Cover Page for Protocol

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Official title of study:	A Study to Evaluate Flash Glucose Monitoring Based Titration of Once-weekly Insulin Icodec in Insulin-naïve Participants with Type 2 Diabetes
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Protocol

Protocol Title: A Study to Evaluate Flash Glucose Monitoring Based Titration of Once-weekly Insulin Icodec in Insulin-naïve Participants with Type 2 Diabetes

Substance: **Insulin icodec**

Universal Trial Number: U1111-1271-9296

IND Number 137406

.

Study phase: 3b

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Protocol attachment I and II country list of key staff and relevant departments and suppliers

1 Protocol summary

1.1 Synopsis

This is an interventional, multi-centre, single country, single arm, treat-to-target, and open-label study.

Rationale:

This is a 26-week study designed to explore the titration of once-weekly insulin icodec using flash glucose monitoring (FGM). The study will evaluate this titration method in insulin-naïve participants with type 2 diabetes (T2D) treated with non-insulin antidiabetic drugs, in whom the initiation of basal insulin is indicated. With combined use of once-weekly basal insulin icodec and exclusion of the need for self-measured blood glucose (SMBG) determinations by blood glucose meter to guide titration, increased convenience in basal insulin therapy is expected.

Overall, the findings of the current study will be important for providing guidance for titration of insulin icodec for patients with T2D using FGM device system.

Objectives, endpoints and estimand:

Primary objective

To explore the effect on glycaemic control of FGM-based titration of once-weekly insulin icodec in combination with non-insulin antidiabetic drugs in insulin-naïve individuals with T2D.

Key exploratory objective

To explore safety and glycaemic control including FGM-based metrics of once-weekly insulin icodec in combination with non-insulin antidiabetic drugs in insulin-naïve individuals with T2D.

Estimand

The primary clinical question of interest is to explore the glycaemic control in terms of change in glycated haemoglobin (HbA_{1c}) 26 weeks after initiation of FGM-based titration of once-weekly insulin icodec in combination with non-insulin antidiabetic drugs in insulin-naïve T2D patients in need of basal insulin therapy had these patients been able to adhere to both the FGM-based titration and the once-weekly insulin treatment.

The intercurrent event of discontinuing both once-weekly insulin icodec treatment and use of the FGM-based titration will be handled by the hypothetical strategy.

Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From initiation week 0 (V3) to week 26 (V26)	%-point

Abbreviation: HbA_{1c} = glycated haemoglobin.

Key exploratory endpoint

Endpoint title	Time frame	Unit
TIR 3.9-10.0 mmol/L (70-180 mg/dL)	From week 22 (P23) to week 26 (V26)	% of readings
TBR <3.0 mmol/l (54 mg/dL)	From week 22 (P23) to week 26 (V26)	% of readings
TAR >10.0 mmol/L (180mg/dL)	From week 22 (P23) to week 26 (V26)	% of readings

Abbreviations: TAR = time above range; TBR = time below range; TIR = time in range.

Overall design:

This interventional, multi-centre, single country, single arm, treat-to-target, open-label study will include 50 participants who will initiate once-weekly insulin icodec.

The study duration is approximately 35 weeks and consists of:
- an up to 2-week screening period
- a 2-week run-in period with FGM
- a 26-week intervention period with FGM
- a 5-week follow-up period with FGM

Study intervention groups and duration:

The study duration is approximately 35 weeks. All subjects will be assigned to receive once-weekly insulin icodec throughout the 26-week treatment period. After the end of study intervention visit, participants 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 study:
- Insulin icodec 700 units/mL, subcutaneous, solution for injection, 3 mL PDS290 pre-filled pen-injector

Number of participants:

Approximately 67 participants will be screened to achieve 50 subjects assigned to the trial product.

Participant characteristics:

Key inclusion criteria:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Age above or equal to 18 years at the time of signing informed consent.
3. Diagnosed with T2D ≥180 days before screening.
4. HbA_{1c} from 7.0%-11.0% (53.0-96.7 mmol/mol) both inclusive at screening confirmed by central laboratory analysis.
5. Insulin-naïve. However, short term insulin treatment for a maximum of 14 consecutive days before screening is allowed, as is prior insulin treatment for gestational diabetes.
6. Stable daily dose(s) ≥90 days before screening of any of the following antidiabetic drug(s) or combination regimen(s) at effective or maximum tolerated dose as judged by the investigator:
   - Any metformin formulations ≥1500 mg or maximum tolerated or effective dose or

- Any metformin combination formulations ≥1500 mg or maximum tolerated or effective dose or
- Other antidiabetic Drugs including combination products (≥half of the maximum approved dose according to local label or maximum tolerated or effective dose) of the classes specified below:
  - Sulfonylureas[b]
  - Meglitinides (glinides)[b]
  - Dipeptidyl peptidase-4 (DPP-4) inhibitors
  - Sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors
  - Thiazolidinedione
  - Alpha-glucosidase inhibitors
  - Oral combination products (for the allowed individual oral antidiabetic drugs
  - Oral or injectable glucagon-like peptide-1 (GLP-1) receptor agonists

[b]. Treatment with sulfonylureas and glinides must be discontinued at the initiation visit.

7. Intensification with basal insulin is indicated to achieve fasting glycaemic target (4.4-7.2 mmol/L; 80-130 mg/dL) at the discretion of the treating investigator.
8. Body mass index (BMI) ≤40.0 kg/m^2

Key exclusion criteria:

1. Unwilling or unable to avoid concomitant medication e.g., ascorbic acid (vitamin C) that can influence the FGM sensor throughout the study and contraindications e.g., implanted medical devices such as pacemakers.
2. Any episodes of diabetic ketoacidosis within 90 days before screening as declared by the participant or in the medical records.
3. Myocardial infarction, stroke, transient ischaemic attack or hospitalisation for unstable angina pectoris within 180 days before the day of screening and between screening and initiation visits.
4. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.
5. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g., treatment with orlistat, thyroid hormones, or corticosteroids).
6. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within 90 days before the day of screening or in the period between screening and initiation visits. Pharmacological pupil dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

Data monitoring committee: No

1.2 Flowchart

	Section	Screening	Run-in	Initiation	Treatment period							Follow-up	
Visit		V1	V2	V3	P4-P12	V13	P14-P20	V21	P22- P24	P25	V26	V27	V28
Timing of Visit (Weeks)		≥-4	-2	0	1-9	10	11-17	18	20-24	25	26	28	31
Visit Window (Days)	4.1	+10	+3	0	±3	±3	±3	±3	±3	±3	±3	+1	+1
SUBJECT RELATED INFORMATION AND ASSESSMENTS													
Informed Consent and Demography	10.1.3	X											
Eligibility Criteria	5.1, 5.2, 5.5	X	X	X									
Medical History/Concomitant Illness	8.2	X	X										
Concomitant Medication	6.8	X	X	X	X	X	X	X	X	X	X	X	X
Body Measurements	8.2.2	X									X		
Vital Signs	8.2.3	X									X		
Physical Examination	8.2.2	X									X		
Tobacco Use	5.3.2	X											
ECG	8.2.5	X									X		
Eye Examination	8.2.4	X									X		
Childbearing Potential	10.4.1	X											
Pregnancy Test	8.2.7	X		X									X
SAFETY													
Adverse Event	8.3, 10.3				X	X	X	X	X	X	X	X	X
Hypoglycaemic Episodes	10.6				X	X	X	X	X	X	X	X	X

	Section	Screening	Run-in	Initiation	Treatment period							Follow-up	
Visit		V1	V2	V3	P4-P12	V13	P14-P20	V21	P22- P24	P25	V26	V27	V28
Timing of Visit (Weeks)		≥-4	-2	0	1-9	10	11-17	18	20-24	25	26	28	31
Visit Window (Days)	4.1	+10	+3	0	±3	±3	±3	±3	±3	±3	±3	+1	+1
Laboratory Assessments	10.2	X		X		X		X			X		
HbA_{1c}	10.2	X		X		X		X			X		
TRIAL MATERIAL													
Drug Dispensing	6.2			X		X		X					
REMINDERS													
Training in trial product, pen-handling	6.1			X		X		X					
Hand out study phone and training in FGM system	6.1, 8.1.1		X										
FGM fitting	6.1, 8.1.1		X	X									
FGM compliance check	6.4, 8.1.1			X	X	X	X	X	X	X	X	X	
Hand out and instruct in BG-meter	6.1		X										
Hand out and instruct in diary	6.1			X									
Last dose on trial product	4.1									X			
End of study intervention	4.1, 7.1										X		
End of study	4.1												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 (2021),[2] the estimated worldwide diabetes prevalence was 537 million, with a prediction that by 2045, the number of people with diabetes will have increased to 784 million.

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

The FreeStyle Libre 2 Flash Glucose Monitoring System is an integrated continuous glucose monitoring device indicated for diabetes management in persons aged 4 or older. It is intended to replace self-measured blood glucose by blood glucose (BG) meters for diabetes treatment decisions. In addition, the system also detects trends and track patterns and aids the user in detecting hyperglycaemic and/or hypoglycaemic episodes and intended to communicate with digitally connected devices. The FreeStyle Libre 2 consists of a sensor that communicates during a scan to display device (reader or compatible mobile device) providing the user with real-time glucose measurement (current glucose value, trend arrow and historical glucose graph) for treatment decisions. The FreeStyle Libre 2 is used for intermittently scan continuous glucose monitoring, opposed to real time continuous glucose monitoring hereafter referred to as flash glucose monitoring (FGM).

With the expected rise in continuous glucose monitoring use among patients with T2D on basal only treatment, the Endocrine Society and American Association of Clinical Endocrinology (AACE) recommend continuous glucose monitoring over self-measured blood glucose (SMBG) measurements[4] and further note the reduced risk and frequency of hypoglycaemia.

2.1 Study rationale

This is a 26-week study designed to explore the FGM-based titration of once-weekly insulin icodec. The study will evaluate this titration method in insulin-naïve participants with T2D treated with non-insulin antidiabetic drugs, in whom the initiation of basal insulin is indicated. With combined use of once-weekly basal insulin icodec and exclusion of the need for SMBG determinations by BG meter to guide titration, increased convenience in basal insulin therapy is expected.

Overall, the findings of the current study will be important for providing guidance for titration of insulin icodec for patients with T2D using FGM device system.

2.2 Background

Diabetes mellitus

T2D is characterised by insulin resistance, impaired insulin secretion, increased hepatic glucose output due to glucagon dysregulation resulting in chronic hyperglycaemia.[5] The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver.[6] The current treatment cascade follows a stepwise approach comprising lifestyle changes in combination with pharmacological intervention. In many countries, metformin is recommended as initial pharmacological therapy, followed by combination therapy with other oral anti-diabetic drugs, glucagon-like peptide 1 receptor agonists (GLP-1 RA) and/or insulin as the disease progresses.[7] On average, after failure of diet and exercise alone, subjects require a new intervention with glucose-lowering agents every 3-4 years in order to obtain/retain good glycaemic control.[8] Clinical inertia, often resulting from a resistance to insulin initiation and intensification, is a major contributing factor to subjects with T2D who are not achieving recommended glycaemic targets.[9, 10] Increased convenience is believed to support timely insulin initiation in the treatment for T2D and thereby overcoming the clinical inertia associated with insulin initiation.

