Cover Page for Protocol

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Sponsor trial ID:	NN1436-4481
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Protocol

Effectiveness and safety of once weekly insulin icodec used with DoseGuide versus once daily basal insulin analogues in an insulin naïve type 2 diabetes population in a clinical practice setting

ONWARDS 5

Substance: Insulin icodec

Universal Trial Number: U1111-1247-5279

EudraCT Number: 2020-000476-38

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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 2.0	23 November 2020	All countries
Original protocol version 1.0	12 November 2020	All countries

Overall rationale for preparing protocol, version 2.0:

Section # and name	***Description of change***	***Brief rationale***
Section 10.3.5 Reporting of SAEs	Safety Information Form reporting timelines updated to 5 days	Safety reporting timeline was incorrectly stated as 7 days, has been corrected to ensure correct reporting.

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

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

1 Protocol summary

1.1 Synopsis

Rationale:

The present trial is a 52-week trial designed to investigate the effectiveness and safety of once weekly insulin icodec used with DoseGuide in comparison to once daily basal insulin analogues both in combination with any non-insulin antidiabetic medication in insulin-naïve subjects with type 2 diabetes mellitus (T2D) in a clinical practice setting. This trial will provide data on adherence, persistence (stay-time on treatment, rate of discontinuation) and patient reported outcomes. In addition, the trial will provide long-term exposure data (52 weeks). The long-acting basal insulin products currently approved for treatment of T2D are administered once or twice daily. The once weekly treatment regimen for insulin icodec would become a more convenient basal insulin which could improve treatment adherence and overcome insulin initiation barriers as compared to once daily or twice daily basal insulin for subjects with T2D.

Objectives and endpoints:

The primary objective of this trial is to demonstrate the effectiveness on glycaemic control of once weekly insulin icodec used with DoseGuide in combination with non-insulin anti-diabetic drugs in insulin naïve subjects with T2D in a clinical practice setting. This includes comparing the treatment difference in change from baseline in HbA_{1c} between insulin icodec and once daily basal insulin analogues after 52 weeks of treatment to a non-inferiority limit of 0.3%.

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline week 0 (V2) to week 52 (V6)	%-point

The estimand is the 'treatment policy estimand' defined as the treatment difference between insulin icodec used with DoseGuide and basal insulin analogues of the change in HbA_{1c} from baseline to week 52 for all randomised subjects, irrespective of adherence to randomised treatment and changes to antidiabetic 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). This estimand aims to reflect effectiveness of the treatment on a population level in clinical practice.

Overall design:

This is a 52-week, randomised, open label, parallel-group, active-controlled, multi-centre, multi-national trial with real world elements comparing insulin icodec versus once daily basal insulin analogues among insulin naïve T2D subjects in which insulin initiation is needed. Subjects randomised to insulin icodec will use insulin icodec with the DoseGuide App to guide their titration.

The decision that insulin initiation is indicated is at the investigator's discretion. Potential eligible subjects will be identified by the investigator and all eligible subjects should be provided with the subject information document and asked if they would like to participate in the trial. The investigator will have determined the subjects eligible for treatment with basal insulin including insulin icodec prior to informed consent. Which basal insulin the subjects are to initiate, either

insulin icodec or the once daily basal insulin analogue selected prior to randomisation by the investigator as per standard of care, will be allocated by 1:1 randomisation.

Key inclusion criteria:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female.
3. Age above or equal to 18 years at the time of signing informed consent.
4. Diagnosed with T2D ≥ 180 days prior to the day of screening.
5. HbA_{1c} above 7.0% (53 mmol/mol) as measured by central lab.
6. Insulin naïve. However, short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed, as is prior insulin treatment for gestational diabetes.
7. Stable daily dose(s) ≥ 90 days prior to the day of screening of any of the following antidiabetic drug(s) or combination regimen(s):
    a. Any metformin formulations ≥ 1500 mg or maximum tolerated or effective dose.
    b. Any metformin combination formulations ≥ 1500 mg or maximum tolerated or effective dose.
    c. Any of the following non-insulin antidiabetic drug classes including combinations (≥ half of the maximum approved dose according to local label or maximum tolerated or effective dose):
        i. Sulfonylureas
        ii. Meglitinides (glinides)
        iii. DPP-4 inhibitors
        iv. SGLT2 inhibitors
        v. Thiazolidinediones
        vi. Alpha-glucosidase inhibitors
        vii. Oral combination products (for the allowed individual Oral Antidiabetic Drugs (OADs))
        viii. Oral or injectable GLP-1-receptor agonists
8. Intensification with insulin is indicated to achieve glycaemic target (4.4-7.2 mmol/L, 80-130 mg/dL) at the discretion of the treating investigator.

Key exclusion criteria:

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice).
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening. *
5. Any disorder which in the investigator's opinion might jeopardise subject's safety.

**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

Number of subjects:

Approximately 1200 subjects will be screened to achieve 1096 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 a 52-week randomised treatment period and a 5-week follow-up period. Subjects will be randomised 1:1 to receive either insulin icodec or a once daily basal insulin analogue. Subjects randomised to insulin icodec will initiate with and use the DoseGuide App to support titration. 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, s.c., solution for injection, 3 mL PDS290 pre-filled pen-injector
- DoseGuide System
- Insulin Glargine 100 units/mL, s.c., solution for injection, 3 mL SoloSTAR pre-filled pen-injector
- Insulin Glargine 300 units/mL, s.c., solution for injection, 1.5 mL SoloSTAR pre-filled pen-injector
- Insulin Degludec 100 units/mL, s.c., solution for injection, 3 mL PDS290 pre-filled pen-injector

Data monitoring committee: No

1.2 Flowchart

Procedure	Protocol Section	Screening	Randomisation	Treatment				Follow-up	Follow-up	Early Discontinuation Follow up visit
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V6A
Timing of visit/trial day (weeks)		≤-2	0	13	26	39	52	54	57	52
Visit window (weeks)				±2	±2	±2	±2	+1	+1	±2
Informed consent and demography	Appendix 3 10.3	X								
Tobacco and nicotine products use	5.3.2	X								
Eligibility Criteria	5.1 5.2	X	X							
Concomitant illness/medical history	8.2	X	X							
Concomitant medication	6.5	X	X	X	X	X	X	X	X	X
Vital signs	8.2.3	X					X			
Physical examination	8.2.2	X					X			
Body measurements	8.2.2	X					X			X
Eye examination	8.2.5	X					X			
ECG	8.2.4	X			X		X			
Pregnancy test	8.3.5 Appendix 4 10.4		X						X	
Laboratory assessments	Appendix 2 10.2	X	X	X	X	X	X			X

Procedure	Protocol Section	Screening	Randomisation	Treatment				Follow-up	Follow-up	Early Discontinuation Follow up visit
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V6A
Timing of visit/trial day (weeks)		≤-2	0	13	26	39	52	54	57	52
Visit window (weeks)				±2	±2	±2	±2	+1	+1	±2
HbA_{1c}		X	X	X	X	X	X			X
Adverse event	8.3 Appendix 3 10.3 & 6 10.6			X	X	X	X	X	X	X
Self-measured plasma glucose	8.1.1		X	X	X	X	X	X	X	
Hypoglycaemic episodes	Appendix 8 10.8		X	X	X	X	X	X	X	
Clinical outcome assessments	8.1.2		X		X		X			
Training in trial product, Pen-handling	6.1		X	X	X	X				
Drug dispensing	6.2		X	X	X	X				
Hand out and training in medical device	6.1		X	X	X	X				
End of trial	4.4								X	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.[1] 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.[2]

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, increased treatment adherence and persistence[3] 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 a 52-week trial designed to investigate the effectiveness and safety of once weekly insulin icodec used with DoseGuide in comparison to once daily basal insulin analogues both in combination with any non-insulin antidiabetic medication in insulin-naïve T2D subjects in a clinical practice setting. This trial will provide data on adherence, persistence (stay-time on treatment, rate of discontinuation) and patient reported outcomes. In addition, the trial will provide long-term exposure data (52 weeks) for insulin icodec. The long-acting basal insulin products currently approved for treatment of T2D are administered once or twice daily. The once weekly treatment regimen for insulin icodec would become a more convenient basal insulin which could improve treatment adherence and overcome insulin initiation barriers as compared to once daily or twice daily basal insulin for subjects with T2D.

Overall, the result of the present trial will be important for evaluating the safety and effectiveness of insulin icodec in a clinical practice setting and will be part of the clinical development programme for the marketing authorisation approval of insulin icodec.

2.2 Background

Diabetes mellitus

T2D is characterised by insulin resistance, impaired insulin secretion, increased hepatic glucose output due to glucagon dysregulation resulting in chronic hyperglycaemia.[4] The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver.[5] The current treatment cascade follows a stepwise approach comprising lifestyle changes in

combination with pharmacological intervention. Metformin is recommended as initial pharmacological therapy, followed by combination therapy with other oral antidiabetic drugs (OADs), glucagon-like peptide 1 receptor agonists (GLP-1) and/or insulin as the disease progresses.[6] On average, after failure of diet and exercise alone, patients require a new intervention with glucose-lowering agents every 3-4 years in order to obtain/retain good glycaemic control.[7] Clinical inertia, often resulting from a resistance to insulin initiation and intensification, is a major contributing factor to patients with T2D who are not achieving recommended glycaemic targets.[8, 9] Increased convenience is believed to support timely insulin initiation in the treatment for T2D and thereby overcoming the clinical inertia associated with insulin initiation.

Insulin icodec

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

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

Three phase 2 trials in subjects with T2D have recently been completed, NN1436-4465, NN1436-4383 and NN1436-4466. Once weekly insulin icodec was shown to provide comparable glucose lowering effects and similar safety profile to insulin glargine (IGlar) U100 in subjects with T2D. Results from these trials were used in the development of the insulin icodec titration guideline (Appendix 9 (Section 10.9)).

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)[10] and any updates hereof.

DoseGuide System

The DoseGuide System provides dose recommendations via the DoseGuide App for once weekly insulin icodec. The DoseGuide System is a cloud-based system containing a titration algorithm to provide dose guidance in accordance with standard clinical practice and the insulin icodec titration guidance (Appendix 9, Section 10.9). The DoseGuide System is considered an investigational software as a medical device (SaMD) in this trial and is documented as compliant with standards and regulations for medical devices in the trial countries.

