVA model with region, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment 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.

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

Missing time in target range 3.9 – 10.0 mmol/L (70-180 mg/dL) (TIR) from week 22 to week 26 will be imputed from trial participants who are from the insulin degludec 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 insulin degludec treatment. Specifically, the imputations and analyses will be carried out as follows:

- First, one thousand (1000) copies of the dataset will be generated for TIR.
- Second, for each dataset copy, an ANCOVA model will be fitted to TIR values for subjects who completed their randomised treatment in the insulin degludec 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, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment and randomised treatment as fixed factors. The estimates and SDs for the 1000 data sets will be pooled to one estimate and associated SD using Rubin's rule.

Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction from baseline week 0 (V2) to week 26 (V28)

The change in DTSQs in total treatment satisfaction from baseline to week 26 will be analysed using the same model as specified for change in FPG, but the corresponding baseline value will be used as a covariate.

Change in HbA_{1c} from baseline week 0 (V2) to week 52 (V54)

The change in HbA_{1c} from baseline to week 52 will be analysed similar to the primary endpoint specified above.

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 26 (V28).
- 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 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 nocturnal 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).

For subjects who discontinued their randomised treatment, the number of episodes in the missing period (time of follow-up 2 visit (V56) to planned end of the main-on-treatment period) will be imputed using a multiple imputation technique, assuming that the event rate pre-follow-up 2 visit (V56) follows the respective treatment groups rate whilst post-follow-up 2 visit (V56) event rate is the rate of the comparator 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, screening HbA_{1c} < 8% (yes/no), pre-trial basal insulin treatment and randomised treatment as fixed factors and the logarithm of the main-on-treatment period as offset.
- Second, based on the estimated parameters for the comparator 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.

The following hypoglycaemic endpoints will be analysed separately using the method described above, substituting the main-on-treatment period with the on-treatment period:

- Number of severe hypoglycaemic episodes (level 3), from baseline week 0 (V2) to week 57 (V56).
- 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 57 (V56).
- 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 57 (V56).
- Number of nocturnal 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 57 (V56). Nocturnal hypoglycaemic episodes are hypoglycaemic episodes occurring between 00:01 and 05:59 both inclusive.

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 in a similar manner as 'time in target range 3.9 – 10.0 mmol/L (70-180 mg/dL)' 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 where time spent below or above range will be analysed separately using a negative binomial model on the number of recorded measurements below and above range, respectively, with a log-link function and the logarithm of the total number of recorded measurements as offset. The model will include randomised treatment and region as factors. Further details will be provided in the SAP.

Mean total weekly insulin dose from week 24 (V26) to week 26 (V28) and mean total weekly insulin dose from week 50 (V52) to week 52 (V54)

Mean weekly insulin dose during the last 2 weeks of treatment (from week 50 to week 52) and during the last 2 weeks in the main part (from week 24 to 26) will be log-transformed and analysed separately using the same statistical model as specified for change in FPG. Pre-trial (baseline) total weekly insulin dose will be log-transformed and included as a covariate in the model.

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.

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 both the main-on-treatment and 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

The trial does not include a formal interim analysis. However, the reporting will be split into a main phase and an extension phase, where the results of the main phase can be reported possibly before LPLV. Subjects will provide consent for the full length of the trial. To preserve trial integrity during the extension phase, dissemination of results from the main phase will, during the extension phase, initially be limited to communication internally and with regulatory authorities.

9.6 Data monitoring committee

This section is not applicable for this trial.

9.7 Reporting of the main part of the trial

A database lock is planned shortly after last subject last visit of the main part of the trial. The results from this main part will thereafter be reported. The complete trial will be reported after database lock of the extension part.

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[21] and applicable ICH Good Clinical Practice (GCP) Guideline[22]
- Applicable laws and regulations
- The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR 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 CTR 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[22], Declaration of Helsinki[21] 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

The site will be offered a communication package for the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the subjects. The written information will be translated and adjusted to local requirements and distributed to 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. The safety committee may recommend unblinding of any data for further analysis, and in this case an internal trial independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

10.1.6.2 Trial safety group

This section is not applicable for this trial.