Insulin icodec

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

The development programme for insulin icodec is currently ongoing. Eight (8) clinical pharmacology studies, NN1436-4314 (T2D), NN1436-4226 (renal impaired), NN1436-4422 (T1D), NN1436--4462 (T2D), NN1436-4225 (T1D), NN1436-4569 (T2D), NN1436-4570 (hepatic impairment) and NN1436-4571 (Chinese participants with T2D) have been completed. Furthermore, three phase 3a trials have been completed (NN1436-4478, NN1436-4479 and NN1436-4480) and two have completed the main phase (NN1436-4477, NN1436-4625). No unexpected safety concerns were identified.

Three phase 2 studies in participants with T2D have 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 participants with T2D. Results from these studies were used in the development of the insulin icodec titration guideline (Appendix 7 [Section 10.7]).

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

Study population

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

For more information on the study population, see Sections 5, for more information regarding inclusion and exclusion criteria see Sections 5.1 and 5.2, respectively.

2.3 Benefit-risk assessment

The main benefits and risks related to participation in the study are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of insulin icodec may be found in the investigator's brochure (IB)[11].

2.3.1 Risk assessment

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

Table 2-1 Risk assessment

Identified/Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention (insulin icodec)		
Identified risk: Hypoglycemia	Hypoglycemia is an anticipated undesirable effect related to the pharmacological mechanism of insulin.	The risk of hypoglycaemia is mitigated with the use of an open 1 device throughout the study, providing interstitial glucose measurement at all times, glucose trending arrows and an alarm when glucose is measured below 55 mg/dL. Blood glucose measurements by BG meter will be recommended when participants experience symptoms of hypoglycaemia, if symptoms are not consistent with the flash glucose readings and during the first 12 hours of wearing each device. The risk of hypoglycaemia is addressed in the SI-IC and IB[11]. Subjects are provided with a guidance on hypoglycaemia awareness and rescue actions.

Identified/Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Identified risk: Injection site reactions	Injection site reactions may occur with all injectable drugs. Injection site reactions were reported in the insulin icodec clinical phase 1, phase 2 and completed phase 3 trials.	Subjects are instructed by the investigators on the most appropriate injection techniques. Recommendations on rotation of the site of injection are included in the trial protocol and SI-IC. Investigators and subjects will be instructed to monitor for injection site reactions at the place of injection for early detection. Investigators should ensure careful monitoring and medical evaluation in case of injection site reaction occurrence. The risk of injection site reactions is described in the IB[11] and the SI-IC.
Identified risk: Hypersensitivity	Hypersensitivity reactions may potentially occur following injection of therapeutic proteins. Reactions have been observed in previous insulin icodec trials.	Known or suspected hypersensitivity to trial product(s) or related products is an exclusion criterion in the clinical trial. Subjects and investigators will be instructed in signs and symptoms of hypersensitivity reactions and subjects will be instructed to contact the site immediately in case of signs of systemic hypersensitivity. The risk of hypersensitivity reactions is described in the IB[11] and SI-IC.
Identified risk: Peripheral Oedema	Insulin, including insulin icodec, may cause sodium retention and oedema. In the clinical development programme, events of peripheral oedema were observed in trial subjects treated with insulin icodec.	Subjects and investigators will be instructed in signs and symptoms of peripheral oedema. Risk of peripheral oedema is described in the IB[11] and SI-IC.
Potential risks: Immunological events – formation of neutralising insulin antibodies	Antibodies to exogenously delivered insulin are common with insulin treatment but are not often clinically significant.	Investigators will closely monitor the glycaemic control of each participant throughout the trial. In case lack of clinical effect is observed, rescue medication will be provided if deemed necessary and subject is to discontinue the study intervention (Section 7.1) The risk of antibody formation leading to change in clinical effect is described in the IB[11] and SI-IC. For more information, please refer to Section 7.1

Identified/Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	In NN1436-4478, -4479, -4480 and -4625 the number of subjects that developed anti-insulin icodec antibodies at any time during the trial was between 70.2% and 79.0%, of which the large majority had antibodies cross-reacting with human insulin (67.9% to 77.4% of the total). In N1436-4478, -4479 and -4480 no significant correlation between the change of anti-insulin icodec antibodies titre from baseline to follow up and rate of severe (level 3) or clinically significant (levels 2) hypoglycaemia has been found. Results for NN1436-4625 still pending. No apparent relationship between antibody titres and change in HbA1c or weekly insulin dose was observed.	
Study 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 areas. To minimize the risk as much as possible, the following measures have been taken: • Cautious subject recruitment planning ensures controlled subject enrolment in countries where the COVID-19 pandemic is evaluated to be sufficiently under control, and at sites where health care resources are evaluated to be adequate. • On-site visits will be well-prepared and as short as possible. Physical contact between subjects and site staff will be limited to the extent possible, and protective measures will be implemented (e.g., use of masks, sanitizers, no aerosol-generating procedures etc. according to the local practice).
Other		
For more information regarding the known and expected benefits and risks of the FreeStyle Libre 2 FGM system, please refer to the locally approved user guide.		

Abbreviations: BG = blood glucose; COVID-19 = Corona virus Disease-2019; FGM = flash glucose monitoring; HbA_{1c} = glycated haemoglobin; IB =-investigator brochure; SI-IC = subject information-inform consent.

2.3.2 Benefit assessment

Insulin icodec is currently in development for treatment of diabetes mellitus. In both clinical and non-clinical trials, insulin icodec has shown to have a long and stable pharmacokinetic (PK) and pharmacodynamic (PD) profile, supporting a once-weekly treatment. Currently available long-acting basal insulin products need to be administered once-daily to provide 24-hour coverage. Market research has shown that people with diabetes, put value in reducing the number of insulin injections[12]. Therefore, the treatment adherence and quality of life are expected to increase by introducing a once-weekly basal insulin treatment. Furthermore, FGM devices aid detecting hyperglycaemic and/or hypoglycaemic episodes and thereby promote mitigation of these risks. FGM devices are intended to replace BG meters for diabetes treatment decisions and by combining the use of once-weekly basal insulin icodec and exclusion of SMBG measurements, increased convenience in basal insulin therapy is expected.

The trial population will consist of insulin-naïve subjects with T2D. For all subjects participating in this 26-week trial, the anticipated benefits include improved glycaemic control. The titration algorithm (Appendix 7, Section 10.7), which specifies recommended adjustments of basal insulin dose at different interstitial glucose levels, will be used to support physician's decisions. Subjects will receive intense medical care by means of contact with the sites weekly or every other week.

2.3.3 Overall benefit-risk conclusion

Insulin icodec is efficacious at clinically relevant doses. FGM-based titration of insulin icodec aims to achieve good glycaemic control without increasing the risk of hypoglycaemic events.

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

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

More detailed information about the known and expected benefits and risk of insulin icodec can be found in the IB[11].

3 Objectives, endpoints and estimand

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	Title	Time frame	Unit
• To explore the effect on glycaemic control of FGM-based titration of once-weekly insulin icodec in combination with non-insulin antidiabetic drugs in insulin-naïve individuals with T2D.	Primary:		
	• Change in HbA_{1c}	From initiation week 0 (V3) to week 26 (V26)	%-point
Exploratory	Title	Time frame	Unit
• To explore safety and glycaemic control including FGM-based metrics	Exploratory		
	• Number of severe hypoglycaemic episodes (level 3)	From initiation week 0 (V3) to week 26 (V26)	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 initiation week 0 (V3) to week 26 (V26)	Number of episodes
	• Mean weekly insulin dose	From week 24 (V24) to week 26 (V26)	U
	• TIR 3.9-10.0 mmol/L (70-180 mg/dL)	From week 22 (P23) to week 26 (V26)	% of readings
	• TBR <3.0 mmol/l (54 mg/dL)	From week 22 (P23) to week 26 (V26)	% of readings
	• TAR >10.0 mmol/L (180mg/dL)	From week 22 (P23) to week 26 (V26)	% of readings
	• Participant achieved treatment target of HbA_{1c} <7 % (Yes/No)	Week 26 (V26)	Count of participant

Abbreviations: BG = blood glucose; FGM = flash glucose monitoring; HbA_{1c} = glycated haemoglobin; T2D = type 2 diabetes; TAR = time above range; TBR = time below range; TIR = time in range.

Primary estimand

The primary clinical question of interest is to explore the glycaemic control in terms of change in glycated haemoglobin (HbA_{1c}) 26 weeks after initiation of FGM-based titration of once-weekly insulin icodec in combination with non-insulin antidiabetic drugs in insulin-naïve T2D patients in need of basal insulin therapy had these patients been able to adhere to both the FGM-based titration and the once-weekly insulin treatment.

The intercurrent event of discontinuing both once-weekly insulin icodec treatment and use of the FGM-based titration will be handled by the hypothetical strategy.

4 Study design

4.1 Overall design

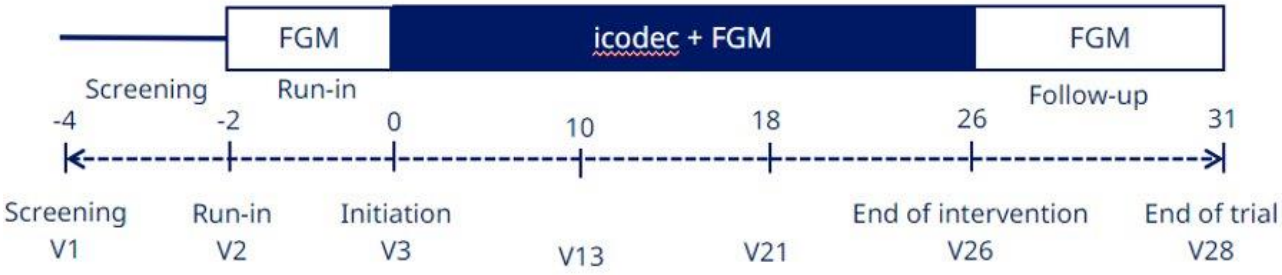
This is an interventional multi-centre, single country, single arm, treat-to-target, and open-label study. The study is designed to explore the initiation and titration of once-weekly insulin icodec using FGM device system in combination with non-insulin antidiabetic drugs in insulin-naïve participants with T2D. The study will include 50 participants who will initiate the trial product.

The study duration is approximately 35 weeks and consists of:

- an up to 2-week screening period
- a 2-week run-in period with FGM
- a 26-week intervention period with FGM
- a 5-week follow-up period with FGM

The overall study design is outlined in Figure 4-1 and the detailed visit schedule can be found in the flowchart (Section 1.2).

Figure 4-1 Study design



The study will include:

- Screening visit (V1)
- Run-in visit (V2)
- Initiation[a] visit (V3)
- Phone contacts (P4-12) each week from study initiation to week 18 (V21)
- Dedicated onsite visits at week 10 (V13) and week 18 (V21)
- Phone contacts (P14-20) each week between week 11 (P14) to week 18 (V21)
- Phone contacts (P22-25) every second week from week 18 (V21) to end of study intervention (V26)
- Dedicated phone contact (P25) for last dose one week before end of study intervention.
- Dedicated end of study intervention visit (V26) at week 26, scheduled one week after last dose of insulin icodec
- 2 follow-up visits for continued adverse event (AE) collection visits (V27 and V28) at week 28 and week 31. The last follow-up, which is the end of study visit (V28) at week 31, is scheduled to take place 6 weeks after the last insulin icodec dose, i.e., 5 weeks after end of study intervention visit (V26) at week 26.

a. The initiation visit is same as enrolment as in RTSM/IWRS.

Potential eligible participants will be identified by the investigator and all eligible participants should be provided the participant information/informed consent document and asked if they would like to participate in the study. The investigator will have determined the participant eligibility for treatment with basal insulin prior to informed consent.

For treat-to-target monitoring of continuous glucose and for insulin titration decisions throughout study intervention, Novo Nordisk will provide all participants with a FGM device system. For titration guidance see Appendix 7, Section 10.7.