A comprehensive overview of the DoseGuide System is available in the current edition of the investigator's brochure for the DoseGuide System and any updates hereof.

Once daily basal insulin analogues

The comparator in this trial is commercially available once daily basal insulin analogues: insulin glargine U100, U300 and insulin degludec U100, fixed combinations with basal insulin are not allowed.

The investigator will determine the subject eligible for treatment with basal insulin and select a once daily basal insulin analogue for the patient as per standard of care prior to randomisation (V1). Subjects will then be randomised to either receive insulin icodec or the once daily basal insulin analogue selected.

For further details on the once daily basal insulin analogues, please refer to the respective Investigator's Brochure, EMA Summary of Products Characteristics (SmPC), US Prescribing Information or locally approved Product Information.

Trial population

The trial population will consist of insulin naïve subjects with T2D on any non-insulin antidiabetic medication. The trial population has been chosen to mimic a relatively broad insulin naïve T2D patient group expected to receive the drug once marketed. Subjects should be indicated for intensification with insulin to achieve glycaemic target at the investigator's discretion. Eligible subjects will be identified by the investigator within the normal clinical practice setting.

For more information on the trial population, see Sections 4.2, for more information regarding inclusion and exclusion criteria see Sections 5.1 and 5.2, respectively

2.3 Benefit-risk assessment

2.3.1 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[10] and the DoseGuide System[11] may be found in the respective Investigator's Brochures and any updates hereof.

For more information about known and expected benefits and risks for once daily basal insulin analogue comparators, refer to the respective Investigator's Brochure, EMA SmPC or locally approved Product Information for the relevant product.

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.

A Trial Risk Assessment has been carried out in accordance with ISO 14155:2020 to identify potential additional risks associated with the participation in this trial compared to not participate.[12] The scope of the Trial Risk Assessment includes all procedures, products and their associated

residual risks, examined alone and in combination. Procedures similar to the standard clinical practice for treatment of subjects with T2D initiating basal insulin for the first time are outside scope of the Trial Risk Assessment. Key risks identified in the detailed Trial Risk Assessment are included below.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
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 10.3.3)
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 8.9.1 and Appendix 3 (Section 10.3.3).
Potential risk: 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 medication will be provided if deemed necessary. In the case of systemic hypersensitivity reaction blood sampling for assessment of antibodies against insulin icodec, as well as other assessments will be conducted. For more information please refer to Section 8.9.1 and Appendix 3 (Section 10.3.3)
DoseGuide System		

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Potential risk: Subject receives too high a dose recommendation of insulin icodec	Subjects may receive too high a dose recommendation of insulin icodec due to unexpected error when using the DoseGuide System	The DoseGuide System is developed as a medical device. Risks associated with technical failures and human factors have been mitigated as far as possible through a Risk Management Process. Please see the Investigator's Brochure[11] for the DoseGuide System for further details. Investigators are trained in using the DoseGuide System by Novo Nordisk and will be provided with a DFU for the DoseGuide Portal. Subjects are trained in using the DoseGuide App by their investigator and will be provided with a DFU for the DoseGuide App. Subjects are trained to reach out to their investigator if issues occur between visits.
Potential risk: Subject receives too low a dose recommendation of insulin icodec	Subjects may receive too low a dose recommendation of insulin icodec due to unexpected error when using the DoseGuide System.	
Insulin Degludec		
For more information about known and expected risks for insulin degludec, please refer to the Investigator's Brochure[13], EMA SmPC[14], US Prescribing Information[15] or locally approved Product Information for the relevant product.		
Insulin Glargine		
For more information about known and expected risks for insulin glargine, please refer to the EMA SmPC[16], US Prescribing Information[17] or locally approved Product Information for the relevant product		
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 minimise 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).
Other		

DFU: Directions for use, IB: Investigator's Brochure, SI-IC: Subject Information, Informed Consent Form, SmPC: Summary of Product Characteristics

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 been shown to have a long and stable PK and PD profile, supporting a once weekly treatment. Currently available long-acting basal insulin products need to be administered once 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[18]. Therefore, the treatment adherence and quality of life are expected to increase by introducing a once weekly basal insulin treatment. Further insulin icodec will be used together with DoseGuide which will provide a patient-facing titration guidance to aid subjects with titration.

The trial population will consist of insulin naive subjects with T2D. For all subjects participating in this 52-week trial, the anticipated benefits include improved glycaemic control. The titration algorithm (Appendix 9, Section 10.9), which specifies recommended adjustments of basal 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.

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. The titration algorithm implemented in the DoseGuide System is based on the completed clinical trials and is similar in all phase 3a trials. The DoseGuide System has been developed to be, and is documented as, compliant with applicable standards and regulations for medical devices.[11]

As an overall assessment, Novo Nordisk evaluates that the benefit-risk balance of insulin icodec used with DoseGuide 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.

3 Objectives and endpoints

3.1 Primary, secondary and exploratory objective and estimand

3.1.1 Primary objective

To demonstrate the effectiveness on glycaemic control of once weekly insulin icodec used with DoseGuide in combination with non-insulin anti-diabetic drugs in insulin naïve subjects with T2D in a clinical practice setting. This includes comparing the difference in change from baseline in HbA_{1c} between insulin icodec used with DoseGuide and once daily basal insulin analogues after 52 weeks of treatment to a non-inferiority limit of 0.3%.

3.1.2 Secondary objective

To compare effect on safety and patient reported outcomes related to treatment satisfaction and compliance of once weekly insulin icodec used with DoseGuide versus once daily basal insulin analogues both in combination with any non-insulin antidiabetic drugs in insulin-naïve subjects with T2D in a clinical practice setting.

Estimand:
The estimand is the 'treatment policy estimand' defined as the treatment difference between insulin icodec used with DoseGuide and basal insulin analogues of the change in HbA_{1c} from baseline to week 52 for all randomised subjects, irrespective of adherence to randomised treatment and changes to antidiabetic background medication. The following intercurrent events will be handled by the treatment policy strategy: discontinuation of investigational medical products, and withdrawal from the trial (measurements collected after these intercurrent events are used in the primary analysis). This estimand aims to reflect effectiveness of the treatment on a population level in clinical practice.

3.2 Primary, secondary and exploratory endpoints

3.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline week 0 (V2) to week 52 (V6)	%-point

3.2.2 Secondary endpoints

3.2.2.1 Supportive secondary endpoints

Supportive secondary effectiveness endpoints

Endpoint title	Time frame	Unit
Time from baseline to treatment discontinuation or intensification	From baseline week 0 (V2) to week 52 (V6)	Days
Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction	From baseline week 0 (V2) to week 52 (V6)	Score of 0-36. 6 items scored on a scale of 0 to 6. The higher the score the greater the satisfaction with treatment.
Trim-D (Treatment Related Impact Measure for Diabetes) compliance domain	At end of treatment week 52 (V6)	Score of 4-20. 4 items scored on a scale of 1 to 5 Transformed to a 0-100 scale with higher scores corresponding to better compliance.

Supportive secondary safety endpoints

Endpoint title	Time frame	Unit
Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V8)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 57 (V8)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V8)	Number of episodes

3.2.3 Exploratory endpoints

Endpoint title	Time frame	Unit
Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 52 (V6)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 52 (V6)	Number of episodes
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 52 (V6)	Number of episodes

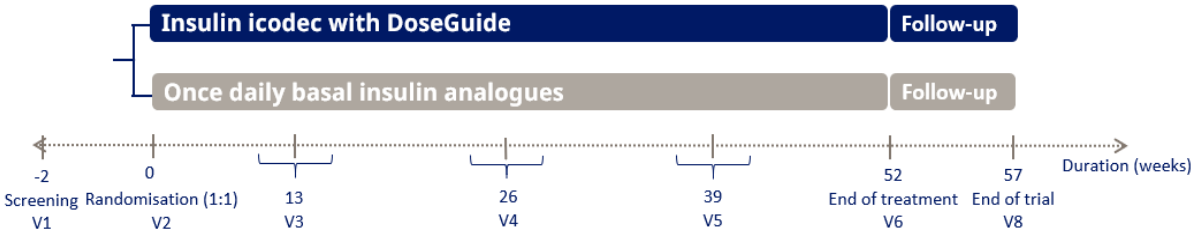
4 Trial design

4.1 Overall design

This is a 52-week, randomised, open label, parallel-group, active-controlled, multi-centre, multi-national trial with real world elements comparing insulin icodec used with DoseGuide versus once daily basal insulin analogues among insulin naïve T2D subjects in which insulin initiation is needed.

The trial duration is approximately 59 weeks, consisting of a 2-week screening period, followed by a 52-week randomised treatment period and a 5-week follow-up period. The overall trial design and visit schedule are outlined in Figure 4-1 and trial flowchart (see Section 1.2), respectively.

Figure 4-1 Trial design



Sites will be primarily selected based on generalisability and previous research experience, thus both primary care and endocrinologist settings will be selected. The investigator will preferably be the subject's practicing physician who in clinical practice would be initiating the subject on insulin.

The decision that insulin initiation is indicated is at the investigator's discretion. Potential eligible subjects will be identified by the investigator and all eligible subjects should be provided the subject information document and asked if they would like to participate in the trial. The investigator will have determined the subjects eligible for treatment with basal insulin including insulin icodec prior to informed consent; however, the allocation to initiate insulin icodec or once daily basal insulin analogue will be made by randomisation. Subjects will be randomised 1:1 to receive either insulin icodec or the once daily basal insulin analogue selected by the investigator prior to randomisation as per standard of care. No stratification will be conducted.

Diagnostic and monitoring procedures outside of normal clinical practice are employed to ensure sufficient AE collection to comply with phase 3a requirements and further described below. The trial will include: Informed consent, randomisation and treatment initiation visit (dedicated randomisation visit), a dedicated trial visit at 13, 26 and 39 weeks and a dedicated end of treatment visit at 52 weeks scheduled one week after the last dose of once weekly insulin icodec administration.