10.1.6.3 Data monitoring committee

This section is 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 CTR.

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 (ICMJE)[23], the Food and Drug Administration Amendment Act (FDAAA)[24], European Commission Requirements[1, 25, 26] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The primary completion date (PCD) is the last assessment of the primary endpoint, and is for this trial last subject first treatment (LSFT) + 26 weeks corresponding to visit 28. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 28. 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 or designee (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 CRF is revoked or the CRF is temporarily unavailable:

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

- Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.
- Monitors will review the subject's medical records and other source data to ensure consistency and/or identify omissions compared to the CRF.

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 CRF 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 recorded directly into the eCRFs and will be considered source data.

- Data in the service providers' database is considered source data e.g. eDiaries, CGM and laboratory.
- 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 CTR for this trial.

One or two investigators will be appointed by Novo Nordisk to review and sign the CTR (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 CTR is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

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

In all cases, the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. 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.[27]

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 CTR.
- 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 (V1*, V2, V12, V20, V28, V38, V46*, V54, V28A*, V54A*) *HbA_{1c} only	• Fasting plasma glucose (FPG)[1] • HbA_{1c}
NOTE: [1]A FPG result <3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as an AE 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, V38, V54)	• Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Thrombocytes
Biochemistry[1] (V1, V12, V28, V38, V54)	• Alanine Aminotransferase (ALT) • Albumin • Alkaline phosphatase • Aspartate Aminotransferase (AST) • Creatinine • Potassium • Sodium • Bilirubin
Lipids (V2, V12, V28, V38, V54)	• Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • or IRB/IECTriglycerides
Pregnancy Testing (V2, V56)	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test[2]
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation, eGRF 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, V38, V54, V56) • Insulin-icodec serum concentration (V4, V8, V12, V20, V28, V38, V54, V56)
Notes: [1]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Section 10.3 (Hy's Law) and Section 7.1. [2]Local urine testing will be standard unless serum testing is required by local regulation .	

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 unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of an IMP.

Events meeting 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 NOT 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 (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of events for adjudication and AEs requiring additional data collection

Description of events 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. Source data should be in accordance with Section 8.3.

- 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, diarrhoea, 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[28]. 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[29]. 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[30]. 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 or use of wrong device
  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 (e.g. hypoglycaemia or other), 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 NIMP (insulin aspart) 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 brochure and/or product information, for 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.