Throughout the study, the investigator will remind the participants to follow the study procedures and requirements, to ensure participants compliance. The investigator should retrain participants when needed and assess the compliance at each contact (visit or phone) by evaluating the glycaemic control, wearing of the FGM, adherence to the visit schedule and completion of the participants diary, including FGM values for titration, dose, and hypoglycaemia reporting. If a participant is found to be non-compliant, the investigator will remind the participant to ensure compliance.

Treatment with sulfonylureas and glinides must be discontinued at the initiation visit (V3) at week 0.

If either/both insulin icodec treatment and use of FGM system are permanently discontinued, the participant should be asked to attend the end of study intervention visit corresponding to visit 26 as soon as possible and have the follow-up visits (V27 and V28) scheduled 3 and 6 weeks after their last insulin icodec dose.

4.2 Scientific rationale for study design

The study is designed to explore the FGM based titration of once-weekly insulin icodec in combination with non-insulin antidiabetic drugs in insulin-naïve participants with T2D.

To explore the impact of FGM-based titration of insulin icodec on glycaemic control, change in HbA_{1c} from baseline to end of study intervention was chosen as primary endpoint. To further explore the impact on glycaemic control, the achievement of an HbA_{1c} value below 7% was chosen as an exploratory endpoint. This is in line with the American Diabetes Association (ADA) recommendation that the glycaemic target for non-pregnant adults with diabetes is an HbA_{1c} value below 7.0% and lowering HbA_{1c} below or around 7.0% has been shown to reduce microvascular complications and macrovascular disease.[13]

The addition of a continuous glucose monitoring positively influences the diabetes management, measured by improvements in HbA_{1c} and time in range (TIR).[14] This study employs a run-in period of 2 weeks before initiating insulin icodec treatment to ensure patients are familiar with the use of the FGM system. Due to the long half-life, the effect of insulin icodec may persist longer than compared to previous once-daily basal insulin – including possible hypoglycaemic episodes. The FGM system will therefore be used throughout the follow-up period for better monitoring of the glucose lowering effect of insulin icodec.

The treatment duration of 26 weeks is evaluated to be adequate time for assessing effect on glycaemic control and safety. This duration will also allow for up-titration of insulin icodec. The

treat-to-target approach has been chosen in order to ensure optimal titration of insulin icodec based on FGM values with the aim of improving HbA_{1c} in the period.[15]

Titration of insulin icodec should be conducted in accordance with the titration guideline, see Appendix 7 (Section 10.7) where three pre-breakfast FGM measurements will be used to titrate insulin icodec.

FGM system will provide ongoing data on interstitial glucose allowing remote monitoring of glycaemic control. The visit frequency has been designed to meet data collection requirements along with sufficient AE collection to comply with phase 3 requirements is ensured.

During the study intervention period, the participants will have dedicated site visits at 10 and 18 weeks of treatment. In addition, weekly phone contacts (P4-P12 and P14-P20) are scheduled until week 18 (V21) after which, phone contacts are scheduled for every second week (P22-24). A final dedicated phone contact at week 25 (P25) is scheduled to ensure last dose of trial product one week before end of study intervention at week 26 (V26). The last follow-up, which is the end of study visit (V28), is planned to be 5 weeks after the last dose of insulin icodec, allowing appropriate time for wash-out of the study drug, following at least 5 half-lives of insulin icodec. Additional site visits or phone contacts according to local clinical practice or individual need are an option throughout the study period.

The study population will be restricted to insulin-naïve participants on current treatment with non-insulin antidiabetic drugs and/or non-insulin injectables. Pre-study treatment with all non-insulin antidiabetic drugs is allowed, however, to decrease the risk of hypoglycaemia, sulfonylureas and glinides must be discontinued at the initiation visit.

The defined inclusion and exclusion criteria will limit the study population to participants without advanced co-morbidity and/or unstable diabetic eye disease. This is to avoid compromising the safety of the study participants. The HbA_{1c} limits of 7.0%-11.0% (53.0-85.8 mmol/mol) have been chosen to include participants needing intensification of their antidiabetic treatment.

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

4.2.1 Patient input into design

Not applicable for this study.

4.3 Justification for dose

Insulin icodec should be initiated at 70 U once-weekly. One (1) U of insulin icodec has similar glucose lowering effect as 1 U of a once-daily basal insulin with 100 U/mL. Therefore, once-weekly dosing corresponds to seven times the daily dose of a once-daily basal insulin.

The PK/PD properties of insulin icodec following 5 weeks of once-weekly dosing in participants with T2D (study 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 participants 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 U/kg).

Initiation and titration of insulin icodec should be conducted in accordance with the titration guideline aided by the FGM system, see Appendix 7 (Section 10.7).

4.4 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit.

The primary endpoint is evaluated at visit 26 (week 26). The primary completion date (PCD) is defined as the date of visit 26 (week 26) on which the last participant in the clinical study has an assessment for the primary endpoint. If the last participant is withdrawn early, the PCD is considered the date when the last participant would have completed visit 26. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to Food and Drug Administration Amendment Act (FDAAA) (Section 10.1.7).

5 Study population

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

Pre-screening is defined as review of the patient medical records, including handing out participant information, as well as database review. Any pre-screening activities must be documented on site by the investigator.

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Age above or equal to 18 years at the time of signing informed consent.
3. Diagnosed with T2D ≥180 days before screening.
4. HbA_{1c} from 7.0%-11.0% (53.0-96.7 mmol/mol) both inclusive at screening confirmed by central laboratory analysis.
5. Insulin-naïve. However, short term insulin treatment for a maximum of 14 consecutive days before the day before screening is allowed, as is prior insulin treatment for gestational diabetes.
6. Stable daily dose(s) ≥90 days before screening of any of the following antidiabetic drug(s) or combination regimen(s) at effective or maximum tolerated dose as judged by the investigator:
   - Any metformin formulations ≥1500 mg or maximum tolerated or effective dose or
   - Any metformin combination formulations ≥1500 mg or maximum tolerated or effective dose or
   - Other antidiabetic Drugs including combination products (≥half of the maximum approved dose according to local label or maximum tolerated or effective dose) of the classes specified below:
     - Sulfonylureas[b]
     - Meglitinides (glinides)[b]
     - Dipeptidyl peptidase-4 (DPP-4) inhibitors
     - Sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors
     - Thiazolidinedione
     - Alpha-glucosidase inhibitors
     - Oral combination products (for the allowed individual oral antidiabetic drugs
     - Oral or injectable glucagon-like peptide-1 (GLP-1) receptor agonists

[b]. Treatment with sulfonylureas and glinides must be discontinued at the initiation visit.

7. Intensification with basal insulin is indicated to achieve fasting glycaemic target (4.4-7.2 mmol/L; 80-130 mg/dL) at the discretion of the treating investigator.
8. Body mass index (BMI) ≤40.0 kg/m^2.
9. Able and willing to adhere to the protocol including wearing FGM sensor provided based on the Investigator's judgment.

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

1. Known or suspected hypersensitivity to study intervention(s) or related products.
2. Previous participation in this study. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using adequate contraceptive method, as defined in Appendix 4 (Section 10.4).
4. Participation (i.e., signed informed consent) in any interventional, clinical study within 90 days before the day of screening. Note: Simultaneous participation in a study 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 the day of screening in the current study.
5. Unwilling or unable to avoid concomitant medication e.g., ascorbic acid (vitamin C) that can influence the FGM sensor throughout the study and contraindications e.g., implanted medical devices such as pacemakers (see Section 6.8 for more information on concomitant medication).
6. Any disorder, except for conditions associated with type 2 diabetes mellitus, which in the investigator's opinion might jeopardise participants safety or compliance with the protocol.
7. Any episodes of diabetic ketoacidosis within 90 days before screening as declared by the participant or in the medical records.
8. Myocardial infarction, stroke, transient ischaemic attack or hospitalisation for unstable angina pectoris within 180 days before the day of screening and between screening and initiation visits.
9. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.
10. Planned coronary, carotid or peripheral artery revascularisation.
11. Renal impairment with estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73m^2 at screening.[16]
12. Impaired liver function, defined as Alanine Aminotransferase (ALT) ≥2.5 times or Bilirubin >1.5 times upper normal limit at screening.
13. Inadequately treated blood pressure defined as systolic ≥180 mmHg or diastolic ≥110 mmHg at screening.
14. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days before the day of screening. However, short term insulin treatment for a maximum of 14 consecutive days and prior insulin treatment for gestational diabetes are allowed.
15. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g., treatment with orlistat, thyroid hormones, or corticosteroids).
16. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within 90 days before the day of screening or in the period between screening and initiation visits. Pharmacological pupil dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.
17. Presence or history of malignant neoplasm or in situ carcinomas (other than basal or squamous cell skin cancer, low-risk prostate cancer, or in-situ carcinomas of the cervix or carcinoma in situ/high grade prostatic intraepithelial neoplasia) within 5 years before the day of screening as declared by the participant or in the medical records.

18. Use of any medication with unknown or unspecified content within 90 days before the day of screening.

5.3 Lifestyle considerations

While wearing the FGM sensor, participants will be asked to comply with requirements described in Section 8 "Study assessments and procedures".

5.3.1 Meals and dietary restrictions

Not applicable for this study.

5.3.2 Caffeine, alcohol and tobacco

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

5.3.3 Activity

Not applicable for this study.

5.3.4 Other restrictions

Not applicable for this study.

5.4 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently eligible for participation according to the inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants 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 performed in the system (Randomisation and Trial Supplies Management system [RTSM]/Interactive Web Response System [IWRS]).

Individuals who do not meet the criteria for participation in this study may not be rescreened. If the participant 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 parameter(s).

5.5 Run-in exclusion criteria, run-in failures, and initiation criterion

First dose must only be administered after baseline assessments related to primary and/or exploratory endpoints are completed.

5.5.1 Run-in exclusion criteria

The participant must be withdrawn from the study during the run-in period, if the following applies after screening and before or at initiation:

- Pregnancy
- Intention of becoming pregnant

- Participation in another clinical study of an approved or non-approved investigational medicinal product or device.
- Apparent intolerance or hypersensitivity to FGM sensor.

To be initiated, all run-in exclusion criteria must be answered “no”.

5.5.2 Run-in failures

Run-in failures are defined as participants who are not eligible to initiate trial product (i.e., has met one of the run-in exclusion criteria or has not met the initiation criteria).

A screen failure session must be made in the RTSM/IWRS and the end of study form must be completed in the electronic case report form (eCRF) together with the reason for not continuing in the study.

No follow-up visit should take place and no additional assessments are needed.

5.5.3 Initiation criterion

To initiate study treatment, the below initiation criteria must be answered “yes”:

- Participants able and willing to adhere to the protocol including requirements in regard to wearing the FGM sensor, based on the investigator’s opinion.

6 Study intervention(s) and concomitant therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Trial products comprise investigational medicinal products (IMPs), including placebo and comparators, non-investigational medicinal products (NIMPs) and/or investigational medical devices.

6.1 Study intervention administered

Table 6-1 (for the IMP) provides an overview of the study interventions.

Investigational medicinal products (IMP)

Table 6-1 Investigational medicinal product

Intervention name	Insulin icodec
Intervention type	IMP, test product
Pharmaceutical form	Solution for injection
Route of administration	Subcutaneous (into the thigh, upper arm or abdomen)
Trial product strength	700 U/mL
Recommended initial dose	70 U
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 kept. A rotation of injection site within the same area is recommended.
Sourcing	Manufactured and supplied by Novo Nordisk A/S
Packaging and labelling	• 3 mL PDS290 prefilled pen-injector • Labelled and packaged by Novo Nordisk A/S • Labelled in accordance with Annex 13[17], local regulations and study requirements

• Participants should administer insulin icodec at site at initiation visit (V3).