After end of treatment subjects will be transferred to a marketed product at the discretion of the investigator. AE collection will continue with 2 follow-up contacts (V7 and V8). The follow-up period is 5 weeks. Due to different dosing intervals (weekly vs daily) and the longer half-life of insulin icodec, the last follow-up visit (V8) is scheduled to take place 6 weeks after the last dose of once weekly insulin icodec and 5 weeks after the last dose of once daily basal insulin analogue.

Additional visits are allowed throughout the trial. It is anticipated that investigators, as the subjects' physicians, ensure subjects undergo medical evaluation at regular intervals over the course of the trial as per standard of care. Subjects will be encouraged to reach out proactively if experiencing any alterations to their wellbeing which may represent an AE. AEs will be assessed at all contacts and subjects will have an eDiary to report hypoglycaemic episodes (Appendix 8, Section 10.8).

To allow treatment according to local practice all non-insulin antidiabetic medications as standard of care are allowed at the investigator's discretion during the trial. Add-on, discontinuation or dose modification of non-insulin antidiabetic medications is allowed at any time during the trial.

If the randomised basal insulin treatment is discontinued, intensification to basal bolus regimen is needed or use of DoseGuide is permanently discontinued, the subject should attend an early discontinuation follow-up visit (V6A) and continue marketed antidiabetic medications including insulins at the discretion of the investigator for the remainder of the trial.

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

4.2 Scientific rationale for trial design

The trial is designed to investigate the effectiveness on glycaemic control and safety of insulin icodec used with DoseGuide in comparison to standard of care once daily basal insulin analogues both in combination with any non-insulin antidiabetic medication in insulin naïve T2D subjects in a clinical practice setting. The basal insulin analogues chosen as comparators in this trial have been selected based on their suitability for a once daily injection as well as being widely used for initiating insulin therapy in insulin naïve T2D patients.

Assessing effectiveness requires a less stringent sponsor-controlled schedule to allow physicians to tailor their diabetes management to the individual subject. The trial design and subsequent visit frequency has been chosen to meet data collection requirements whilst allowing for local clinical practice to be maintained. Investigators, as the subjects' physicians, are expected to schedule additional visits as they deem relevant. It is therefore expected that the investigator together with the patient agrees to a tailored visit schedule during the conduct of the trial in addition to the planned visits according to the flow chart.

The treatment duration of 52 weeks is evaluated to be adequate time for assessing effectiveness on glycaemic control and safety. This duration will also allow for up-titrating of the basal insulin.

A centralized treat-to-target approach will not be applied as titration of basal insulin analogues should be done according to local labelling and clinical practice. Use of a marketed titration support mobile app or tool to aid titration of the once daily basal insulin analogue comparators is allowed at the discretion of the investigator.

Titration of insulin icodec should be conducted in accordance with the titration guideline, see Appendix 9 (Section10.9). Titration of insulin icodec will be aided by use of the DoseGuide System, which calculates the dose recommendations with the same titration algorithm as outlined in the titration guideline and will provide insulin icodec dose recommendations via the DoseGuide app to subjects. (see the current DoseGuide System IB for more information).

During the treatment period, the subjects will have dedicated site visits every three months, in accordance with recommended clinical practice, with the option of additional site visits or phone contacts according to local clinical practice or need. The last follow-up visit is planned to be 6 weeks after the last dose of insulin icodec, allowing appropriate time for wash-out of trial drug, following at least 5 half-lives of insulin icodec.

Subjects included in the trial can be on any non-insulin antidiabetic medication, however to minimise the risk of hypoglycaemia subjects treated with glinides or sulfonylureas (either alone or in combination with other OADs) will be asked to reduce the dose by approximately 50% at the discretion of the investigator. Underlying diseases such as recent cardiac problems, impaired liver or renal function will be documented prior to treatment initiation but are not exclusion criteria. However, any condition considered to jeopardise subject's safety as assessed by the investigator will exclude the subject from trial participation. As no human data are available on pregnancies following exposure to insulin icodec, female subjects of childbearing potential can only be recruited if adequate contraceptive methods are used (see Appendix 4, Section 10.4).

Overall, the eligibility criteria will allow for enrolment of a relatively broad insulin naïve T2D population resembling one of the key target populations for insulin icodec use.

4.3 Justification for dose

Insulin icodec should be initiated at 70 units once weekly with aid from the DoseGuide App. One unit of insulin icodec has similar glucose lowering effect to one unit of insulin glargine 100 units/mL and one unit of insulin degludec 100 units/mL, and therefore once weekly dosing corresponds to seven times the daily dose of a once daily basal insulin comparator. Basal insulin analogue comparators should be initiated as per the discretion of the investigator based on local clinical practice.

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

After randomisation, subjects will initiate insulin injections and this treatment should continue until 52 weeks after randomisation where the subjects come in for the end of treatment visit (V6).

Initiation and titration of daily basal insulin analogues will be done according to approved label and local clinical practice. Initiation and titration of insulin icodec should be conducted in accordance with the titration guideline aided by the use of the DoseGuide App, see Appendix 9 (Section 10.9).

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 the following criteria apply:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female.
3. Age above or equal to 18 years at the time of signing informed consent.
4. Diagnosed with T2D ≥ 180 days prior to the day of screening.
5. HbA_{1c} above 7.0% (53 mmol/mol) as measured by central lab.
6. Insulin naïve. However, short term insulin treatment for a maximum of 14 days prior to the day of screening is allowed, as is prior insulin treatment for gestational diabetes.
7. Stable daily dose(s) ≥ 90 days prior to the day of screening of any of the following antidiabetic drug(s) or combination regimen(s):
    a. Any metformin formulations ≥ 1500 mg or maximum tolerated or effective dose.
    b. Any metformin combination formulations ≥ 1500 mg or maximum tolerated or effective dose.
    c. Antidiabetic Drugs including combination products (≥ half of the maximum approved dose according to local label or maximum tolerated or effective dose):
        - Sulfonylureas
        - Meglitinides (glinides)
        - DPP-4 inhibitors
        - SGLT2 inhibitors
        - Thiazolidinediones
        - Alpha-glucosidase inhibitors
        - Oral combination products (for the allowed individual Oral Antidiabetic Drugs (OADs))
        - Oral or injectable GLP-1-receptor agonists
8. Intensification with insulin is indicated to achieve glycaemic target (4.4-7.2 mmol/L; 80-130 mg/dL) at the discretion of the treating investigator.

5.2 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice).
4. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening. *
5. Any disorder which in the investigator's opinion might jeopardise subject's safety.

**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

Fasting is defined as at least 8 hours without food and drink intake, except for water and other prescribed medication.

5.3.2 Caffeine, alcohol and tobacco

Tobacco use is defined as smoking at least once 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.

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

Treatments include the investigational medicinal products (Section 6.1) and investigational medical device (Section 6.1.1.1) provided by Novo Nordisk.

Investigational medicinal products (IMP)

All investigational medical products (IMPs) provided by Novo Nordisk are listed in Table 6-1.

Table 6-1 Investigational medicinal product provided by Novo Nordisk

Trial product name:	Insulin icodec 700U/mL *(IMP, test product)*	Insulin Degludec 100U/mL *(IMP, reference therapy)*	Insulin Glargine 100U/mL *(IMP, reference therapy)*	Insulin Glargine 300U/mL *(IMP, reference therapy)*
Dosage form	Solution for injection	Solution for injection	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)	Subcutaneous (into the thigh, upper arm or abdomen)	Subcutaneous (into the thigh, upper arm or abdomen)
Recommended initial dose	Please refer to Appendix 9	Please refer to Appendix 9	Please refer to Appendix 9	Please refer to Appendix 9
Dosing instructions	Administer insulin icodec once weekly, on the same day each week, at any time of the day. The day of weekly administration can be changed if necessary, by up to 3 days. A minimum of 4 days between injections should always be ensured.	Administer insulin degludec once daily at any time of the day, but at the same time every day throughout the trial. Rotation of injection site is recommended.	Administer insulin glargine once daily, at any time of the day but at the same time every day throughout the trial. Rotation of injection site is recommended.	Administer insulin glargine once daily, at any time of the day but at the same time every day throughout the trial. Rotation of injection site is recommended.
Packaging	3 mL PDS290 pre-filled pen-injector	3 mL PDS290 pre-filled pen-injector	3 mL SoloSTAR pre-filled pen-injector	1.5 mL SoloSTAR pre-filled pen-injector

- Subjects should administer insulin icodec at site at the randomisation visit (V2).
- Subjects should initiate basal insulin analogues as per clinic's standard of care.
- Subjects should be instructed to discard the needle after each injection and store the pen-injector without a needle attached.
- Subjects should be instructed to use one pen injector for the full in-use time period (see TMM). The subjects should change the pen-injector only if the inuse time is passed or a full dose can no longer be given.

Non-investigational medicinal products (NIMP)

After randomisation subjects can continue add-on or remove non-insulin anti-diabetic medication in agreement with the investigator and according to local clinical practice throughout the entire trial; however, subjects with glinides or sulfonylureas (either alone or in combination with other OADs) will be asked to reduce the dose by approximately 50% at the discretion of the investigator, at randomisation. There is no requirement that background medication should be stable or maintained at the pre-trial dose and dose adjustments are allowed during the entire treatment period. Please see section 6.5 for reporting of concomitant anti-diabetic medications.

In addition, the background medication:

- is considered to be non-investigational medicinal product (NIMP)
- will not be provided by Novo Nordisk and should be purchased or otherwise delivered to subjects in accordance with local health plans unless otherwise required by local regulations.

- should be used in accordance with standard of care or local label in the individual country at the discretion of the investigator

Auxiliary supplies

Table 6-2 Auxiliary supplies

Auxiliary	Details
Needles for the PDS290 and SoloSTAR pre-filled pen-injectors	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. The same needle length and gauge must be used for all subjects.
eDiary	Subject Mobile App, HCP Web Portal, & Cloud Service
Directions for Use	Directions for use will be provided electronically via the eDiary for the insulin icodec 700 U/mL PDS290 pen-injector and in paper format for the insulin degludec PDS290 and SoloSTAR pre-filled pen-injectors. Directions for use will be provided in a paper format for the DoseGuide App

6.1.1 Medical devices

6.1.1.1 Investigational medical device

DoseGuide System

The DoseGuide System provides automated dose guidance for insulin icodec to subjects with T2D. The intended use of the DoseGuide System is to aid in the treatment of T2D by providing dose guidance to the patient treated with insulin icodec as basal only treatment. The DoseGuide System is developed by Novo Nordisk.

