Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT06340854
Sponsor trial ID:	NN1436-7724
Official title of study:	A Study to Evaluate the Efficacy and Safety of Once-weekly Insulin Icodec when Switching from Daily Basal Insulins Compared to Once-daily Insulin Glargine U100 in Adults with Type 2 Diabetes
Document date	02 April 2024

Protocol

Protocol Title:

A Study to Evaluate the Efficacy and Safety of Once-weekly Insulin Icodec when Switching from Daily Basal Insulins Compared to Once-daily Insulin Glargine U100 in Adults with Type 2 Diabetes

Short Title:

A Research Study to See How Switching from a Daily Basal Insulin to a New Weekly Insulin, Insulin Icodec, Helps in Reducing the Blood Sugar Compared to Daily Insulin Glargine in Adults with Type 2 Diabetes

Substance Name: Insulin Icodec

Protocol Version Number: Version 2.0

Protocol Version Applicability: Global

Universal Trial Number: U1111-1292-6151

EU CT Number: 2023-506084-34

IND Number: 137406

Study Phase: 3b

Sponsor Name: Novo Nordisk A/S
Sponsor Legal Address: Novo Alle, 2880 Bagsværd, Denmark

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

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
Protocol version 2.0	02 April 2024	All
Original protocol version 1.0	13 October 2023	All

Protocol version 2.0 (02 April 2024)

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of the 16 April 2014.[1]

Overall rationale for preparing protocol, version 2.0

Version 2.0 of the protocol was prepared to address requests raised by Food and Drug Administration dated 12 February 2024. The overall rationale for updating the protocol is to update the imputation model for change in time in range (TIR) and any other supportive endpoint referring to change in TIR from last available planned on-treatment without initiation of bolus insulin treatment (LAOT-WOB) to LAOT. Deleted text is written as ~~strikethrough~~ and new text in *italics*.

Section # and name	Description of change	Brief rationale
Header Page	Added the "*sponsor name and sponsor address*"	Updated to align with the new protocol template.
5.3.1, Meals and dietary restrictions	Added the text "*For all scheduled activities, meal and dietary restrictions are not applicable. In the case of potential lack of efficacy as described in Section 7.1, participants attend an unscheduled visit in a fasting state for blood sampling. Fasting is defined as at least 8 hours without food and drink intake, except for water and prescription medications. Trial product and other glucose lowering agents should be withheld on the day of the fasting visit until blood sampling has been performed. All other prescription medication should be taken as usual. If the participant attends this visit in a non-fasting state, the blood sampling is to be rescheduled.*"	Clarifying edit.
6.8, Dose modification	Section and text added *"6.8.1 Rescue medicine. Not applicable for this*	Clarifying edit.

Section # and name	Description of change	Brief rationale
	study. In case of lack of efficacy, please refer to Section 7.1."	
Section 9.2, Analysis sets	Text added "*all PROs*" in the evaluation list along with all efficacy, and all CGM metrics to be evaluated using the full analysis set and the in-study data points set.	Clarifying edit.
Section 9.3.2.2, Main analytical approach	Text updated "participants who ~~experience intercurrent events~~ *discontinue investigational intervention*".	Clarifying edit.
Section 9.3.2.2, Main analytical approach; Section 9.3.3.1.1, Supportive secondary efficacy estimands, and 9.3.3.1.2, Supportive secondary safety estimands	Text deleted "~~without initiation of bolus insulin treatment for more than 2 weeks (WOB)~~".	To comply with request from Health Authorities.
9.3.3.1.2, Supportive secondary safety estimands	"~~minutes~~" has been replaced with "*recorded measurements*".	Clarifying edit.

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1 Protocol summary

1.1 Synopsis

This is an interventional, multi-national, multi-centre, randomised, parallel-group, treat-to-target, open-label, active-comparator study.

Rationale:

This is a 26-week study designed to investigate the effect on glycaemic control, safety and patient-reported outcomes (PROs) of once-weekly insulin icodec, switched unit-to-unit from a daily basal insulin, versus once-daily insulin glargine U100, both treatment arms with or without non-insulin anti-diabetic drugs, in adults with type 2 diabetes (T2D) treated with basal insulin.