• Participants should be instructed to discard the needle after each injection and store the pen-injector without a needle attached.

For information on insulin icodec, please refer to the insulin icodec IB[11].

Abbreviations: IMP = investigational medicinal product; IB = investigator brochure.

Non-investigational medicinal products (NIMP)

Participants should continue their pre-study non-insulin antidiabetic background medication throughout the entire study, except for treatment with sulfonylureas and glinides, which must be discontinued at the initiation visit (V3). The dose and dosing frequency of pre-study non-insulin antidiabetic background medication should not be changed during the study unless due to safety concerns,

The background medication:

- is considered to be a NIMP.
- will not be provided by Novo Nordisk and should be purchased or otherwise delivered to participants in accordance with local health plans.
- should be used in accordance with standard of care or local label at the discretion of the investigator.

Training

The investigator must document that training in the directions for use (DFU) or manufacturer's user guide for all study interventions listed below, has been given to the participants orally and in writing.
At the run-in visit (V2):

- FGM system
- BG meter

At the initiation visit (V3).

- PDS290 prefilled pen-injector (direction for use [DFU])
- Diary

Training should be repeated if needed to ensure correct use of the study interventions.

Auxiliary supplies including medical devices not under investigation

Auxiliary supplies are listed in Table 6-2.

Table 6-2 Auxiliary supplies provided by Novo Nordisk A/S

Auxiliary	Model	Details	Manufacturer
Needles	NovoFine® needles or similar according to local requirements	Only needles with a maximum length of 6 mm provided and approved by Novo Nordisk must be used for administration of insulin icodec. Needles must be discarded after each injection and the pen-injector should be stored without a needle attached.	Novo Nordisk
FGM device	FGM system: FreeStyle Libre 2 sensor & FreeStyle Libre 2 mobile app on provisioned study phone	At the run-in visit (V2 [week -2]), participants must be instructed on how to use FGM system (Sensor + Libre 2 mobile app). The Libre 2 mobile app will be available on Novo Nordisk provisioned study phones. For further information on the FGM system, please refer to the manufacturer's guide provided.	Abbott Diabetes Care
BG meter (including auxiliaries)	FreeStyle Precision NEO Blood Glucose Monitoring System	At the run-in visit (week -2 [V2]), participants must be instructed on how to use the BG meter. For further information on the BG meter, please refer to the manufacturer's guide.	Abbott Diabetes Care
Study phone	iPhone	Novo Nordisk provided smartphone as carrier for Freestyle Libre 2 mobile app	Apple
Directions for Use		Directions for use will be provided for the insulin icodec 700 U/mL PDS290 pen-injector in paper format.	Novo Nordisk

Abbreviations: BG = blood glucose; FGM = flash glucose monitoring.

6.2 Preparation, handling, storage and accountability

Only participants enrolled in the study may use study intervention and only delegated site staff may supply or administer study intervention.

Investigational medicinal products (IMP)

- Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the RTSM/IWRS. Trial product will be distributed to the trial sites according to screening and trial product initiation.
- 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 participant before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the Trial Materials Manual (TMM).
- The investigator or designee is responsible for trial product accountability and record maintenance (i.e., receipt, accountability and final disposition records).
- The investigator or designee must instruct the participant in what to return at next visit.
- The investigator or designee must instruct the participant on how to manage the in-use time of the dispensed products.
- 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 (used or un-used), expired or damaged trial products (for technical complaint samples, see Appendix 5 [Section 10.5]) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products, including expired or damaged products, must be accounted by the site and/or reconciled by the monitor, at the latest at closure of the site.
- Drug accountability must be performed on pen-injector level as returned either as used/partly used, unused or lost. Drug accountability should also be performed in the RTSM/IWRS.

Study phone

- The Novo Nordisk provided study phones must be returned by the participant at the end of study visit (V28).
- All returned, unused or damaged study phones must be stored separately and returned at the latest at closure of the site.

6.3 RTSM/IWRS

- This is an open-label, non-randomized study.
- All participants will be screened and initiated/enrolled using the RTSM/IWRS.
- Trial product will be allocated by the RTSM/IWRS and dispensed by the investigator at the study visits summarised in the flowchart (Section 1.2).

6.4 Study intervention compliance

Drug treatment compliance

Throughout the study, the investigator will remind the participants to follow the study procedures and requirements to encourage participant compliance.

When participants self-administer trial product at home, compliance with trial product administration will be assessed, and the assessment documented in source documents at each visit where information is available. If any suspicion of non-compliance arises, the site must enter into a dialogue with the participant, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Accountability information; counting returned trial product, visual inspection of pens
- Review of insulin dosing diaries, FGM profiles and hypoglycaemia reporting.
- Evaluating glycaemic control and adherence to the visit schedule
- Questioning of participants

Trial product start and stop dates will be recorded in the case report form (CRF).

6.5 Dose modification

Insulin icodec doses are adjusted according to the titration guidelines based on pre-breakfast fasting FGM values as described in Appendix 7 (Section 10.7).

6.5.1 Dose escalation studies

Not applicable for this study.

6.6 Continued access to study intervention after end of study

When discontinuing study intervention, the participant should be transferred to a suitable marketed product at the discretion of the investigator.

6.7 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 participant for overdose-related AEs/serious adverse events (SAEs) and laboratory abnormalities until the blood glucose is normalised and (or) signs/symptoms have been relieved.

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

- Mild hypoglycaemia can be treated by oral administration of glucose or sugary products.
- Severe hypoglycaemia, where the subject is not able to treat him/herself, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the subject dose not respond to glucagon within 10-15 minutes. If the subject

has been unconscious, administration of oral carbohydrates is recommended for the subject upon regaining consciousness, in order to prevent a relapse.

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

For more information on overdose, also consult the current version of the insulin icodec IB[11].

6.8 Concomitant therapy

Any medication that the participant is receiving at the screening visit (V1) or receives until end of study (V28) must be recorded along with:

- Select predefined medication. If not listed, enter trade name or generic name
- Primary indication
- Dates of administration including start and stop dates
- Doses and frequency
- Relevant for participants in COVID-19 studies: Type of study and type of drug

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

6.8.1 Rescue medicine

Not applicable for this study.

7 Discontinuation of study intervention and participant discontinuation/withdrawal

Discontinuation of specific sites or of the study as a whole is detailed in Appendix 1 (Section 10.1.11).

7.1 Discontinuation of study intervention

Study intervention may be discontinued at any time during the study at the discretion of the participant or at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Efforts must be made to have the participants who discontinue insulin icodec attend the end of study intervention visit 26 as soon as possible. Two (2) follow-up visits (V27 and V28) must be conducted 3 and 6 weeks respectively after the participants last insulin icodec dose. The visit window is plus 1 day for both visits V27 and V28.

Subjects who prematurely discontinue insulin icodec should continue to use the FGM device until V28, 6 weeks after last dose of insulin icodec. Only participants who withdraw consent will be considered as withdrawn from the study. Participants must be informed about the continued scientific importance of their data, even if they discontinue study intervention.

Insulin icodec must be discontinued, if any of the following applies for the participant:

1. Safety concern related to trial product or unacceptable intolerability
2. Pregnancy
3. Intention of becoming pregnant
4. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study
   Note: Simultaneous participation in a study with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or post-infectious conditions is allowed at the investigator's discretion without discontinuation of study intervention.
5. Permanent discontinuation of FGM system use during the treatment period.
6. Lack of efficacy, defined as fulfilment of ALL 4 criteria below:
   - no reduction in HbA_{1c} measured by central laboratory from initiation of study intervention (V3) to week 10 (V13) or to week 18 (V21) AND
   - the pre-breakfast FGM readings on 3 consecutive days higher than 240 mg/dL (13.3 mmol/L) within the last two weeks period despite appropriate dose adjustments, AND
   - a confirmatory fasting plasma glucose exceeding 240 mg/dL (13.3 mmol/L) as measured by central laboratory. The subject should come in for an unscheduled visit as soon as possible (within one week), the next scheduled visit should not be awaited, AND
   - no treatable intercurrent cause (e.g., non-compliance) for the hyperglycaemia at the investigator's judgment.

See the flowchart (Section 1.2) for data to be collected at the time of study intervention discontinuation (end of study intervention visit 26) and follow-up and for any further evaluations that need to be completed.

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

7.1.1 Temporary discontinuation of study intervention

The subject should adhere to the treatment to the extent possible, with the exception of any AEs such as hospitalisation or safety concerns, at the discretion of the investigator. Subjects who have temporarily discontinued trial product are allowed to restart trial product, unless any of the discontinuation criteria specified in Section 7.1 applies. Treatment discontinuation and treatment resume must be registered in RTSM/IWRS when a participant discontinues or resumes study intervention.

7.1.2 Rescue criteria

Not applicable for this study.

7.2 Participant discontinuation/withdrawal from the study

A participant may withdraw consent at any time at his/her own request.

If a participant withdraws consent or is withdrawn by the investigator prior to study intervention initiation/receipt of study intervention, he/she will not be asked to have any follow-up assessments performed. The following data must be collected: Demography, eligibility criteria, date of informed consent, date of screening and the date when participants participation ended. The end of study form must be completed.

If a participant withdraws consent or is withdrawn by the investigator after study intervention initiation/receipt of study intervention, the investigator must ask the participant if he/she is willing, as soon as possible, to have assessments performed according to visit 26. See the flowchart (Section 1.2) for data to be collected.

Final trial product accountability must be performed even if the participant is not able to come to the site. A discontinuation session must be made in the RTSM/IWRS.

If the participant withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent for the purpose of the study or scientific research.

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

Although a participant 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 participants rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the CRF.

7.2.1 Replacement of participants

If a participant discontinues study intervention, withdraws consent or is withdrawn by the investigator, he/she will not be replaced.

7.3 Lost to follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, at least three telephone calls and, if necessary, a certified letter to the participants last known mailing address or local equivalent methods). These contact attempts should be documented in the participants source document.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants who initiated study intervention, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 Study assessments and procedures

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

- Informed consent must be obtained before any study-related activity, see Appendix 1 (Section 10.1.3).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all inclusion criteria and none of the exclusion criteria.
- The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, participants will be provided with a card stating that they are participating in a study and giving contact details of relevant site staff that can be contacted in case of emergency.
- Adherence to the study design requirements, including those specified in the flowchart (Section 1.2), is essential and required for study conduct. This includes adherence to the use of the FGM device throughout the study period.
- 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. At the initiation visit (V3),
  - Run-in exclusion criterion and initiation criteria must be assessed prior to other assessments
  - Blood sample collection and weight must be assessed prior to dosing of trial product.
- Review of diaries, electrocardiogram (ECG), laboratory reports, etc., must be documented in the source documents or the participants medical record. If clarification of entries or discrepancies in the diary is needed, the participant must be questioned, and a conclusion made in the participants source documents. Care must be taken not to bias the participant (refer Section 6.4).
- At each visit, investigator should review any reported hypoglycaemic episodes in the diary, check severity, and confirm symptoms and document these in source documents or participants medical record.
- Review of LibreView must be documented in source documents or in participants medical record.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 (Section 10.2) for further details on laboratory samples.

8.1 Efficacy assessments

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

8.1.1 FGM system and scanned values

When using the FGM system, the sensor detects glucose levels via enzymatic or non-enzymatic reaction with glucose in the interstitial fluid, creating a signal that can be converted to a sensor glucose (SG) value.