The DoseGuide System consists of the DoseGuide App for subjects and the DoseGuide Portal for investigators, both integrated with the DoseGuide Cloud, where the dose recommendations are calculated. The DoseGuide System utilises measurements from a blood glucose meter (BG meter) via Bluetooth as well as injection history and pre-breakfast fasting SMPG provided by the subject. The investigator sets up the subject profile in the DoseGuide Portal according to the titration guidance, as specified in this trial protocol. The subject requests and receives dose recommendations in the DoseGuide App.

No procedures related to the DoseGuide System are included in this trial.

More information about the use of the DoseGuide System for the investigator can be found in the IB for the DoseGuide System and in the DFU for the DoseGuide Portal. Information about use of the DoseGuide App for the subject is provided in the DFU for the DoseGuide App. See the IB for the DoseGuide System for version numbers of its components.

Training in the DoseGuide System

The investigator must document that training in the DFU for the DoseGuide App has been given to the subjects orally and in writing at randomisation (V2) and should be repeated during the trial to ensure correct use of the medical device.

6.1.1.2 Non-investigational medical device

Needles for pre-filled pen-injectors are listed in Table 6-2.

Blood Glucose Meter (BG Meter)

For self-measuring of blood glucose during the trial, subjects will be provided with a BG meter at randomisation (V2) including auxiliaries and instructions for use.

At randomisation (V2) the subjects must be instructed in how to use the BG meter. For subjects randomised to basal insulin analogues, the BG meter should be paired to the eDiary as described in the site guide. For subjects randomised to insulin icodec, the BG meter should be paired with the DoseGuide App as described in the DoseGuide Portal .

For further information on the BG Meter, please refer to the manufacturer's manual.

6.2 Preparation/handling/storage/accountability

Only subjects randomised to treatment may use trial product and only delegated site staff may supply trial product. Trial product includes both the investigational medical product and the investigational medical device.

Investigational medicinal products

- Acceptable temperature ranges and conditions for storage and handling of trial products when not in use and when in use are described in the Trial Material Manual (TMM) and trial product label.
- 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.
- Drug accountability should be performed at pen level

- 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.

Investigational medical device

- The investigational medical device described in Section 6.1.1.1 will be supplied by Novo Nordisk and is only applicable for subjects randomised to insulin icodec.
- The investigator or designee is responsible for DoseGuide App device accountability via subject access control through DoseGuide portal.
- Device accountability should be performed at subject account level.
- The provisioned study phone is not considered a medical device, but a carrier of the apps to be used in the trial.
- The provisioned study phones must be returned by the subject at the end of trial visit.
- All returned, unused or damaged study phones must be stored separately and returned at the latest at closure of the site.
- Investigator accountability is not applicable for the DoseGuide Portal and the DoseGuide Cloud. Instead, Novo Nordisk will control and restrict access to these systems.

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 blinded adjudication of selected events. All subjects will be centrally screened and randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed/allocated at the trial visits summarised in the flowchart.

6.4 Treatment compliance

Drug treatment compliance

Throughout the trial, the investigator will encourage subject's compliance as per standard clinical practice.

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

- Drug accountability information; counting returned trial product, visual inspection of pens
- Review of DoseGuide App, SMPG profiles, insulin dose and hypoglycaemia reporting via HCP web portals.
- Evaluating glycaemic control and adherence to the visit schedule

- If any suspicion of non-compliance arises the site should enter into a dialogue with the patient as per standard clinical practice. This dialogue must be documented in the medical record.

DoseGuide App Compliance

The DoseGuide App is only applicable for subjects randomised to insulin icodec. Subjects should initiate insulin icodec with DoseGuide to aid titration.

Permanent suspension of the DoseGuide App will result in discontinuation of insulin icodec treatment.

6.5 Concomitant medication

Any medication other than the IMP and pre-trial non-insulin anti-diabetic medication that the subject is receiving from the screening visit (V1) until end of trial (V8) visit must be recorded along with:

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

Concomitant medication (diabetes)

Any anti-diabetic medication that the subject receives from screening (V1) to end of trial (V8) must be recorded in a separate concomitant medication (diabetes) form in the eCRF. This does not include the IMP (insulin icodec or basal insulin analogue) that the subject was randomised to at V2.

The following information must be recorded for oral antidiabetic drugs (OADs), GLP-1 RAs and insulin products including post-treatment insulin in the follow-up period:

- Trade name and generic name
- Doses and frequency (e.g. once daily, twice daily)
- Dates of administration including start and stop dates

If the investigator chooses to initiate anti-diabetic medication or change dose of pre-trial anti-diabetic background medication prior to end of treatment, this should be registered in the eCRF as change in concomitant medication (diabetes). If subject requires intensification of basal insulin or continuous use of bolus insulin, please see Section 7.

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

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

6.5.1 Rescue medication or Rescue therapy

This section is not applicable for this trial

6.6 Dose modification

Insulin icodec doses are adjusted according to the titration guidelines based on SMPG values as described in Appendix 9 (Section 10.9).

The recommended insulin icodec doses are provided directly to subjects randomised to insulin icodec via the DoseGuide App. The subject receives dose recommendations through the DoseGuide App within the scope of a pre-planned treatment program from the investigator.

The titration algorithm may not be applicable in certain clinical situations and the recommended doses can therefore be overruled. The investigator can view and change the dose recommendation based on the data collected via the DoseGuide Portal at his/her discretion. The investigator can also suspend or re-initiate use of the DoseGuide App at his/her discretion. Permanent discontinuation of the DoseGuide App will lead to discontinuation of insulin icodec treatment (see Section 6.4 and 7).

For more information on the DoseGuide System, please refer to the IB and any updates thereof.

Titration of once daily basal insulin analogue comparators is at the discretion of the investigator as per the clinic's standard of care. The recommended doses for all once daily basal insulin analogues will be based on local label. Use of titration assistant applications or other tools is at the discretion of the investigator.

Please see the Insulin Titration Guideline (Appendix 9, Section 10.9) for more information.

6.7 Treatment after end of trial

When discontinuing trial product, the subject should be transferred to a suitable marketed product at the discretion of the investigator and according to local clinical practice. If the switch to post-trial treatment includes a new insulin treatment, please refer to the titration guideline Appendix 9 (Section 10.9).

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.

Efforts must be made to have the subjects who discontinue IMP attend the end of treatment visit (V6) as soon as possible to collect the required data for the analysis of the primary endpoint. Two follow-up visits, V7 and V8, must be performed after discontinuation of the IMP. V7 and V8 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 analogue. It is stressed that the visit window is plus 7 days for both V7 and V8. Further, it is important that discontinued subjects come in for the discontinuation follow-up visit V6A, 52 weeks after the randomisation visit.

Continue to collect, record and report AEs as described in Section 8.3.

Only antidiabetic medication should be collected and recorded in the eCRF until V6A for discontinued subjects, no other concomitant medication will be collected. Please, refer to Section 6.7 for treatment after end of trial.

Subjects who prematurely discontinue IMP should keep the study phone (containing the eDiary and DoseGuide App) and return it at V8.

Subjects who prematurely discontinue insulin icodec should terminate use of the DoseGuide App but continue to use the eDiary. Permanent discontinuation of DoseGuide App will result in discontinuation of insulin icodec.

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 IMP. Further, the site should stay in contact with discontinued subjects by phone and/or site visits to motivate subjects to attend the discontinuation visits until the discontinuation follow-up visit (V6A). 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. Patients should be advised not to participate in other clinical trials while participating in this trial. If done, treatment with trial product should be disctoninued.*
5. Switch to another basal insulin analogue
6. Intensification to a basal bolus regime or continuous use of bolus insulin

**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's discretion without discontinuing trial product*

The primary reason for discontinuation of IMP 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.

If temporary or permanent discontinuation of DoseGuide App is related to a technical complaint or for safety reasons please see Appendix 5, Section 10.5.

A subject who does not fulfil the eligibility (inclusion/exclusion) criteria must not be randomised. Randomisation in violation of any of the eligibility criteria is Good Clinical Practice (GCP) non-compliance and must be reported to the sponsor without delay. This will be handled as an

important protocol deviation, and the independent ethics committee/institutional review board (IEC/IRB) and regulatory authorities must be notified according to local requirements.

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

7.1.1 Temporary discontinuation of trial treatment

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

7.1.2 Rescue criteria

This section is not applicable for this trial.

7.2 Subject discontinuation/withdrawal from the trial

A subject may withdraw consent at any time at his/her own request. If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to end of treatment visit (V6). See flowchart (1.2) for data to be collected.

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

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

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

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

7.2.1 Replacement of subjects

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

7.3 Lost to follow-up

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

Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject. These contact attempts should be documented in the subject's source document. Should the subject continue to be unreachable at end of trial (V8), 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.

- 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.
- At screening, after confirming eligibility, the investigator will select the once daily basal insulin analogue suitable for the subject. At V2, the subject will be randomised to either insulin icodec or the once daily basal insulin analogue selected at screening.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential for trial conduct however 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 assessments related to the eDiary, BG meter and DoseGuide System at randomisation visit (V2) is as follows:
    - 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 eDiary HCP web portal, and if the subject is randomised to insulin icodec also in the DoseGuide Portal
    - Subjects should be provided with a study phone and instructed in how to use the eDiary and the DoseGuide App if randomised to insulin icodec
    - The BG meter should be paired with the DoseGuide App (for subjects randomised to insulin icodec) or to the eDiary (for subjects randomised to basal insulin analogues).
    - SMPG should be measured using the BG meter (and transferred to the eDiary or DoseGuide App)
    - Dosing of trial product (and entry of dose in eDiary or DoseGuide App)
- For information regarding the eDiary and eDiary web portal use please refer to the site guide.
- For information regarding the DoseGuide System please refer to the IB or the DFUs.
- Please refer to Section 6.4 for treatment compliance.
- For data entered in the eDiary and DoseGuide System via the study phone, eDiary and DoseGuide databases are considered source data. The investigator should review all the data for the subjects through the eDiary web portal and the DoseGuide Portal, before or during each visit/phone contact and report any AEs in the eCRF.
- Source data of clinical assessments performed and recorded in the eCRF must be available and will usually be in the subject's medical records. Additional recording to be considered

source data include, but is not limited to laboratory reports, BGM, pictures and ECG recordings.