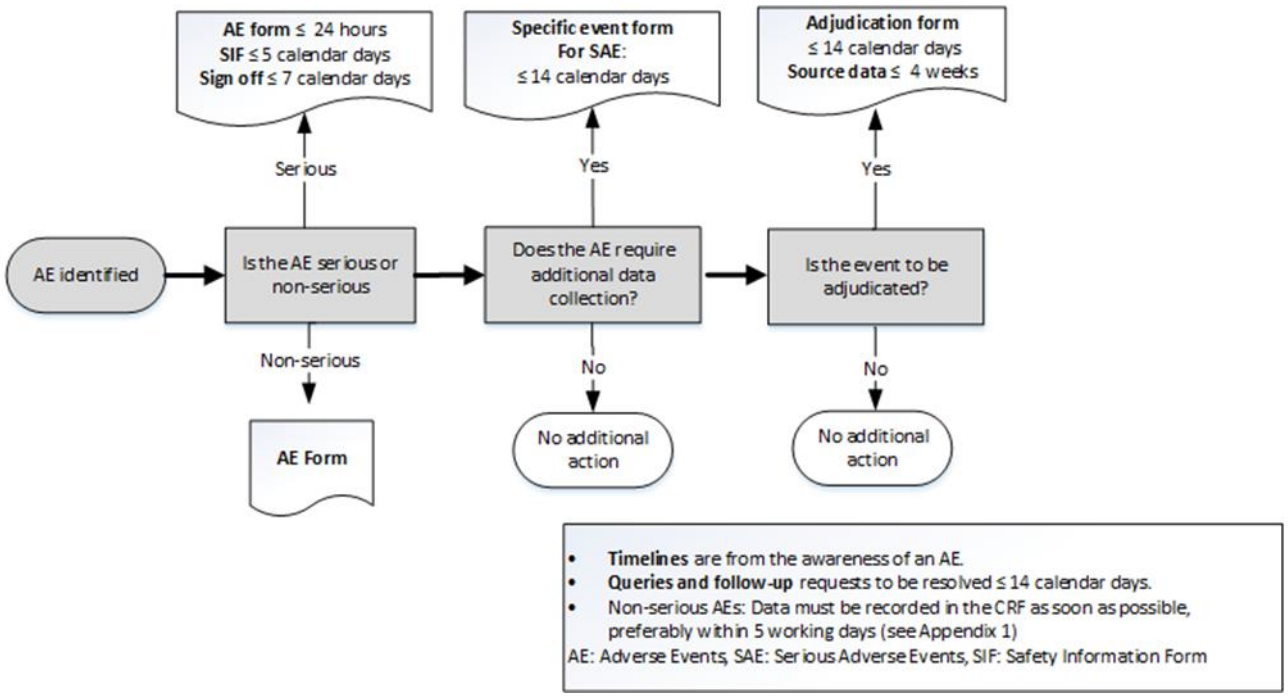
Follow-up of AE and SAE
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity 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, the investigator should provide Novo Nordisk with a copy of 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 below. Source data should be in accordance with Section 8.3. • If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the CRF is unavailable for more than 5 calendar days, then the site will use the safety information form (see box below). • The site will enter the SAE data into the CRF as soon as it becomes available. • 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 the figure below):
  • 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



Source data should be in accordance with Section 8.3

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 Roche 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 (e.g. amenorrhea in adolescents or athletes), 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 effective contraception method.

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 degludec or insulin aspart in seminal fluid is unlikely[31]

Female subjects
Female subjects of childbearing potential are eligible to participate if they agree to use at least an acceptable effective method of contraception consistently and correctly as described in Table 10-3 . As a minimum, contraception should be maintained until treatment discontinuation[32].

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, Section 10.2 and the trial flowchart, Section 1.2).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 a subject's pregnancy (see Figure 10-2).
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate which will be forwarded to Novo Nordisk 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 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 a 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 possibly/probably related to the IMP by the investigator will be reported to Novo Nordisk as described in Section 10.3. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

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

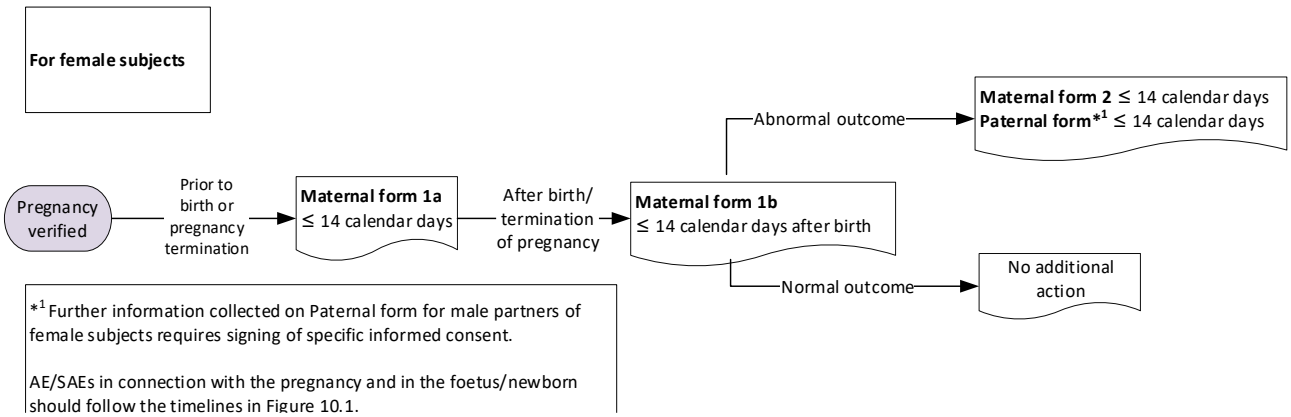


Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy.