There is a good correlation between the BG levels measured in capillary blood and SG levels/interstitial glucose levels measured in the subcutaneous interstitial fluid. However, there is a 5-15 minute delay between SG and BG. The delay may contribute to the sensor inaccuracy when rapid BG changes occur, but it is insignificant at stable BG[18].

The FGM system is factory calibrated and manufactured with minimal sensor-to-sensor variation. The FGM system provides further instruction on when a user should make an additional check using a BG meter (see below).

Participants will be equipped with the FGM system, a BG meter with auxiliaries and a mobile phone including the FreeStyle Libre 2 App at the run-in visit (V2), until the end of the follow-up period (V28). The FGM system should be used for the measurements required in the protocol. The FGM readings will be unblinded to both the participant and investigator.

FGM fitting and training

The site staff will closely supervise and assist on fitting of the sensor on the subject during the first site visits (V2, V3). Thereafter participants will be distributed sufficient FGM sensors to replace a sensor every 14 days between the visits. Training in the FGM system is the responsibility of the investigator or site staff at the relevant visits. For information on fitting and changing of the FGM sensor, please refer to the manufacturer's manual and FGM participant guide provided.

Participants should be instructed to scan their FGM sensor at least 4 times daily (pre-breakfast, pre-lunch, pre-dinner, and before bedtime) from run-in visit 2 (V2) to the end of study (V28).

Participants must be instructed to remove the FGM sensor prior to an X-ray, magnetic resonance imaging or computed tomography scan.

FGM data upload

Upon each FGM sensor scanning the FGM data will automatically be uploaded via the FreeStyle Libre 2 App on the smartphone.

Pre-breakfast daily FGM scanned value

Participants should be instructed to annotate their pre-breakfast scanned values on the three mornings before (2 days before, 1 day before, and on the morning of) each injection. 'Pre-breakfast' should be added as a note for the pre-breakfast scan in the mobile app.

The scanned values with note will then appear in the LibreView system at the investigator site staff will transcribe the FGM values with 'Pre-breakfast' note into the CRF within 24 hours after the contact for titration of insulin icodec.

Selected titration data (e.g., pre-breakfast FGM scanned values and dose data) from the CRF will be used during the trial for central titration surveillance, to ensure compliance with the titration guideline in Appendix 7 (Section 10.7) and will not be reported in the clinical trial report. All data will be stored by Novo Nordisk (see Appendix 1, Section 10.1).

FGM compliance check

The investigator should review LibreView prior to each visit/phone contact to confirm participant compliance in use of the FGM system as described in the flowchart (Section 1.2).

Self-measured plasma glucose

Participants will be provided with a BG meter including auxiliaries for assurance of safety in alignment with the manufacturer guide and particularly for confirming hypoglycaemic events (see Appendix 6, Section 10.6).

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 measurements in accordance with the manufacturers user guide and should be used if:

- A low glucose warning appears after an FGM scanned value is low (below 40 mg/dL)
- A high glucose warning appears after an FGM scanned value is high (above 400 mg/dL)
- Participant symptoms do not match the scanned FGM value
- When the FGM system indicates a need for a BG meter check (see manufacturers guide).

Participants should be instructed in when to perform additional BG meter checks and how to record the results of the low self-measured plasma glucose (SMPG) values in their diaries, see Appendix 6, Section 10.6. If obtained via phone, and a discrepancy is later detected, the values in the eCRF must be corrected.

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

8.1.2 Clinical efficacy

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

8.2 Safety assessments

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

Medical history is a medical event that the participant experienced prior to the time point from which AEs are collected.

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 study procedures performed before exposure to study intervention under clinical investigation.

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

8.2.1 Insulin dose

The prescribed insulin doses will be determined by the investigator in accordance with the titration guideline (Appendix 7, Section 10.7).

During the trial, starting at initiation (V3), subjects must be instructed to report date, dose and time of once weekly insulin injection in the diary. Please refer to Appendix 7 (Section 10.7) for more information.

The investigator must record the following in the eCRF:
- First and last date on trial product
- First and last dose of trial product.

For dosing of insulin prescribed in the follow-up period please see Section 6.4.

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
- Neurological
- Musculoskeletal system
- Skin

Investigators should pay special attention to clinical signs related to previous serious illnesses. The physical examination will be confirmed in the eCRF.

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

Body measurements (e.g., height and weight) will also be measured and recorded as specified in the flowchart (Section 1.2).
- Body weight should be measured in pounds (lb) without coat and shoes wearing only light clothing. Body weight will be recorded to one decimal.
- Body weight should be assessed with the same equipment throughout the trial, if possible.
- Height should be measured in centimetres (cm) or inches (in) without shoes. Height will be recorded to the nearest whole number.
- From the body weight and height, the BMI will be calculated at visit 1 (V1) and recorded in the participants medical records.

8.2.3 Vital signs

- Pulse rate, as well as systolic and diastolic blood pressure will be assessed.
- Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., no use of television, cell phones).
- Blood pressure and pulse rate measurements will be assessed sitting with a completely automated device. Manual techniques must be used only if an automated device is not available.
- Blood pressure and pulse rate are collected at screening and end of study intervention.
- Blood pressure 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. No more than four measurements should be performed.
  - The mean systolic blood pressure and diastolic blood pressure values are calculated based on the last 2 measurements.
  - The last 2 systolic and last 2 diastolic blood pressure measurements should be recorded in the eCRF. The eCRF will calculate the mean of the last 2 measurements.
- Pulse rate will be measured in connection to the blood pressure measurements.
  - The mean pulse rate value is calculated based on the last 2 pulse rate measurements.
  - The pulse rate for the last 2 measurements should be recorded in the eCRF. The eCRF will calculate the mean of the last 2 measurements.

8.2.4 Eye examination

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

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

If the participant 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 participant has experienced worsening of visual function since the last examination. If the applicable eye examination was performed before the participant signed the informed consent form, it must be documented that the reason for performing the examination was not related to this study.

After initiation of study intervention an eye examination must be performed according to above as per protocol flowchart (Section 1.2). The investigator should indicate the outcome of each eye examination. Relevant findings prior to randomisation must be recorded as concomitant illness/medical history. While relevant findings occurring after randomisation should be reported as an AE, please refer to Section 8.3 and Appendix 3 (Section 10.3).

Eye examinations required at the end of study intervention (V26) 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 study intervention visit. The investigator should indicate the outcome of each eye examination.

8.2.5 Electrocardiograms

- A 12-lead ECG will be obtained as outlined in the flowchart (Section 1.2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and corrected QT interval (QTc) intervals.
- 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 (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 laboratory manual and the protocol flowchart (Section 1.2).

8.2.7 Pregnancy testing

Women of childbearing potential (WOCBP) should only be included after a negative, highly sensitive urine pregnancy test (refer to Appendix 2 [Section 10.2]).

Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected. Additional pregnancy testing should be performed during the treatment period, if required locally, refer to Appendix 8 (Section 10.8).

8.3 Adverse events and other safety reporting

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

The definition of AEs and SAEs and the AEs requiring additional data collection can be found in Appendix 3 (Section 10.3).

Some AEs require additional data collection on a specific event form. The relevant events are listed below in Table 8-1.

Hypoglycaemic episodes

In the event of a hypoglycaemic episode, participant should enter the SMPG value in the hypoglycaemic episode form in his/her paper diary (see also Section 10.3). 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 in the eCRF, an AE form and a safety information form must be completed in the eCRF.

A low scanned FGM value cannot be used to complete the hypoglycaemic episode form.

For more information on hypoglycaemic episodes, please refer to Appendix 6, Section 10.6.

Table 8-1 AEs requiring additional data collection

Event type	AE requiring additional data collection
Medication error	X
Misuse and abuse	X
Hepatic events	X

Abbreviation: AE = adverse event.

Definitions and reporting timelines for the events mentioned in the above table can be found in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE information

All AEs and SAEs specified in Section 8.3 must be collected and reported. From visit 3 (V3) and until the last follow-up visit (V28), in accordance with the flowchart (Section 1.2) or whenever within the above time period the site becomes aware of an AE or SAE.

Conditions present prior to the timepoint from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or during other study-related procedures performed before exposure to study intervention under clinical investigation, will be recorded as medical history/concomitant illness.

AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3). All SAEs must be recorded and reported to Novo Nordisk or designee within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk or designee within 24 hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discontinued from/completed the study, and the investigator considers the event to be related to the IMP or related to study participation, the investigator must promptly notify Novo Nordisk.

8.3.2 Method of detecting AEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

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

8.3.3 Follow-up of AEs

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

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk or designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 study intervention under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB)/independent ethics committee (IEC), and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR).

An investigator who receives an investigator safety report describing an 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of pregnancies in female participants will be collected after first exposure to IMP 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. For details regarding collection and reporting of pregnancy information, please refer to Appendix 4 (Section 10.4).

8.3.6 Cardiovascular and death events

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

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable for this study.

8.3.8 Adverse event of special interest

Not applicable for this study.

8.3.9 Technical complaints

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

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

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

8.4 Pharmacokinetics and pharmacodynamics

Not applicable for this study.

8.5 Genetics

Not applicable for this study.

8.6 Biomarkers

Not applicable for this study.

8.7 Immunogenicity assessments

Not applicable for this study.

8.8 Human biosamples

Not applicable for this study.

8.9 Health economics

Not applicable for this study.

9 Statistical considerations

The statistical analysis plan (SAP) will be finalised prior to first participant 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.

9.1 Statistical hypotheses

No confirmatory statistical hypotheses are planned to be tested.

9.1.1 Multiplicity adjustment

Not applicable for this study.

9.2 Analysis sets

The following participant analysis sets are defined:

Participant analysis set (PAS)	Description
Full analysis set (FAS)	All participants assigned to study intervention.
Safety analysis set	All participants who are exposed to study intervention.

The following data points sets are defined:

Defined data points set (DPS)	Description
DPS1	For participants who discontinue both FGM titration and icodec treatment, observations from the time of both discontinuations and onwards will not be included. All other data will be included.
DPS2	All observed data will be included in the analysis set irrespective of use FGM based titration or treatment with once-weekly insulin icodec.

Abbreviation: FGM = flash glucose monitoring.

FAS and DPS1 are used to present the efficacy data.

Safety analysis set and DPS2 are used to present safety data.

9.3 Statistical analyses

9.3.1 General considerations

Two-sided 95% confidence intervals (CI) will be reported.

If not otherwise specified, a baseline measurement is defined as the last available measurement prior to exposure to study intervention.

9.3.2 Primary endpoint analysis

The primary endpoint is change in HbA_{1c} from initiation week 0 (V3) to week 26 (V26).

The primary endpoint will be analysed by a mixed model for repeated measurements (MMRM) with an unstructured covariance matrix. The model will include visit as fixed factor and baseline HbA_{1c} as a covariate. Interactions between visit and baseline HbA_{1c} will also be included in the

model. All post-initiation values obtained at planed visits that are in DPS1 will be included in the analysis.

9.3.3 Secondary endpoint analysis

Not applicable for this study.

9.3.4 Exploratory endpoints analysis

For details on analysis of exploratory endpoints, please refer to the SAP (Appendix 16.1.9).

9.3.5 Safety analyses

All safety analyses will be made on the safety analysis set. The standard safety assessments (AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively, including any notable changes of clinical interest in laboratory parameters.

9.3.6 Other analyses

For other analyses, please refer to the SAP (Appendix 16.1.9).

9.4 Interim analysis

Not applicable for this study.

9.5 Sample size determination

The sample size is determined such that the change in HbA_{1c} from initiation to week 26 (V26) can be estimated with sufficient precision.