- Review of data on HCP web portal, ECG, laboratory reports, eye- and physical examinations must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the eDiary, or DoseGuide App is needed, the subject must be questioned, and a conclusion made in the subject's source documents, the eDiary can be updated retrospectively if applicable. Care must be taken not to bias the subject. The investigator should ensure that the ePRO questionnaires are completed by the subject in the eDiary.
- 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.

8.1.1 Self-measured plasma glucose (SMPG)

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 the SMPG measurements required in the protocol, as described in the flow chart 1.2.

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

Pre-breakfast daily SMPG

Subjects should be instructed to measure their pre-breakfast SMPG daily from the day after randomisation (V2) to end of treatment (V6) and to transfer the SMPG values into the DoseGuide App (for subjects randomised to insulin icodec) or the eDiary (for subjects randomised to basal insulin analogues). Subjects should specify pre-breakfast SMPG in the corresponding App. Pre-breakfast SMPG should be measured daily from end of treatment (V6) to end of trial (V8) and captured in the eDiary for all subjects.

Selected titration data (e.g. certain SMPGs and dose data) will be used during the trial for central titration surveillance, to ensure compliance with DoseGuide supported titration 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 Clinical outcome assessments

The PRO questionnaires are to be completed by the subject without assistance of the site personnel. The questionnaires should be completed on site before any other visit related procedures are conducted. The three questionnaires take approximately five minutes to complete.

The following PRO questionnaires will be supplied in the eDiary in a linguistically validated version in all languages relevant for this trial:

- Diabetes Treatment Satisfaction Questionnaire (DTSQ)
  - The questionnaire has been designed to measure satisfaction with diabetes treatment regimens in people with diabetes. The DTSQ questionnaire will be measured at baseline (V2), during conduct (V4) and end of treatment (V6).
- Treatment Related Impact Measure for Diabetes (TRIM-D) Compliance domain
  - The TRIM-D questionnaire was developed to capture the impact of diabetes treatment on patients' functioning and well-being. The compliance domain from the questionnaire will be used to measure the compliance between the treatment groups. The compliance domain of TRIM-D will be measured end of treatment (V6).
- Diabetes Pen Experience Version 3.0 (DPEM)
  - The questionnaire is designed to measure patients experience of insulin injection pen in terms of easiness, convenience and satisfaction. The DPEM questionnaire will be measured at end of treatment (V6).

8.1.3 Clinical efficacy laboratory assessments

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

8.2 Safety assessments

Safety assessments should be carried out as per clinic's standard of care if not otherwise specified and in accordance with the flowchart (1.2).

A **concomitant illness** is any illness that is already present at the time point from which AEs are collected or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Medical history is a medical event that the subject experienced prior to the time point from which AEs are collected. Only relevant medical history as judged by the investigator will be recorded in the eCRF.

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

8.2.1 Insulin dose

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

While using the HCP web portal for titration of once daily basal insulin analogues, the daily insulin prescribed at this contact should be entered by investigator.

The investigator must record the following in the eCRF for all subjects

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

For information about recommended insulin doses please see Appendix 9, Section 10.9

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 and 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 AE (See Appendix 3, Section 10.3).

Body measurements (e.g. height and weight) will be measured and recorded as specified in the flowchart 1.2

- Body weight should be measured in kilogram (kg) or pounds (lb). Body weight will be recorded to one decimal.
- Height should be measured in centimetres (cm) or inches (in) at screening visit (V1) without shoes. Height will be recorded to the nearest whole number.

8.2.3 Vital signs

- Pulse rate, as well as systolic and diastolic blood pressure will be assessed as specified in the flowchart 1.2.
- Manual techniques must be used only if an automated device is not available.
- Blood pressure and pulse rate at V1 and V6 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 (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, cell 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, and the results must be interpreted by the investigator before randomisation in order to determine the eligibility of the subject.
- The ECG required at V4 and the end of treatment (V6) visit can be obtained within 2 weeks prior to the visit, and the results must be available for evaluation at the 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 AE (see Appendix 3, Section 10.3).

8.2.5 Eye examination

Uncontrolled and potentially unstable diabetic retinopathy or maculopathy 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. The eye examination should be performed as a fundus photography (e.g. 2-field 60 degree or better, colour or red-free) or by slit-lamp biomicroscopy examination (e.g. using a pre-corneal or corneal contact lens examination). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

If the subject had such an eye examination performed within 90 days prior to screening, the investigator may base his/her evaluation upon the results of that examination. The examination must be repeated before randomisation if the subject has experienced worsening of visual function since the last examination. If the applicable eye examination was performed before the subject signed the informed consent form, it must be documented that the reason for performing the examination was not related to this trial.

Eye examinations required at the end of treatment (V6) visit can be performed within 2 weeks prior to the visit, if results are available for evaluation at the visit. For discontinued subjects, eye examination can be performed up to 2 weeks after the end of treatment visit.

The investigator should indicate the outcome of each eye examination. Relevant findings prior to randomisation must be recorded as concomitant illness/medical history. While relevant findings occurring after randomisation should be reported as an AE, please refer to Appendix 3 (Section 10.3).

8.2.6 Clinical safety laboratory assessments

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

8.3 Adverse events and serious adverse events

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

Investigators should train subjects to contact the site ongoingly throughout the duration of the trial in case of adverse events.

The definition of AEs and SAEs can be found in Appendix 3 and Appendix 6 (Section 10.3 and Section 10.6), along with a description of AEs for adjudication and AEs requiring additional data collection.

All AEs and investigational medical device deficiencies (DoseGuide System) that could have led to an SAE are reportable, see Appendix 5, (Section 10.5).

All AEs occurring in subjects randomised to icodec require completion of specific adverse event investigational medical device form (Appendix 6, Section10.6).

In addition, some AEs require additional data collection on a specific event form. This includes medication error, misuse and abuse of IMP. The relevant events are listed below in Table 8-1.

AEs for adjudication require data collection on an adjudication form. Event adjudication will be performed in randomised subjects and will be evaluated by an independent external event adjudication committee (EAC) in a blinded manner, please refer to Section 10.1.6.3.

Refer to Appendix 3 (Section 10.3) and Appendix 6 (Section10.6)for further details on reportable adverse events and reporting timelines (Figure 10-1).

Hypoglycaemic episodes

Hypoglycaemic episodes require data collection on a hypoglycaemic episode form in the eDiary for all randomised subjects. Non-serious hypoglycaemic episodes do not require an AE form to be completed. 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 completed in the eCRF, please refer to Appendix 3 (Section 10.3). If a non-serious hypoglycaemic episode is related to a DoseGuide System technical complaint, this should be reported along with the technical complaint, please refer to Appendix 5 (Section 10.5) For more information on hypoglycaemic episodes, please refer to Appendix 8 (Section 10.8).

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 (MI) 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 are to be reported and sent for adjudication, however the EAC will only confirm strokes.

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

Events for Adjudication

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 (see 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 V8 at the time points specified in the flowchart and as needed per the discretion of the investigator. For patients discontinuing IMP prematurely AEs must also be collected from V8 until the Early Discontinuation Follow-up visit (V6A).

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) for the IMP and Appendix 6 (Section10.6) for the investigational medical device. 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) for the IMP and Appendix 6 (Section 10.6) for the investigational medical device.

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) for IMP and Appendix 6 (Section 10.6) for the investigational medical device.

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 reaction (SUSAR) (for IMP) and unanticipated serious adverse device effect (USADE) (for the investigational medical device).

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

8.3.5 Pregnancy

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

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

8.3.6 Cardiovascular and death events

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

8.3.7 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 i.m. or s.c. by a trained person, or by glucose given i.v. by a medical professional. Glucose must also be given i.v., if the patient does not respond to glucagon within 10-15 minutes. If the patient has been unconscious, administration of oral carbohydrates is recommended for the subject upon regaining consciousness, in order to prevent a relapse.

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

For more information on overdose, also consult the current version of the insulin icodec investigator's brochure and any updates hereof.

Treatment for overdose of once daily basal insulin analogues should be at the discretion of the investigator and per standard care, for more information, consult the current version and any updates hereof of the Investigator's Brochure, EMA Summary of Products Characteristics (SmPC), US Prescribing Information or locally approved Product Information for the relevant product.

8.5 Pharmacokinetics

This section is not relevant for this trial

8.6 Pharmacodynamics

This section is not relevant for this trial

8.7 Genetics

This section is not relevant for this trial

8.8 Biomarkers

This section is not relevant for this trial.

8.9 Immunogenicity assessments

8.9.1 Hypersensitivity

Subjects and investigators will be instructed to detect signs and symptoms of systemic hypersensitivity. In the event of a systemic hypersensitivity (not locally at the injection site), the patient 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 CTR.

For retention of residual hypersensitivity samples, please refer to Appendix 7, 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 relevant for this trial.

9 Statistical considerations

9.1 Statistical hypotheses

The primary hypothesis to be tested is that insulin icodec used with DoseGuide is non-inferior to once daily basal insulin analogues in terms of change from baseline to week 52 in HbA_{1c}.

Formally, let D be the treatment difference 'insulin icodec used with DoseGuide' minus 'basal insulin analogues' of the change in HbA_{1c} from baseline to week 52. The null-hypothesis will be tested against the alternative hypothesis of non-inferiority as given by

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

The non-inferiority margin of 0.3%-point is chosen based on the recommendation in the FDA guidance for industry on developing drugs for treatment of diabetes.[19] Also, this margin is considered to provide sufficient assay sensitivity based on the below considerations:

- The margin does not represent an unacceptable loss of efficacy with insulin icodec relative to treatment with a basal insulin analogue
- It represents less than 50% of a suitably conservative estimate of insulin glargine's treatment effect on HbA_{1c} in a placebo-controlled trial in insulin naïve subjects (-0.85%-point $[-1.04; -0.66]_{95\%CI}$ versus placebo), which demonstrated insulin glargine's superiority[20].
- Other basal insulin analogues have previously been shown to yield similar reductions in HbA_{1c} compared to insulin glargine.