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

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.

The investigator must complete the technical complaint form in the CRF within:

- 5 days calendar for all 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[33], ADA[34], ISPAD[35] type 1 diabetes outcomes program[36], ATTD[37]. Severe hypoglycaemia as defined by Seaquist[38] and ISPAD[35].		

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.[38]

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[34]

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[38].

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[38].

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

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 degludec, both in combination with mealtime insulin aspart.

- ***Insulin icodec*** should be taken once weekly on the same day of the week.
  - At randomisation (V2)
    - Subjects that prior to randomisation received insulin glargine U300 or received basal insulin twice daily should receive a dose which consists of total daily basal insulin dose before randomisation x7 + 50% (Table 10-5) regardless of their HbA_{1c} at screening.
    - Subjects with HbA_{1c} <8% (64 mmol/mol) at screening should receive a dose which consists of total daily basal insulin dose before randomisation x7 + 50% (Table 10-5)
    - Subjects with HbA_{1c} ≥ 8% (64 mmol/mol) at screening should receive a dose which consists of total daily basal insulin dose before randomisation x7 + 100% (Table 10-6)

The following weekly dose (V3) for all subjects should be the total daily dose x7. In the following table the weekly V2 and V3 doses for subjects receiving from 10 U to 100 U per day have been calculated. Please note that the displayed values are rounded off to the nearest dose divisible by 10.

Table 10-5 V2 and V3 doses for subjects that prior to randomisation received insulin glargine U300 or received basal insulin twice daily, or subjects with HbA_{1c} <8% (64 mmol/mol) at screening

Total daily dose before randomisation	V2 insulin icodec dose	V3 insulin icodec dose	Total daily dose before randomisation	V2 insulin icodec dose	V3 insulin icodec dose
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			

Table 10-6 V2 and V3 doses for subjects with $HbA_{1c} \geq 8\%$ (64 mmol/mol) at screening

Total daily dose before randomisation	V2 insulin icodec dose	V3 insulin icodec dose	Total daily dose before randomisation	V2 insulin icodec dose	V3 insulin icodec dose
10	140	70	56	780	390
11	150	80	57	800	400

12	170	80	58	810	410
13	180	90	59	830	410
14	200	100	60	840	420
15	210	110	61	850	430
16	220	110	62	870	430
17	240	120	63	880	440
18	250	130	64	900	450
19	270	130	65	910	460
20	280	140	66	920	460
21	300	150	67	940	470
22	310	150	68	950	480
23	320	160	69	970	480
24	340	170	70	980	490
25	350	180	71	990	500
26	360	180	72	1010	500
27	380	190	73	1020	510
28	390	200	74	1040	520
29	410	200	75	1050	530
30	420	210	76	1060	530
31	430	220	77	1080	540
32	450	220	78	1090	550
33	460	230	79	1110	550
34	480	240	80	1120	560
35	490	250	81	1130	570
36	500	250	82	1150	570
37	520	260	83	1160	580
38	530	270	84	1180	590
39	550	270	85	1190	600
40	560	280	86	1200	600
41	570	290	87	1220	610
42	590	290	88	1230	620
43	600	300	89	1250	620
44	620	310	90	1260	630
45	630	320	91	1270	640
46	640	320	92	1290	640
47	660	330	93	1300	650
48	670	340	94	1320	660
49	690	340	95	1330	670
50	700	350	96	1340	670
51	710	360	97	1360	680
52	730	360	98	1370	690
53	740	370	99	1390	690
54	760	380	100	1400	700
55	770	390			

- ***Insulin degludec*** should be taken once daily, at any time of the day but preferably 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 of insulin icodec and insulin degludec 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.

Adjustment of insulin icodec and degludec will be done in accordance with the table below (Table 10-7).