In a previous study with insulin icodec in insulin-naïve T2D subjects (NN1436-4465) using the same titration algorithm but SMPG based titration, the standard deviation of change in HbA_{1c} from baseline to 16 weeks was 0.75%-point. In another previous study of 26 weeks duration in insulin-naïve T2D subjects (NN1436-4383), but with a different titration algorithm, the standard deviation (SD) was found to be 0.76%-point. Hence, the SD for the present study is expected to be 0.8%-point.

Figure 9-1 illustrates the probability of CI width for various change in HbA_{1c} 95% CI width and SDs with a sample size of 50 participants assuming normally distributed data. Figure 9-2 displays the required number of participants for various change in HbA_{1c} from baseline 95% CI widths and SDs. With 50 participants contributing to the analysis, and a SD of 0.8 the width of the 95% CI for change in HbA_{1c} from baseline that can be obtained with at least 90% probability is 0.51% -point. The width that can be obtained with at least 80% probability is 0.5%-point. A precision of 0.5%-point is considered sufficient for this study, hence, 50◦participants will need to be assigned to FGM based titration of once-weekly insulin icodec.

Figure 9-1 Probability of various confidence interval widths for various standard deviations for 50 participants

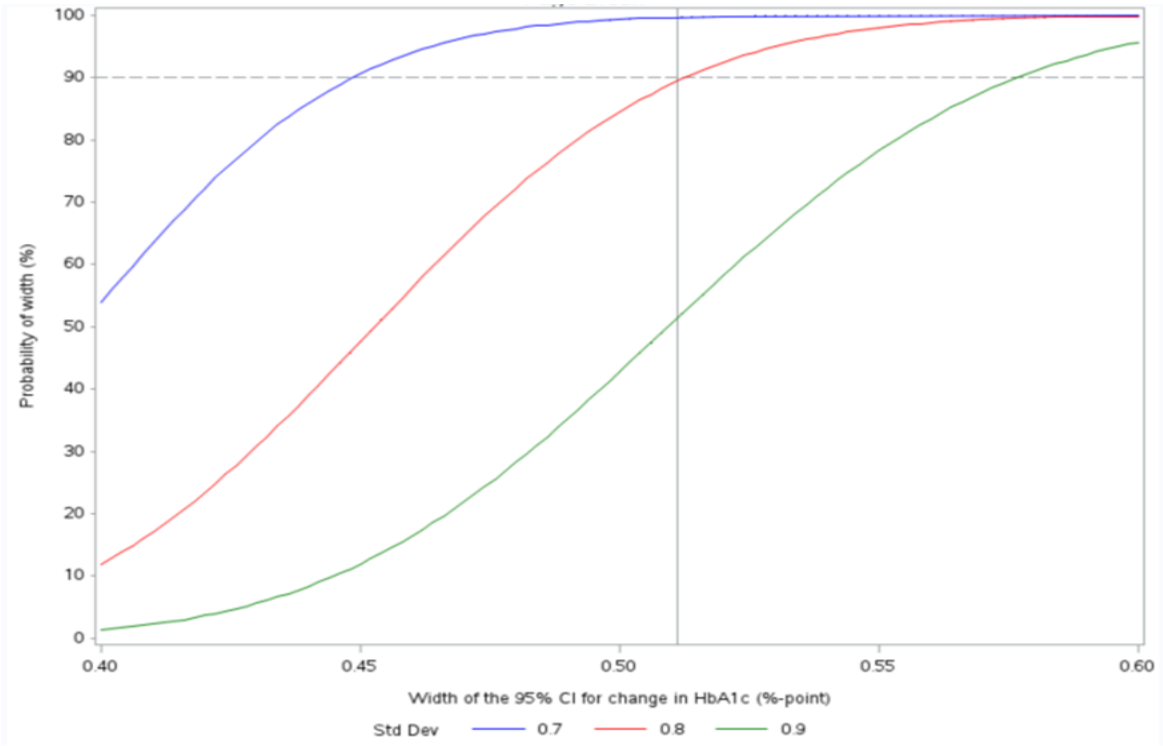
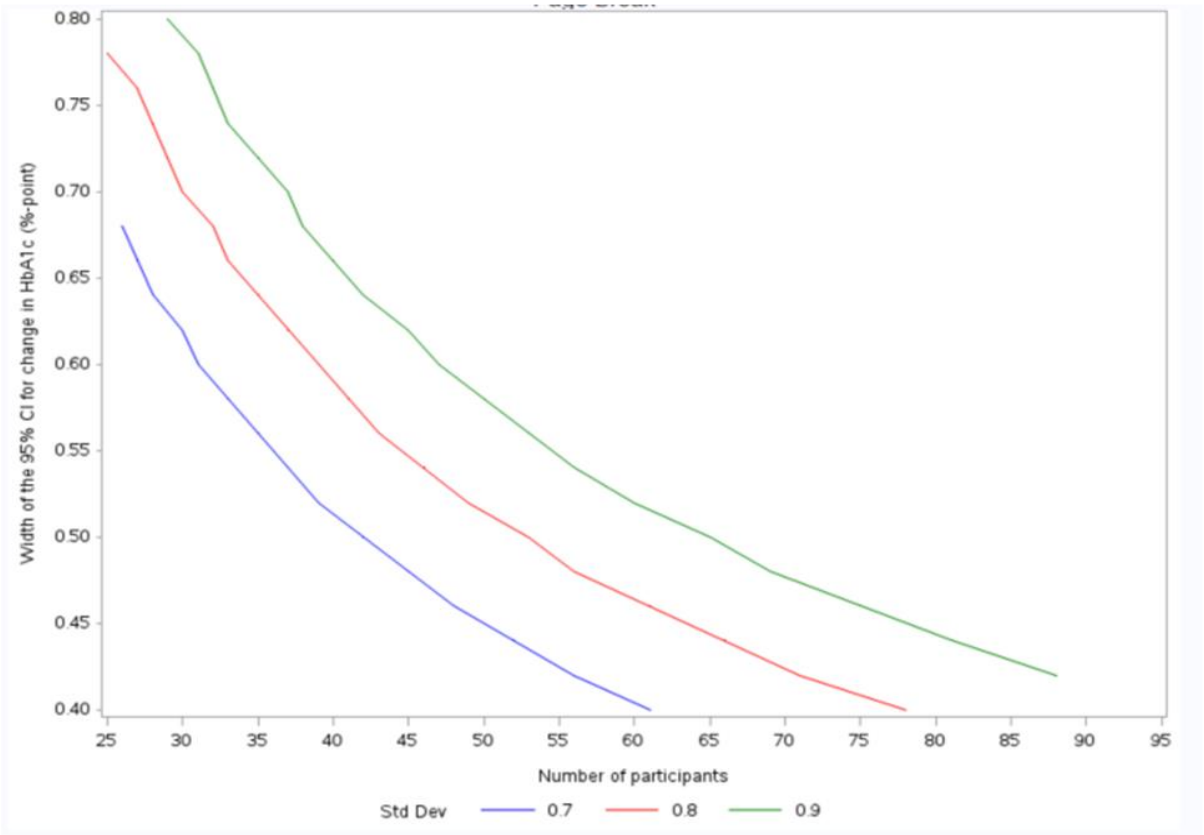


Figure 9-2 Width of the confidence interval by number of participants and various standard deviations



With an expected screening failure rate of 26%, 67 participants need to be screened.

10 Supporting documentation and operational considerations

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

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[19] and applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[20]
- 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 study is initiated.

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical study report (CSR) according to national requirements.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate safety hazard to study participants.

Before a site is allowed to start screening participants, written notification from Novo Nordisk must be received.

The investigator will be responsible for:

- providing written summaries of the status of the study 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 study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- ensuring submission of the CSR 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 study and one year after completion of the study.

Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

10.1.3 Informed consent process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. This includes the use of an impartial witness where required according to local requirements.
- The investigator must ensure the participant ample time to come to a decision whether or not to participate in the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH GCP[20] guidelines, Declaration of Helsinki,[19] privacy and data protection requirements, where applicable, and the IRB/IEC or site.
- The medical record must include a statement that written informed consent was obtained before any study-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 study-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.
- Participants must be re-consented to the most current version of the informed consent form(s) during their participation in the study.
- A copy of the informed consent form(s) must be provided to the participant.

A separate participant information consent form to share information for a male partner of a female participant in case of an abnormal pregnancy or child born with health problem is available for this study (Appendix 4 [Section 10.4]).

10.1.4 Information to participants during the study

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

All written information to participants 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

- Participants will be assigned a 6-digit unique identifier, a subject ID. Any participant records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the participant are transferred to Novo Nordisk.
- The participant and any biological material obtained from the participant will be identified by subject ID, visit number and study ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of participants as required by local, regional and national requirements.

- The participant must be informed about his/her privacy rights, including that his/her personal study-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 participant.
- The participant 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.
- Personal data may be collected from participants due to process requirements from Novo Nordisk's suppliers. This data is needed to ensure that the relevant data analysis for the study can be performed but will not be part of the data transferred to Novo Nordisk, the assessment of the study endpoints or the CSR. A list of any such data values must be kept as part of the study documentation along with an explanation of why it was required.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee. The safety committee may recommend unblinding of any data for further analysis, and in this case an internal study-independent ad hoc group may be established in order to maintain the blinding of the study personnel.

10.1.7 Dissemination of clinical study data

Study information will be disclosed at clinicaltrials.gov and novonordisk-trials.com and, if applicable, also on other national or regional study registries. It will be disclosed according to applicable requirements, relevant recommendations or regulations, such as the Declaration of Helsinki,[19] the International Committee of Medical Journal Editors (ICMJE),[21] the FDAAA,[22] European Commission Requirements[23-25] and in accordance with Novo Nordisk commitment to clinical transparency. If a participant requests to be included in the study via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the participant. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The PCD is the last assessment of the primary endpoint and is for this study last participants first treatment + 26 weeks corresponding to visit V26. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit V26. 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 study including quality checking of the data.
- To demonstrate his/her oversight of the collected data, the investigator should sign the eCRF on a regular basis during the conduct of the study as well as at the end of the study, as described in the CRF completion guideline.

- All participant data relating to the study will be recorded on eCRFs unless transmitted electronically to Novo Nordisk or designee (e.g., laboratory and diary data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The 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 study intervention not yet allocated to a participant
- 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 study-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 study. If the electronic source data 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).
- Study monitors will perform ongoing source data verification of critical data points to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents. Study monitors will perform ongoing source data review to ensure that the study is being conducted in accordance with the current approved protocol and any other study agreements, ICH GCP[20], and all applicable regulatory requirements, evaluating the adequacy of critical processes at site for the execution of the protocol, collection of study data, to ensure that the safety and rights of participants are being protected.
- 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.
- Quality tolerance limits (QTLs) will be predefined in the relevant monitoring plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the CSR.

10.1.8.3 Protocol compliance

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

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

10.1.9 Source documents

All data entered in the CRF must be verifiable in source documentation, except for the following data that should be recorded directly in the CRFs and will be considered source data:

- The original of the completed diaries must not be removed from the site, unless they form part of the CRF and a copy is kept at the site.
- Data that is transcribed into the CRF 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 participants medical history in source documents, such as participants 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.

If source data is entered directly in a paper CRF, each data entry or clear series of data entries must be signed and dated separately by the study staff making the entry.

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the site. Any source data generated by investigator's subcontractors must be archived and accessible by the site.

Data in the service providers' database are considered source data e.g., laboratory data and FGM.