The following describes the secondary confirmatory hypothesis. In order to control the overall Type I error at a 5% level, two sided, a hierarchical testing procedure will be used. If non-inferiority in glycaemic control is concluded in the primary analysis, confirmatory testing proceeds to the following hypothesis:

- Insulin icodec used with DoseGuide is superior to once daily basal insulin analogues in terms of change in HbA1c from baseline to week 52

Formally, let D be the mean treatment difference 'insulin icodec used with DoseGuide' minus 'basal insulin analogues' of the change in HbA_{1c} from baseline to week 52. The null-hypothesis of insulin icodec used with DoseGuide not superior will be tested against the alternative hypothesis of superiority as given by:

$$H0: D \geq 0.0\% \text{ against } HA: D < 0.0\%$$

9.2 Sample size determination

The sample size is determined in order to have 90% power for declaring non-inferiority with a non-inferiority margin of 0.3%-point with respect to change in HbA_{1c} for the specified estimand and the full analysis set (primary analysis set). Based on CONFIRM, a trial that compared the real-world effectiveness of insulin degludec and glargine U300 in insulin-naïve subjects with T2D in routine US clinical practice, and market analytics on retention and switching from a basal insulin, it is expected that approximately 30% of insulin naïve subjects initiating insulin treatment will discontinue from their assigned insulin treatment within 52 weeks. Of these, one third is likely to switch back to OAD or to a GLP-1, one third to another basal insulin and one third to a basal-bolus treatment regimen.

In the phase 3 randomised clinical trial (RCT) setting with a treat-to-target approach, the SD of HbA_{1c} after 12 months of treatment with a basal insulin has previously been observed to be 1.0% or less (NN1250, NN9068). In-the Explorys, a database of electronic medical records representing 39 integrated healthcare-delivery networks in the US, the SD for HbA_{1c} 12 months (+/- 90 days) after insulin initiation was 1.9 % in T2D subjects not being treated with an insulin for at least 180 days. With the pragmatic nature of the present trial, while still being a randomised trial with pre-defined follow-up of subjects, it is expected that the SD for HbA_{1c} after 12 months will be elevated compared to what is normally observed in a strict treat-to-target RCT by approximately one third of the increase that was seen in the Explorys database. I.e., the SD for the present trial is assumed to be 1.3%.

A treatment difference of 0.0%-point in subjects completing 52 weeks of treatment is expected. It is further conservatively assumed that the treatment difference will be 0.15%-point in favour of basal insulin analogues for subjects discontinuing randomised treatment prior to week 52. Accounting for treatment discontinuation, an adjusted treatment difference of 0.045%-point in favour of basal insulin analogues is therefore expected for the estimand.

The trial should be powered to be able to demonstrate non-inferiority of insulin icodec used with DoseGuide versus once daily basal insulin analogues as well as having reasonable power to detect a treatment difference of 0.3%-point in favour of insulin icodec used with DoseGuide in all randomised as being statistically significant different from 0.0%-point for the primary endpoint of change in HbA_{1c} from baseline to week 52.

From the above assumptions and requirements, 1096 subjects will be randomised to trial product. This will ensure sufficient power (90%) of confirming non-inferiority while also having sufficient

marginal power (97%) to detect a treatment difference of 0.3%-point in favour of insulin icodec used with DoseGuide in all randomised as being statistically significant different from 0.0%-point.

With an expected screening failure rate of 9%, approximately 1200 subjects will be screened to achieve 1096 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 displaying power for various alternative treatment differences and standard deviations.

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

SD (%-point)	**Treatment difference (%-point)**		
	0.03	0.045	0.06
1.2	96%	94%	91%
1.3	93%	**90%**	86%
1.4	89%	85%	81%

SD: standard deviation. Power is computed for 1:1 randomisation and 1096 subjects randomised.

9.3 Populations for analyses

The following populations are defined:

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

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

The following periods will be considered for the data collected:

In-trial period

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

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

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

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

- The end of trial visit (V8)
- The last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin (corresponding to 5 weeks after the end of the dosing interval for both treatment arms)
- The end-date for the in-trial observation period

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

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

9.4 Statistical analyses

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

9.4.1 General considerations

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

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

- Treatment: Once weekly insulin icodec used with DoseGuide, basal insulin analogues
- Region: Europe, North America

The regions will be defined as follows:

- Europe: Germany, Greece, Hungary, Poland, Serbia, Turkey
- North America: Canada, United States

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

9.4.2 Primary endpoint

The primary endpoint is change in HbA_{1c} from baseline to week 52.

The 'treatment policy' estimand will be estimated based on the full analysis set using all HbA_{1c} measurements obtained at the week 52 visit, especially including measurements from subjects

discontinuing their randomised treatment. Missing HbA_{1c} at the week 52 visit (regardless of treatment completion status) will be imputed from trial participants, who have discontinued their randomised treatment prior to the week 52 visit and have a measurement at the week 52 visit in the following way:

- First, one thousand (1000) copies of the dataset will be generated for HbA_{1c}.
- Second, for subjects who discontinued their randomised treatment at any time prior to the week 52 visit and have an HbA_{1c} measurement at the week 52 visit, the change in HbA_{1c} from last available planned on-treatment (LAOT) value to the week 52 visit will be analysed for each dataset copy using an analysis of covariance (ANCOVA) model with randomised treatment as fixed factor and LAOT value and the time point (study day) of this assessment as covariates. The estimated parameters, and their variances, from the model will be used to impute missing HbA_{1c} values for the change from LAOT to the week 52 visit and subsequently the missing HbA_{1c} value at the week 52 visit.
- For each of the complete data sets, the primary endpoint will be analysed using an ANCOVA model with region and randomised treatment as fixed factors, and baseline HbA_{1c} as a covariate. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule[21].

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

If non-inferiority is confirmed, i.e. if the 95% CI is strictly below 0.3%, then the primary endpoint will further be tested for superiority. Superiority for change in HbA_{1c} will be considered confirmed if the 95% CI is strictly below zero.

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 52 visit are assumed to have a worse outcome in the insulin icodec used with DoseGuide arm and a better outcome in the basal insulin analogues arm compared to what was imputed in the primary analysis. This is done by adding or subtracting values Δ_i to the imputed HbA_{1c} values before analysing the data. The value of Δ_i 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 Δ_i 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

Time from baseline to treatment discontinuation or intensification (from baseline week 0 (V2) to week 52 (V6))

Time from baseline to treatment discontinuation or intensification will be analysed using a stratified log-rank test where randomised treatment will be included as strata in the model. Subjects lost to follow-up or withdrawing from trial before the completion of the treatment period will contribute to the analysis as discontinuing treatment at the time of the end of the in-trial period if the time of discontinuation is unknown. Cumulative incidence function by randomised treatment will be presented together with estimated and relative risks (risk ratio) at week 26 and week 52. The 25%, 50% (median) and 75% percentiles based on the cumulative incidence function will also be presented. For details on additional analyses, please refer to SAP.

Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction from baseline week 0 (V2) to week 52 (V6)

Missing DTSQs scores in total treatment satisfaction at the week 52 visit (regardless of treatment completion status), will be imputed from trial participants who are from the basal insulin analogues group, and who have completed and adhered to their randomised insulin treatment – i.e., data will be imputed based on the assumption that subjects with missing endpoint data will behave like subjects completing the treatment with basal insulin analogues. Specifically, the imputations will be carried as follows:

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

Trim-D (Treatment Related Impact Measure for Diabetes) compliance domain at week 52 (V6)

Trim-D compliance domain at week 52 will be analysed using the same model as specified for change in DTSQs in total treatment satisfaction, but without using the baseline value as a covariate.

Safety endpoints

Hypoglycaemic episodes

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

- Number of severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 57 (V8)
- 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 (V8)

- 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 (V8)

For subjects who discontinued their randomised treatment, the number of episodes in the missing period (time of follow-up 2 (V8) to planned end of the on-treatment period) will be imputed using a multiple imputation technique, assuming that the event rate pre follow-up 2 (V8) follows the respective treatment groups rate whilst post follow-up 2 (V8) event rate is the rate of the basal insulin analogues group. The imputation will be done as follows:

- First, a Bayes negative binomial model with log-link function will be fitted to the event rate data to obtain the posterior distribution of model parameters. The model will include region and randomised treatment as fixed factors and the logarithm of the on-treatment period as offset.
- Second, based on the estimated parameters for the basal insulin analogues 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.

For the definition and classification of hypoglycaemic episodes refer to Appendix 8 (Section 10.8).

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

9.4.4 Exploratory endpoints

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

9.4.5 Other safety analyses

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

9.4.6 Other analyses

For other analyses, please refer to the SAP.

9.5 Interim analyses

Not applicable for this trial.

9.6 Data monitoring committee

Not applicable for this trial.

9.7 Reporting of the main part of the trial

Not applicable for this trial.

10 Supporting documentation and operational considerations

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

10.1.1 Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[22] and applicable ICH Good Clinical Practice (GCP) Guideline[23] and ISO 14155[12]
- 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[23], Declaration of Helsinki[22], ISO 14155[24] and the IRB/IEC or site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form*(s)* during their participation in the trial.
- A copy of the informed consent form*(s)* must be provided to the subject.

10.1.4 Information to subjects during trial

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

All written information to subjects must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

10.1.5 Data protection

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the subject are transferred to Novo Nordisk.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.
- The subject must be informed about his/her privacy rights, including that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the subject.

- The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

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

10.1.6.2 Data monitoring committee

Not applicable for this trial.

10.1.6.3 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)[25], the Food and Drug Administration Amendment Act (FDAAA)[26], European Commission Requirements[27-29] and other relevant recommendations or regulations. If a subject request to be included in the trial via the Novo Nordisk e-mail contact at these websites, 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) + 52 weeks corresponding to visit V6. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit V6. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.