Table 10-7 Adjustment of insulin icodec and insulin degludec

Pre-breakfast SMPG			Icodec adjustment	Degludec adjustment
Value to use	mmol/L	mg/dL	U	U
Lowest of the SMPG values	<4.4	<80	–20	-3
	4.4–7.2	80–130	0	0
	>7.2	>130	+20	+3

Titration of insulin aspart

Titration of insulin aspart can either be adjusted weekly based on pre-prandial and bedtime SMPG values using the algorithm below or based on carbohydrate counting at the investigator's discretion.

Algorithm use:

- In the first 8 weeks after randomisation insulin aspart should be only be adjusted for safety reasons. Thereafter the doses should be considered adjusted weekly by the investigator.
- Dose adjustment will be based on the lowest pre-prandial or bedtime SMPG values measured in the week prior to titration in accordance with Table 10-8.
    - 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 10-8 Insulin aspart

Lowest pre-prandial and bedtime SMPG		Insulin aspart adjustment
mmol/L	mg/dL	U
<4.4	<80	-1
4.4-7.2	80-130	0
>7.2	>130	+1

The subjects can take correction bolus doses in collaboration with the investigator. The investigator should consider using the "100 rule" (for mmol/L) or "1,800 rule" (for mg/dL) to estimate the correction bolus doses.

Carbohydrate counting:

- This method should be reserved to subjects that are willing and able to do so. The subject needs to have prior hands-on experience using this method of determining bolus insulin doses. It is the investigator's responsibility to ensure that the subject is adequately trained. If more training is needed, this should be done in accordance with local practice.
- Insulin aspart should be adjusted daily in accordance with the immediate pre-meal SMPG and carbohydrate content in the meal that the subject is about to eat. To use this method, the investigator needs to determine the insulin-to-carbohydrate ration (I:CHO ratio) and the insulin sensitivity factor (ISF) for each meal and adjust, when needed.
- I:CHO ratio expresses the amount of carbohydrates (in grams) for which IU of bolus insulin that would effectively minimise the postprandial glucose excursion. ISF expresses the expected reduction in plasma glucose concentration, when IU is administered.
- *example:* A subject has pre-prandial plasma glucose of 10.0 mmol/L (180 mg/dL) and intends to eat a meal containing 60 g of carbohydrates. For the given meal the I:CHO ratio has been estimated to 1U:10g and the ISF to be 2.0 mmol/L per 1U (36 mg/dL per 1U) and the target plasma glucose is 7.2 mmol/L (130 mg/dL) in this trial. The bolus dose for this meal can be calculated as follows:
    - To cover the meal carbohydrates: multiply grams of carbohydrates by I:CHO:
    - 60 g x 1U/10 g = 6U
    - To bring the pre-prandial glucose value to target: Subtract the target glucose value from the current pre-prandial glucose value and divide by ISF for this meal:
    - (10.0 mmol/L – 7.2 mmol/L)/2.0 mmol/L/U ~ 1U.
    - Thus, the bolus dose for this meal is 6U + 1U = 7U.

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 measurements and adjust bolus doses if needed. If the missing dose is missed for > 3 days, the subject should await the next planned day of injection. Subjects should perform frequent SMPG measurements to closely monitor their glycaemic control and adjust bolus doses, if needed.

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

It is recommended that the subject is switched from insulin icodec to any available basal insulin at the discretion of the investigator. Regarding the switch from insulin icodec to post-trial basal insulin the following should be considered:

- Calculate the new daily basal insulin dose by dividing the latest insulin icodec dose by 7. For subjects completing the trial the dose taken at V53 will be the latest dose.
- Initiate basal insulin, when pre-breakfast SMPG daily in the follow up-period (after V54) exceeds 10.0 mmol/l (180 mg/dL). It is important that the investigator and the subjects are in close contact to prevent any misunderstanding.
- 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 icodec and insulin degludec or insulin aspart injections
- Ensure transfer of SMPG values with an indication of “pre-breakfast”, “pre-lunch”, “pre-dinner”, “bedtime” or “other” (Section 8.2.1).
- 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 degludec or insulin icodec and insulin aspart doses prescribed at this contact.
- Reasons for deviation from the insulin icodec or insulin degludec 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 Austria:

- **Contraceptive guidance:** A monthly pregnancy test is mandatory for female subjects of childbearing potential.