10.1.10 Retention of clinical study documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this study must be retained by the investigator for 25 years after end of study 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 study documents without involving Novo Nordisk in any way. If applicable, eCRF and other participant 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 participant 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.

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

10.1.11 Study and site closure

Novo Nordisk reserves the right to close the site or terminate the study at any time for any reason at the sole discretion of Novo Nordisk. If the study is suspended or terminated, the investigator must inform the participants 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 study completion. A site is considered closed when all required documents and study 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 participants by the investigator
- discontinuation of further study intervention development.

10.1.12 Responsibilities

The investigator is accountable for the conduct of the study at his/her site and must ensure adequate supervision of the conduct of the study 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 study-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the study. It is the investigator's responsibility to supervise the conduct of the study and to protect the rights, safety, and well-being of the participants.

A qualified physician, who is an investigator or a sub investigator for the study, must be responsible for all study-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 study and the quality of the data produced) in the investigator trial master file. The documents, including the participant identification code list must be kept in a secure locked facility so that no unauthorised 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. This also includes ensuring that no indirect sharing of user credentials for IT systems used in this study takes place (e.g., by not sharing IT equipment with others in a way where user credentials have the

possibility of being shared). 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 participants to a specific qualified physician who will be readily available to participants 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 studies 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 study 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 study 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 study intervention. All information supplied by Novo Nordisk in connection with this study 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 study.

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

Novo Nordisk may publish on its clinical studies website a redacted CSR for this study.

One (1) investigator will be appointed by Novo Nordisk to review and sign the CSR (signatory investigator) on behalf of all participating investigators.

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of studies 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 study will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical study report is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire study.

At the end of the study, 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 study 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 study 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.[26]

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 study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or participants, 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 study.

10.1.14.4 Investigator access to data and review of results

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

Individual investigators will have their own research participants 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 associated to the clinical site or by a laboratory subcontracted by this laboratory unless otherwise noted.

Additional tests may be performed at any time during the study 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 laboratory standard operating procedures (SOPs). These data will not be transferred to the study 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.

The investigator must keep an overview, e.g., a log, of laboratory samples not handled according to the laboratory manual. In addition, the investigator must keep an overview, e.g., a log, of laboratory samples stored at site.

Laboratory samples will be destroyed no later than at end of study or no later than at finalisation of the clinical study report.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism V1, V3, V13, V21, V26	• Glycated haemoglobin (HbA_{1c}) • In case of potential lack of efficacy (Section 7.1): Fasting plasma glucose (FPG)

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology V1,V26	• Haemoglobin • Leucocytes
Biochemistry[a] V1,V26	• Alanine Aminotransferase (ALT) • Albumin • Alkaline phosphatase • Aspartate Aminotransferase (AST) • Bilirubin • Creatinine • Potassium • Sodium
Pregnancy Testing[b] V1, V3, V28	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation

Notes:
[a]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 3 (Section 10.3) (Hy's Law) and Section 7.1.
[b]For women of childbearing potential, as needed, local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC, see Appendix 4 (Section 10.4).

Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate;

10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1 Definition of AE

An AE is any untoward medical occurrence in a clinical study participant that is temporally associated with the use of 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 a IMP.

Events to be reported as AEs:

- 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

Events NOT to be reported as AEs:

- Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions. This includes those conditions identified during screening or identified during other study 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 any untoward medical occurrence that fulfils at least one of the following criteria:

- **Results in death**
- **Is life-threatening**
  - The term ‘life-threatening’ refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalisation or prolongation of existing hospitalisation**
  - Hospitalisation signifies that the participant has been admitted 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, study-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 study inclusion, are not considered AEs or SAEs

- **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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Important medical event:**
  - Medical or scientific judgment should be exercised by the investigator 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 participant 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 must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:
    - Suspicion of transmission of infectious agents via IMP
    - Risk of liver injury defined as alanine aminotransferase (ALT) or asparate aminotransferase (AST) >3x upper limit of normal (ULN) and total bilirubin >2x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of AEs requiring additional data collection

Adverse events requiring additional data collection

An AE requiring additional data collection is an AE where Novo Nordisk has evaluated that additional data is needed in the evaluation of safety.

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 participant, such as:
  - administration of wrong drug

    Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in administration of wrong drug.
  - wrong route of administration, such as intramuscular instead of subcutaneous
  - accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the study participant were likely to happen as judged by the investigator, although they did not necessarily occur.

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)

Note: Medication error, misuse and abuse must always be reported on an AE form and a specific event form must be completed. The AE diagnosis on the AE form must reflect what occurred (e.g., accidental overdose, intentional overdose or other). If the medication error and/or misuse and abuse resulted in a clinical consequence, this must be reported on an additional AE form.

Hepatic events

In all cases where one or more results from liver lab parameters (ALT, AST or ALP) are increased above the limits defined below an AE must be reported and the specific event form (Hepatic Event form) must be completed. Criteria for discontinuation of study intervention may also apply (Section 7.1).

- ALT: >3.0 x ULN if baseline was normal; >3.0 x above baseline if baseline was abnormal
- AST: >3.0 x ULN if baseline was normal; >3.0 x above baseline if baseline was abnormal
- ALP: >2.5 x ULN if baseline was normal; >2.5 x above baseline if baseline was abnormal

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

10.3.4.1 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 participant identifiers, with the exception of the subject ID, must 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 study at the latest. For sign-off of SAE-related forms, refer to “AE and SAE reporting via paper CRF” later in this section.
- Novo Nordisk products used as concomitant medication or NIMP: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as NIMP or concomitant medication in the study, 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 AE to relevant regulatory authorities.

10.3.4.2 Assessment of severity

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

- **Mild**: An event that is easily tolerated by the participant, 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 an SAE. Both AEs and SAEs can be assessed as severe.

10.3.4.3 Assessment of causality

The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

Relationship between an AE/SAE and the relevant IMP 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, should be considered and investigated.

The investigator should use the investigator's brochure of insulin icodec, 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

10.3.4.4 Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved**: The participant 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 participant is expected to recover from the event. This term may also be applicable for AEs ongoing at the time of death (where death was due to another AE).

Note: For SAEs, this term is only applicable if the participant has completed the follow-up period and is expected to recover.

- **Recovered/resolved with sequelae**: The participant 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 participant has not improved, and the symptoms are unchanged, or the outcome is not known. 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 participant died from a condition related to the reported AE. Outcomes of other reported AEs in a participant 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 participant is lost to follow-up

10.3.4.5 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., hypersensitivity reactions, Hy's law). This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information should be recorded in the CRF.

10.3.5 Reporting of SAEs

AE and SAE reporting via CRF

Relevant forms (AE, safety information form and event specific forms if applicable) must be completed in the CRF.

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 forms within the designated reporting timelines (see Table 10-1):

- AE form within 24 hours
- Safety information form within 5 calendar days
- Both forms must be signed within 7 calendar days after first knowledge by the investigator.
- Specific event form within 14 calendar days.

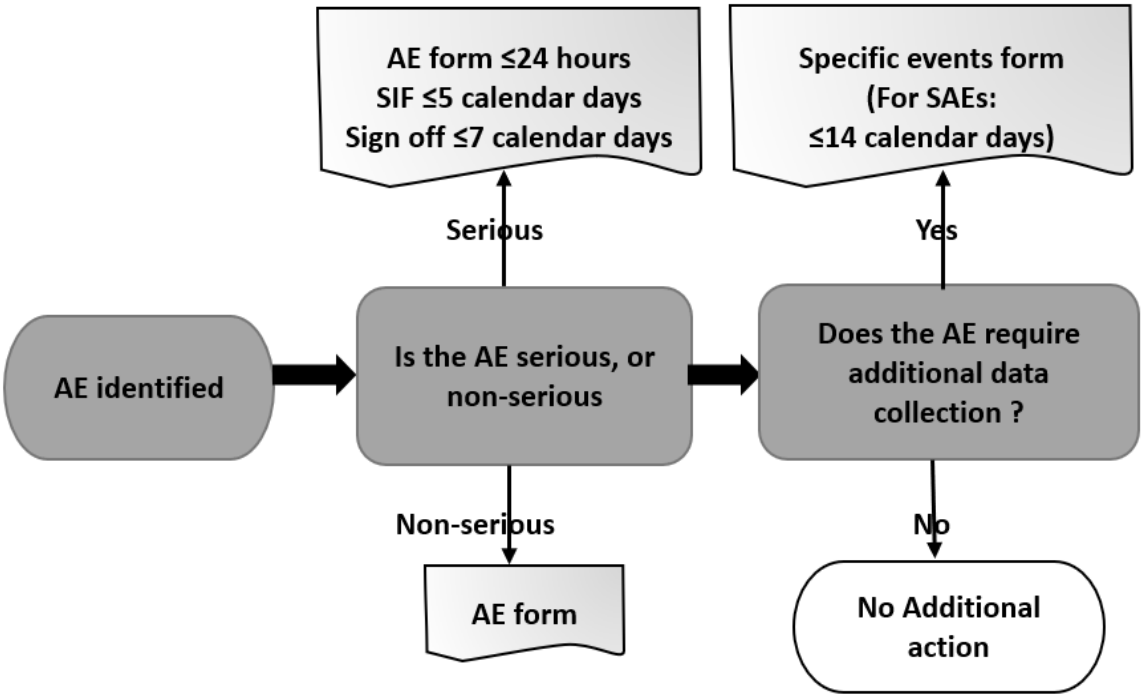
If the eCRF is unavailable for more than 24 hours, then the sites will use the paper AE form, and if the eCRF is unavailable for more than 5 calendar days, then the site will use the paper safety information form. The site should enter the SAE data in the eCRF as soon as it becomes available.

The relevant CRF forms (AE and safety information forms) must be forwarded to Novo Nordisk in accordance with Section 10.1.5.

After the study is completed, the study 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 participant or receives updated information on a previously reported SAE after CRF decommission, the site can report this information on a paper AE and safety information form (see below) or to Novo Nordisk by telephone.

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



Notes:

Timelines are from the awareness of an AE.

Hypoglycaemic episodes should be reported on the hyoglycaemic episodes form. If the hypoglycaemic episodes fulfils the criteria for an SAE then as AE form and a safety information form must also be filled in.

Queries and follow-up requests to be resolved ≤14 calendar days.

In general data must be recorded in the CRF as soon as possible, preferably within 5 working days (see Appendix 1).

Abbreviations: AE = adverse events; CRF = case report form; SAE = serious adverse event; SIF = safety information form.

Contact details for SAE reporting can be found in the investigator trial master file.

10.3.6 Reporting of AEs for non-Novo Nordisk medical devices provided by Novo Nordisk for use in the study

FGM device and BG meter:

All complaints (including AEs considered related to the device) should be reported directly to the manufacturer of the medical device.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

Women of childbearing potential

A women is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.
If fertility is unclear (e.g., amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Females in the following categories are not considered WOCBP

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

    For 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 study enrolment.
3. Postmenopausal female:
    - A postmenopausal state is defined as amenorrhoea for at least 12 months without an alternative medical cause in a female > 45 years of age. Alternative medical causes for amenorrhoea include, but are not limited to, hormonal contraception or hormonal replacement therapy.
    - Females ≥60 years of age can be considered postmenopausal.

Females on hormone replacement therapy and whose menopausal status is in doubt are considered of childbearing potential and will be required to use one of the acceptable contraception methods.

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

10.4.2 Contraceptive guidance

Male participants

No contraception measures are needed for male participants as the risk of teratogenicity/fetotoxicity caused by transfer of insulin icodec in seminal fluid is unlikely.[27]

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly. Table 10-3 lists the acceptable methods of contraception allowed. Local regulations may apply, see Appendix 8 (Section 10.8).