- All subject data relating to the trial will be recorded on electronic CRFs (eCRFs) unless transmitted electronically to Novo Nordisk (e.g. laboratory, DoseGuide System data and eDiary data) or when applicable on paper CRF. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

- The following will be provided as paper CRFs to be used when access to the eCRF is revoked or the eCRF is temporarily unavailable:
    - AE forms
    - Safety information forms
    - Technical complaint forms (also to be used to report complaints on trial product not yet allocated to a subject)
    - Device deficiency that could have led to an SAE form

- Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

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

10.1.8.2 Monitoring

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.

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

10.1.8.3 Protocol compliance

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

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

10.1.9 Source documents

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

- Data in the service providers' database e.g. ePROs, eDiary data and DoseGuide System data, is considered source data.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data reported on the paper CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify subject's medical history in source documents, such as subject's medical record
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical trial documentation

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

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

10.1.11 Trial and site closure

Novo Nordisk reserves the right to close the site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

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

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

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

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

10.1.12 Responsibilities

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

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

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

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

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

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

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

10.1.13 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the trial or by persons for whom the said site or investigator are responsible.

10.1.14 Publication policy

The information obtained during the conduct of this trial is considered confidential and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial.

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

Novo Nordisk may publish on its clinical trials website a redacted 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.[30]

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, V3, V4, V5, V6, V6A)	• HbA_{1c}

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology (V1, V6, V6A)	• Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Thrombocytes • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils
Biochemistry[1] (V1, V6, V6A)	• Alanine Aminotransferase (ALT) • Albumin • Alkaline phosphatase • Aspartate Aminotransferase (AST) • Creatinine • Potassium • Sodium • Total bilirubin
Lipids (V2, V6, V6A)	• Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol

	• Triglycerides • Free fatty acids
Pregnancy Testing (V2, V8)	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]
Other tests	• In case of systemic hypersensitivity (see section 8.9.1): 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. • eGRF calculated by the central laboratory based on the creatinine value using the CKD-EPI equation, eGRF is for screening purposes only.
Notes: [1]Details of required actions for increased liver parameters-are given in Section 10.3 (Hy's Law). [2]Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.	

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

For definitions and procedure for recording, evaluation, follow-up and reporting concerning the investigational medical device (DoseGuide System), please refer to Appendix 6 (Section 10.6)

10.3.1 Definition of AE

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

Events 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 event(s) for adjudication and AEs requiring additional data collection

Description of event(s) for adjudication-and AEs requiring additional data collection (on specific event form)
Events for adjudication An event for adjudication is a selected AE or death evaluated by an independent external EAC in a blinded manner, please refer to Section 10.1.6.3, Table 8-1 and Figure 10-1. • Death   • All cause death • Acute coronary syndrome

- All types of acute myocardial infarction and unstable angina pectoris requiring hospitalisation
- Cerebrovascular event (stroke or transient ischemic attack)
  - Episode of focal or global neurological dysfunction that could be caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or ischemia, with or without infarction
- Heart failure (requiring hospitalisation or urgent outpatient clinic visit due to heart failure)
  - 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[31]. 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[32]. 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[33]. 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 of systemic hypersensitivity must be reported, and in case of systemic hypersensitivity, additional information must be provided on a separate form.

Medication error

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

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

Misuse and abuse

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

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

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

AE and SAE recording

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

Assessment of severity
The investigator will assess severity for each event reported during the trial and assign it to one of the following categories: • **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. • **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities. • **Severe**: An event that prevents normal everyday activities. Note: An AE that is assessed as severe should not be confused with a SAE. Both AEs and SAEs can be assessed as severe.

Assessment of causality

• The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE.
• Relationship between an AE/SAE and the relevant IMP(s) should be assessed as:
  • Probable - Good reason and sufficient documentation to assume a causal relationship.
  • Possible - A causal relationship is conceivable and cannot be dismissed.
  • Unlikely - The event is most likely related to aetiology other than the IMP.
• Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
• The investigator should use the investigator's brochure for insulin icodec and insulin degludec and the EU SmPC, US PI or locally approved label for non-Novo Nordisk marketed products (insulin glargine U100 and U300) 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 and potential Hy´s law). This may include additional laboratory tests (e.g. skin prick test or blood samples) or investigations, histopathological examinations, or consultation with other health care professionals (e.g. liver specialist). If a subject dies during participation in the trial or during a recognised follow-up period, Novo Nordisk may request a copy of the autopsy report including histopathology. New or updated information will be recorded in the CRF.

10.3.5 Reporting of SAEs

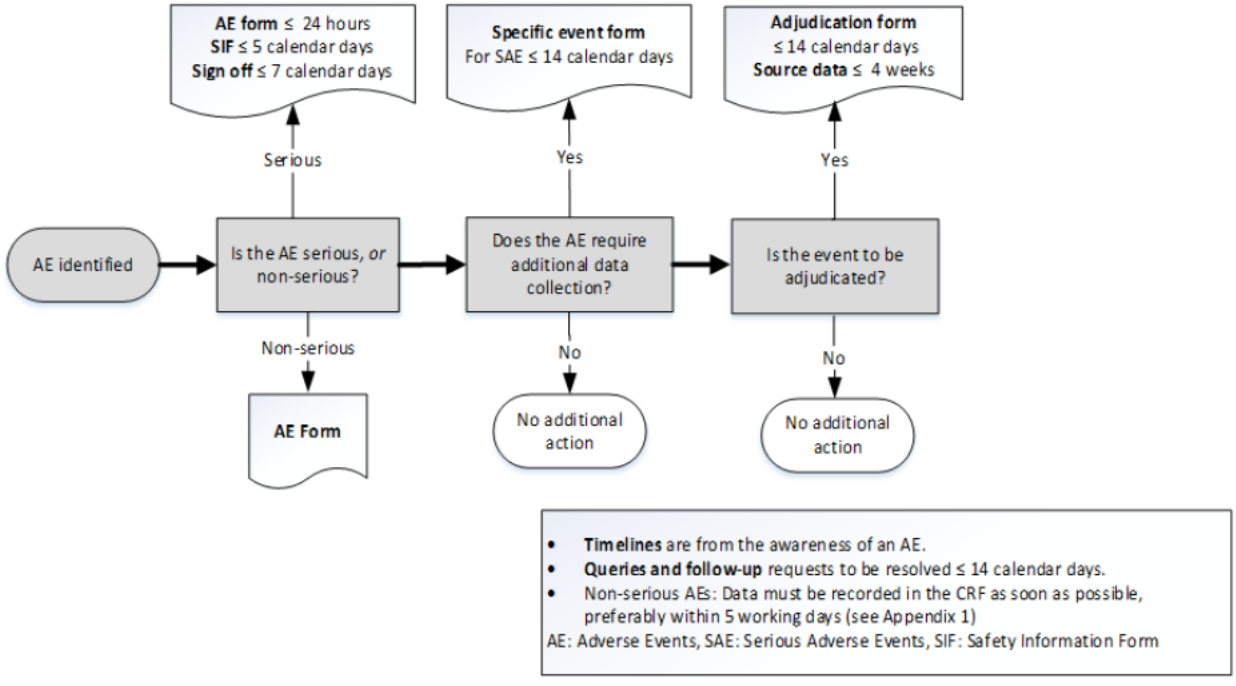
SAE reporting via electronic CRF
• Relevant forms (AE, safety information form and event specific forms if applicable) must be completed in the eCRF. • For reporting and sign-off timelines, see Figure 10-1 below. • If the eCRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the eCRF is unavailable for more than 5 calendar days, then the site will use the paper safety information form (see box below). • The site will enter the SAE data into the eCRF 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 and event specific form (see box below) or to Novo Nordisk by telephone.

AE and SAE reporting via paper CRF

- Relevant CRF forms (AE, safety information form and applicable event specific forms) 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
- All forms must be signed within 7 calendar days after first knowledge by the investigator.
- The specific event form for AEs requiring additional data collection within 14 calendar days

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



Source data should be in accordance with Section 8.3

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-Chek® BG meter: All complaints related should be reported directly to the manufacturer of the medical device. Related AEs should be reported directly to the manufacturer and in the eCRF.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of childbearing potential (WOCBP)

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

Females in the following categories are not considered WOCBP

7. Premenarcheal
8. 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.

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

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

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, insulin glargine or insulin degludec in seminal fluid is unlikely[34].

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 below. As a minimum, contraception should be maintained until treatment discontinuation.

Table 10-3 Acceptable contraceptive methods

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:
ACCEPTABLE EFFECTIVE 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 (Appendix 9, Section10.10).
- WOCBP should only be included after a negative highly sensitive urine pregnancy test (refer to Appendix 2, Section 10.2).
- A pregnancy test should be performed at the end of relevant systemic exposure (refer to Appendix 2, Section 10.2 and the trial flow chart Section 1.2).
- Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.

Collection of pregnancy information

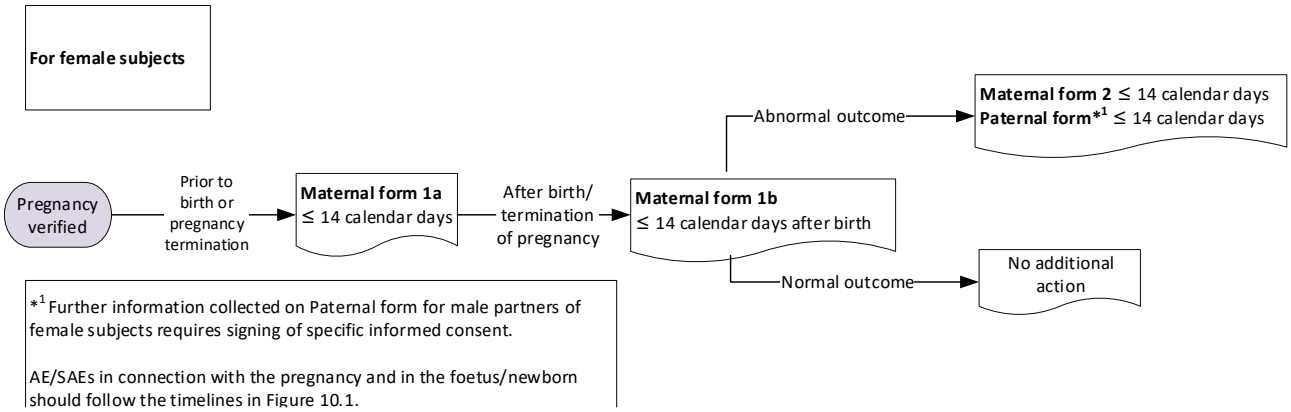
Female subjects who become pregnant

- 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 subject's pregnancy (see Figure 10-2).
- Subject will be followed to determine the outcome of the pregnancy. The investigators will collect follow-up information on subject and neonate which will be forwarded to Novo

Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.