For Canada

- **Retention of clinical trial documentation:** Part C, Division 5 of the Food and Drug Regulations [C.05.012] requires a 25-year retention period

For Germany

- **Demography:** Subject's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth in CRF.

- **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 Germany.**
- **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 Germany.**

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.**

- Drug(s) used in the clinical trial except for IMP(s) include the following Insulin aspart. Please refer to Insulin aspart local package insert, summary of product characteristics, US prescribing information or investigator's brochure for the latest information.

For Russia:

- **Trial governance considerations:** The trial should be conducted in compliance with the protocol, Ministry of Healthcare of Russian Federation' order #200H from April, 01, 2016 "Approval of rules of good clinical practice" and legal requirements of the Russian Federation regulating circulation of medicines.

For Spain:

- **Retention of clinical trial documentation:** 25 years according to the new Spanish Royal Decree 1090/2015.

For Turkey

- Blood samples from Turkey will be analysed by a central lab.
    - This trial is a phase 3 trial.

For USA:

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

For Russia where BG meter is not approved at the time of the final protocol version 2.0:

- The BG meter is regarded as investigational devices and will be labelled to indicate for investigational use only. This 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 Roche 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 must be collected by the investigator.

If BG meter is approved during trial conduct, the procedures above are not applicable anymore and technical complaints reporting should follow the standard vigilance procedures.

For UK:

- **Screen failures**: Minimal information includes informed consent date, demography, screen failure details, eligibility criteria, and serious adverse event (SAE).
- **Discontinuation of trial treatment**: Subjects that are randomised in violation of inclusion and exclusion criteria should be discontinued from the trial treatment.
- **Time period and frequency for collecting AE and SAE information**: All AEs and SAEs must be collected from the time of informed consent and until the end of trial visit as

specified in the flowchart. For subjects discontinuing trial product prematurely SAEs must be collected from the end of trial visit until the discontinuation follow-up 2 visit (V54A).

For India and Russia where CGM is not approved at the time of the final protocol version 2.0:

- 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

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
CGM	continous glucose monitor
CRF	case report form
CTR	clinical trial report
CRO	contract research organisation
DTSQs	Diabetes Treatment Satisfaction Questionnaire
DFU	directions for use
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FGM	flash glucose monitor
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HbA_{1c}	glycated haemoglobin
HCP	health care professional
HRT	hormone replacement therapy
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgE	immunoglobulin E
IMP	investigational medicinal product
INN	international non-proprietary name
ISPAD	International Society for Pediatric and Adolescent Diabetes
IRB	institutional review board
IWRS	interactive web response system

LDL	low-density lipoprotein
LSLV	last subject last visit
NIMP	non-investigational medical product
PCD	primary completion date
PG	plasma glucose
PRO	patient reported outcomes
SAE	serious adverse event
SAP	statistical analysis plan
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
TMM	trial materials manual
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 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 Germany 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
2.3.1 Risk assessment	"section 8.9.2." is deleted from the sentence "For further information on injection site reactions, please refer to ~~section 8.9.2 and~~ Appendix 3 (Section 10.3)".	Correction of reference.
5.1 Inclusion criteria	"basal and bolus insulin analogue regimes" is corrected to "basal and bolus insulin analogue regimens"	Correction of typo
10.1.7 Dissemination of clinical trial data	The primary completion date (PCD) is corrected to last subject first treatment (LSFT) + 26 weeks corresponding to visit 28.	Correction of typo, since the primary endpoint will be assessed at week 26 (visit 28).
10.1.9 Source documents	"ePROs" is deleted.	Correction due to no ePROs in this trial.
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 Germany	To meet local Health Authority request.
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 32 to CTFG guidance is added in appendix 4.	Reference update

11 References

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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.