At least an acceptable contraception should be utilised until the end of treatment (EOT).

Table 10-3 Acceptable contraceptive methods allowed[28]

Acceptable methods[a]
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide[b] • 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. Considered effective, but not highly effective – failure rate of ≥1% per year. b. Male condom and female condom should not be used together (due to risk of failure from friction).

The following methods are not acceptable methods of contraception: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method.

10.4.3 Collection of pregnancy information

Pregnancy testing

- Additional pregnancy testing should be performed during the treatment period, if required locally (Appendix 8, Section 10.8).
- 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.

Female participants who become pregnant

Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.

Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a participants pregnancy (see Table 10-2).

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate which will be forwarded to Novo Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.

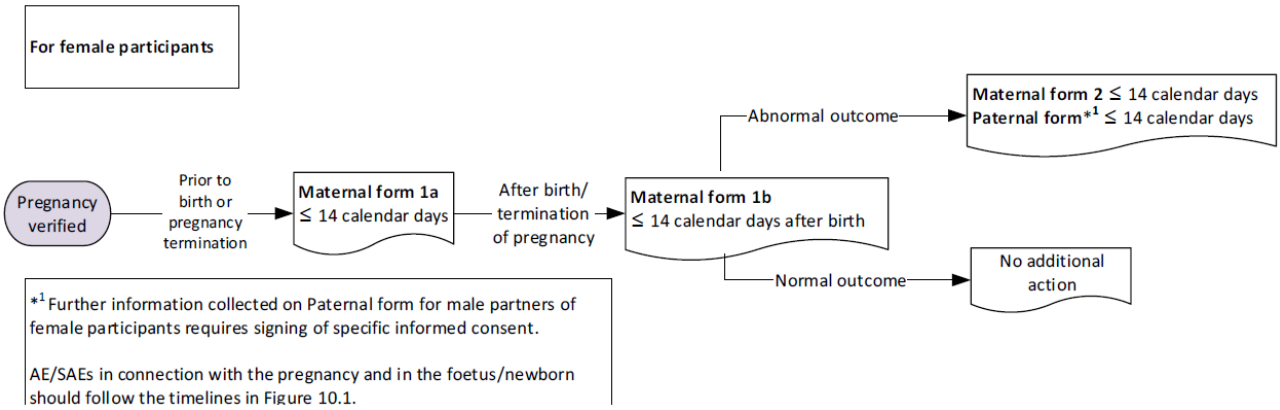
Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, any AE in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding ‘gestational’, ‘pregnancy-related’ or a similar term when reporting the AE/SAE.

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

If the investigator learns of an SAE occurring as a result of a post-study pregnancy which is considered related to the IMP by the investigator, the SAE should be reported to Novo Nordisk as described in Appendix 3 (Section 10.3).

Figure 10-2 Decision tree for determining the forms to complete for collection of pregnancy information and timelines for reporting – For female participants



Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

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

10.5.1 Definition of technical complaint

A technical complaint is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself.

Examples of technical complaints:

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

Time period for detecting technical complaints

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

10.5.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk

For contact details for Customer Complaint Center, please refer to Attachment I.

Technical complaints on products allocated to a participant must be reported on a separate technical complaint form:

1. For products with DUN: One technical complaint form must be completed for each affected DUN.
2. For products without DUN: One technical complaint form must be completed for each batch, code or lot number.

Timelines for reporting technical complaints to Novo Nordisk

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

- 24 hours if related to an SAE
- 5 calendar days for all other technical complaints

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

Follow-up of technical complaints

The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and all associated parts 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 study intervention.

10.5.3 Reporting of technical complaints for products not included in the technical complaint form

Technical complaints on Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk.

10.6 Appendix 6: Hypoglycaemic episodes

Table 10-4 Classification of hypoglycaemia

Classification of hypoglycaemia		
Level	Glycaemic criteria (SMPG)	Description
Hypoglycaemia alert value (level 1)	<70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (level 2)	<54 mg/dL (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (level 3)[1]	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,[29] ADA,[30] ISPAD,[31] type 1 diabetes outcomes program,[32] ATTD.[33] Severe hypoglycaemia as defined by Seaquist[34] and ISPAD.[31] **Abbreviations:** ADA = American Diabetes Association; ATTD = Advanced Technologies & Treatments for Diabetes; IHSG = International Hypoglycaemia Study Group; ISPAD = International Society for Pediatric and Adolescent Diabetes; SMPG = self-measured plasma glucose.		

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.[34]

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.[30]

Nocturnal hypoglycaemia

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

Reporting of hypoglycaemic episodes

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

Reporting of hypoglycaemic episodes by trial BG meters:

- A low scanned FGM (interstitial glucose) value cannot be used to complete the hypoglycaemic episode form.
- Plasma glucose (PG) should always be recorded in the paper diary and eCRF when a hypoglycaemic episode is suspected.

When a participant experiences a hypoglycaemic episode, the participant should record the general information in relation to the hypoglycaemia (timing, PG measurements, symptoms, etc.) as described in the diary. The investigator should ensure correct reporting of the hypoglycaemic

episode and report the hypoglycaemic episode to the CRF. In case a participant is not able to fill in the diary (e.g., in case of hospitalisation), the investigator should still report the hypoglycaemic episode on the hypoglycaemic episodes form.

Upon onset of a hypoglycaemic episode the participant 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.[34]

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 participants 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.[34]

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

Diary review

At each contact the investigator must review the diary data for correct reporting of PG values and hypoglycaemic episodes. In case of incomplete or incorrect data in the diary, the participant must be questioned whether there have been any severe hypoglycaemic episodes since the last visit and report accordingly

For low PG values for hypoglycaemic episodes with incomplete reporting information:

1. If a hypoglycaemic episode form in the diary is not completed by the participant within 7 calendar days of the PG measurement, the episode should be described in the source documents and reported by the investigator on a hypoglycaemic episode eCRF with as much information as possible. If the participant did not need help to get a sugary drink, food, or medicine, Novo Nordisk will only ask for start date due to recall bias.[35, 36]

Re-training of participants

The participant 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.

10.7 Appendix 7: Titration guideline

Titration guidelines have been developed, providing recommended dose adjustments at different FGM values. However, it is recognised that the 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 hypoglycaemia/hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the participants level of glycaemic control, is taken into consideration when decisions on dosing are made. The investigator is responsible for the treatment of the participants and can therefore overrule the guidelines to avoid safety hazards.

Initiation of insulin icodec

At V3 all eligible participants will initiate insulin icodec.

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

The treat-to-target approach will be applied to optimise glycaemic control throughout the trial.

There are no maximum or minimum insulin doses.

Dose adjustment of insulin icodec during the study

After V3 insulin icodec will be adjusted once a week or once every two weeks according to the scheduled visits/phone contacts by the investigator as described below.

The dose adjustment will be based on the three pre-breakfast FGM values as recorded by the patient on the day of titration and on the two days prior to titration.

If one or more FGM values are missing, the dose adjustment should be performed on the remaining FGM values.

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

Table 10-5 Insulin icodec

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

Abbreviation: FGM = flash glucose monitoring.

Deviations from the algorithm

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

Missing insulin icodec dose guidance:

If an insulin icodec dose is missed for ≤3 days after the planned dosing day, participants should inject the planned dose as soon as possible and monitor FGM. If a dose is missed >3 days after the planned dosing day, participants should not inject until the next planned day-of-injection.

Dose recommendation from end of treatment and during follow up

If it is decided that the individual participant should initiate basal insulin treatment after EOT it is recommended that the participant is switched from insulin icodec to any available daily basal insulin at the discretion of the investigator. Regarding switch from insulin icodec to post-trial basal insulin the following should be considered:

- Calculate the new daily basal insulin dose by dividing the latest insulin icodec dose by 7
- Initiate the new daily basal insulin two weeks after the last injection of insulin icodec
- Continue to scan pre-breakfast FGM daily in the follow-up period (5 weeks). If pre-breakfast FGM value exceeds 10.0 mmol/L (180 mg/dL), earlier initiation of daily basal insulin dose should be considered than two weeks after the last dose of insulin icodec
- Consider titrating the basal insulin once or twice weekly according to the pre-breakfast FGM values and the local label of the chosen insulin

Data collection

The following data should be collected by the participant

- Insulin icodec doses taken prior to the visit/phone contact including injection time and date
- The participants should scan FGM four times a day. To ensure FGM data collection four times in a day, it is recommended that the participants scan before breakfast, lunch and dinner and at bedtime. The investigator should review LibreView prior to each visit/phone contact to confirm participant compliance in use of the FGM system as described in the flowchart (Section 1.2).
- Ensure transfer of FGM values that have been scanned before breakfast and identified as "pre-breakfast" values
- Hypoglycaemic episodes

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

- FGM values with an indication of “pre-breakfast” from the three mornings before (2 days before, 1 day before, and on the morning of) each contact.
- Insulin icodec doses prescribed at this contact.
- Reasons for deviation from the titration algorithms, if applicable

Data surveillance

Surveillance of titration data will be performed centrally by Novo Nordisk in an unbiased manner. The data will be reviewed and significant deviations from the titration algorithm will be followed up.

It is important that data regarding dose titration is entered into the eCRF. If delays occur, action cannot be taken in due time before the participants next site visit/phone contact. The aim is to reduce the time periods in which a participant may receive suboptimal treatment.

The titration data should be reviewed by Novo Nordisk within 24 hours (on workdays). The reviewer may contact the investigator by e-mail or phone to clarify reasons for deviation or to request entry of missing data. When the investigator receives an inquiry, a response should be received at Novo Nordisk within 24 hours (on workdays).

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

10.8 Appendix 8: Country-specific requirements

For USA:

- **FDA Form 1572:** All United States investigators will sign FDA Form 1572
- **Retention of clinical trial documentation:** 25 years
- **Financial disclosure:** Verification under disclosures per CFR of Financial Conflict of Interest.

10.9 Appendix 9: Abbreviations

AACE	American Association of Clinical Endocrinology
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
CFR	code of federal regulations
CI	confidence interval
COVID-19	Corona virus Disease-19
CRF	case report form
CSR	clinical study report
DFU	directions for use
DPP-4	dipeptidyl peptidase-4
DPS	data points set
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated Glomerular Filtration Rate
EOT	end of treatment
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FGM	flash glucose monitoring
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide
GLP-1 RA	glucagon-like peptide 1 receptor agonist
HbA_{1c}	glycated haemoglobin
IB	investigator's brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IGlar	insulin glargine
IMP	investigational medicinal product
IND	investigational new drug

IRB	institutional review board
MMRM	mixed model for repeated measurements
NIMP	non-investigational medicinal product
NYHA	New York Heart Association
PAS	participant analysis set
PCD	primary completion date
PD	pharmacodynamic
PK	pharmacokinetic
PG	plasma glucose
QTc	corrected QT interval
QTL	quality tolerance limits
RTSM/IWRS	Randomisation and Trial Supply Management/Interactive Web Response System
SAE	serious adverse event
SAP	Statistical Analysis Plan
s.c	Subcutaneous
SD	standard deviation
SGLT2	sodium-dependent glucose cotransporter 2
SI-IC	subject information-inform consent
SG	sensor glucose
SMBG	self-measured blood glucose
SMPG	self-measured plasma glucose
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
T1D	type 1 diabetes
T2D	type 2 diabetes
TIR	time in range
TMM	trial materials manual
UNL	upper limit of normal
USA	United States of America
V	Visit
WOCBP	women of childbearing potential

10.10 Appendix 10: Protocol amendment history

(Not applicable yet)

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