- Any termination of pregnancy will be reported regardless of the foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding "gestational", "pregnancy related" or similar term when reporting the AE/SAE.
- Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.
- AE/SAE in foetus or newborn child can only be reported on paper AE form and SIF and should follow the timelines in Figure 10-1.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possible/probably related to the IMP by the investigator will be reported to Novo Nordisk as described in Appendix 3 (Section 10.3) . While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

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



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

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

10.5.1 Definition of technical complaint

Technical complaint definition
• A technical complaint is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself. • Technical complaints include the definition of device deficiency, please refer to Appendix 6, Section10.6.

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 the pen-injectors (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen-injector and the needle)
- Problems with the DoseGuide System (e.g. delayed response from the DoseGuide App)

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

10.5.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk
Contact details for Customer Complaint Center, please refer to Attachment I. Technical complaints must be reported on a separate technical complaint form: 1. One technical complaint form must be completed for each affected DUN or technical complaint case for the DoseGuide System. 2. For the investigational medical device (DoseGuide System) evaluate on the technical complaint form if the technical complaint could have led to an SAE. If the technical complaint on an investigational medical device could have led to an SAE, a specific form (Device deficiency that could have led to SAE) must be completed as described in Appendix 6, Section 10.6. If the technical complaint is considered a Use Error (see 10.6.3), the Device Use Error form must be completed.

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within: • 24 hours if technical complaint related to an SAE - 24 hours if technical complaint could have led to an SAE for DoseGuide System • 5 days calendar for all other technical complaints

If the CRF is unavailable, or when reporting a technical complaint on a trial product that is not yet allocated to subject, the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

Follow-up of technical complaints
The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples (except for the DoseGuide System)
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 products not included in technical complaint form
Technical complaints on products not included in the technical complaint form should be reported to local manufacturing authorisation holder.

10.6 Appendix 6: Medical device adverse events, adverse device effects, serious adverse events and device deficiencies: Definition and procedures for recording, evaluating, follow-up, and reporting

10.6.1 Definition of AE and adverse device effects (ADE)

AE and ADE definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in trial subjects, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved, except for events in users or other persons which only include events related to investigational medical devices. • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.6.2 Definition of SAE, serious adverse device effect (SADE) and unanticipated serious adverse device effect (USADE)

An SAE is an AE that:
a. Led to death
b. Led to serious deterioration in the health of the subject that either resulted in: A life-threatening illness or injury. 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. A permanent impairment of a body structure or a body function including chronic diseases. Inpatient or prolonged hospitalization, planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
SADE definition
A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a SAE.
USADE definition
• An USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment analysis report (see Section 2.3). • Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

10.6.3 Definition of device deficiency

Device deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling. Device deficiency is part of technical complaint definition, please refer to Appendix 5.
Use Error definition
• A use error is an act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. • Use error includes slips, lapses, and mistakes. • An unexpected physiological response of the subject does not in itself constitute a use error.

10.6.4 Recording and follow-up of AE and/or SAE and device deficiencies

AE, SAE and device deficiency recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the subject's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF. • For device deficiencies, it is very important that the investigator describes any corrective actions taken to prevent recurrence of the event.
Assessment of intensity
The investigator will make an assessment of intensity for each AE/SAE 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. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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

- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial product administration, will be considered and investigated.
- The investigator will also consult the investigator’s brochure, for marketed products, in his/her 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 for AE or SAE.
- There may be situations in which an AE/SAE has occurred, and the investigator has minimal information to include in the initial report to Novo Nordisk. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.
- The investigator may change his/her opinion of causality in light of follow-up information and send an AE/SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

AE/SAEs should be classified according to four different levels of causality:
1. Not related
2. Possible
3. Probable
4. Causal relationship

1. Not related: Relationship to the device, comparator or procedures can be excluded when:
    - the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
    - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
    - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
    - the event involves a body-site or an organ that cannot be affected by the device or procedure;
    - the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
    - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

2. Possible: The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

3. Probable: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship: the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
   - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has a temporal relationship with investigational device use/application or procedures;
   - the event involves a body-site or organ that
     - the investigational device or procedures are applied to;
     - the investigational device or procedures have an effect on;
   - the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
   - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
   - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
   - harm to the subject is due to error in use;
   - the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

•

Follow-up of AE/SAE/device deficiency

- 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/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to Novo Nordisk within 24 hours of receipt of the information.

10.6.5 Reporting of SAEs

SAE reporting to Novo Nordisk via paper CRF
Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk in accordance with Section 10.1.8.1. Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting time frames: • AE form within 24 hours • Safety information form within 5 calendar days • Device deficiency that could have led to SAE form within 24 hours • All above forms must be signed within 7 calendar days after first knowledge by the investigator.

10.6.6 Reporting of device deficiencies

Reporting to Novo Nordisk
NOTE: There are additional reporting obligations to notify appropriate regulatory authorities and other entities about certain safety information for device deficiencies that could have led to SAEs. The investigator must therefore indicate on the technical complaint form if a technical complaint (device deficiency) could have led to an SAE and complete an additional form (Device deficiency that could have led to an SAE) with details. For reporting timelines, please refer to Appendix 5 (Section 10.5).

10.7 Appendix 7: Retention of human biosamples

Hypersensitivity reaction samples

In case of a systematic hypersensitivity reaction, the additional blood samples taken in relation to the reaction (please refer to section 8.9.1) 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 patient 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.

10.8 Appendix 8: 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[35], ADA[36], ISPAD[37], type 1 diabetes outcomes program[38], ATTD[39]. Severe hypoglycaemia as defined by Seaquist[40] and ISPAD[37].		

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.[40]

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[36]

Nocturnal hypoglycaemia

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

Reporting of hypoglycaemic episodes by BG Meters

Plasma glucose (PG) should always be recorded in the eDiary when a hypoglycaemic episode is suspected.

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 eDiary HCP 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, relevant eCRF forms (AE form and a safety information form) must also be filled in. One AE form 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.[40]

Repeated PG measurements and/or symptoms will by default be considered as one hypoglycaemic episode until a succeeding PG value is ≥ 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved and should be reported as only one hypoglycaemic episode. 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 and/or symptom. 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.[40]

eDiary review

At each contact the investigator should review the eDiary data via the HCP web portal 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 and report accordingly.

For non-serious hypoglycaemic episodes in the insulin icodec arm related to the DoseGuide System, see Appendix 5, Section10.5.

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.

10.9 Appendix 9: Titration guideline

Introduction

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

Initiation of trial products

At randomisation eligible subjects will be randomised to receive once weekly insulin icodec or once daily basal insulin analogue, pre-specified by the investigator at screening.

- ***Insulin icodec*** should be taken once weekly on the same day of the week. The starting dose should be 70U.
- ***Insulin glargine U100 or U300 or Insulin degludec*** (once daily basal insulin analogues) should be taken once daily in accordance with the locally approved label.
- There are no maximum or minimum insulin doses.

Titration of once daily basal insulin analogues

Titration of once daily basal insulin analogue comparators is at the discretion of the investigator according to local clinical practice. The recommended doses for all once daily basal insulin analogues will be based on the locally approved label.

Use of titration assistant applications or other tools is at the discretion of the investigator.

Titration of insulin icodec

Titration of insulin icodec should be guided by the DoseGuide System. In case of temporary suspension of the DoseGuide System, titration of insulin icodec can be done in accordance with the guidance outlined below.

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

After randomisation insulin icodec should be considered adjusted once weekly:

- The dose adjustment will be based on three pre-breakfast SMPG values measured on two day prior to titration and on the day of contact.
- If one or more SMPG values are missing, the dose adjustment should be performed on the remaining SMPG value(s)

Table 10-5 Insulin icodec

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

Deviations from the algorithms

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

Missing insulin icodec dose guidance

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

Dose recommendation from end of treatment and during follow up

If it is decided that the individual subject should continue basal insulin after end of treatment, it is recommended that the subject is switched from insulin icodec to any available basal insulin at the discretion of the investigator. The investigator should instruct the subject in how to switch at the end of treatment visit (V6).

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

- Calculate the new daily basal insulin dose dividing the latest insulin icodec dose by 7
- Initiate the new daily basal insulin **two weeks** after the last injection of insulin icodec
- Continue to measure pre-breakfast SMPG daily in the follow up period. If pre-breakfast SMPG exceeds 10.0 mmol/L (180 mg/dL), it should be considered to initiate the daily basal insulin dose earlier than two weeks after the last dose of insulin icodec
- Consider titrating the basal insulin once or twice weekly according to the pre-breakfast SMPG values and the local label of the chosen insulin.

Data surveillance

It is important that data regarding dose titration is reported in the eDiary or DoseGuide App (see Section 8.2.1).

10.10 Appendix 10: Country-specific requirements

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.
- **Contraception requirements:** Contraception requirements as per CTFG guideline.

For Hungary

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

For Poland

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

For Turkey

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

For USA

- **Retention of clinical trial documentation:** 15 years
- **Financial disclosure:** Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

10.11 Appendix 11: Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ASADE	anticipated serious adverse device effect
AST	aspartate aminotransferase
BG	blood glucose
CRF	case report form
CTR	clinical trial report
DFU	directions for use
DMC	data monitoring committee
DRE	disease related event
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
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HbA_{1c}	glycated haemoglobin
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
LDL	low-density lipoprotein
LSLV	last subject last visit
MIDF	monitor-initiated discrepancy form
NIMP	non-investigational medical product
PCD	primary completion date
PG	plasma glucose
PRO	patient reported outcome
RNA	ribonucleic acid

SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
TMM	trial materials manual
USADE	Unanticipated serious adverse device effect
WOCBP	woman of child bearing potential

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