Objective, estimand and endpoints:

Primary objective

To demonstrate the effect on glycaemic control of once-weekly insulin icodec, switched unit-to-unit from a daily basal insulin, with or without non-insulin anti-diabetic drugs, in participants with T2D treated with basal insulin. This includes comparing the difference in change from baseline in HbA_{1c} between insulin icodec and insulin glargine U100 after 26 weeks of treatment to a non-inferiority margin of 0.3%-point.

Estimand

The primary clinical question of interest is:

What is the treatment difference between once-weekly insulin icodec, switched unit-to-unit from a daily basal insulin, and once-daily insulin glargine U100, both treatment arms with or without non-insulin anti-diabetic drugs, in terms of change in HbA_{1c} from baseline to week 26 in participants with T2D treated with basal insulin, regardless of initiation of bolus insulin treatment for more than 2 weeks and discontinuation of investigational intervention?

The primary estimand is described by the following five attributes:

- Treatment condition: The investigational interventions, both treatment arms with or without non-insulin anti-diabetic drugs, regardless of initiation of bolus insulin treatment for more than 2 weeks and discontinuation of investigational intervention
- Population: Participants with T2D treated with basal insulin
- Endpoint: Change in HbA_{1c} from baseline to week 26
- Remaining intercurrent events: None. The two intercurrent events are captured under treatment condition and handled as follows:
    - Initiation of bolus insulin treatment for more than 2 weeks by the treatment policy strategy
    - Discontinuation of investigational intervention by the treatment policy strategy
- Population-level summary: Difference in mean changes between treatment conditions

Endpoints

The primary endpoint is the change in HbA_{1c} from baseline week 0 (V6) to week 26 (V32).

Overall design:

This is a 26-week randomised, open label, active-controlled, parallel-group, multi-centre, multi-national, treat-to-target study with two treatment arms. Participants will be randomised (1:1) to receive once-weekly insulin icodec or once-daily insulin glargine U100.

The study consists of:

- a 2-week screening period
- a 4-week run-in period with continuous glucose monitoring (CGM)
- a 26-week investigational intervention period
- a 5-week safety follow-up period

Study intervention groups and duration:

The study includes a screening visit (V1) to assess participants eligibility. After screening, all eligible participants will enter the blinded CGM run-in period at the run-in visit (V2). After the run-in period, participants will be randomised (1:1) to receive once-weekly insulin icodec or once-daily insulin glargine U100 at the randomisation visit (V6). After the 26 weeks of treatment, participants will come in for an end-of-intervention visit (V32), which will be one week after the last dose of insulin icodec and on the day of or the day after the last dose of insulin glargine U100. Two safety follow-up visits (V33 and V34) will be performed 2 and 5 weeks, respectively, after the end-of-intervention visit (V32).

Number of participants:

- Number of participants planned to be screened: 533
- Number of participants planned to be randomly assigned to study intervention: 404

Participant characteristics:

The participants will be male or female aged 18 years and above at the time of signing informed consent and meet the following inclusion criteria and none of the following exclusion criteria:

Key inclusion criteria

- Diagnosed with T2D ≥180 days prior to the day of screening.
- HbA_{1c} from 7.0-10.0% (53.0-85.8 mmol/mol), both inclusive, at screening confirmed by central laboratory analysis.
- Treated with once-daily or twice-daily basal insulin (Neutral Protamine Hagedorn insulin, insulin degludec, insulin detemir, insulin glargine 100 U/mL, or insulin glargine 300 U/mL) ≥ 90 days prior to the day of screening with or without any of the following anti-diabetic drugs/regimens with stable doses ≥ 90 days prior to screening: metformin, sulfonylureas, meglitinides (glinides), DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, oral combination products (for the allowed individual oral anti-

diabetic drugs), oral or injectable GLP-1 RAs, injectable GLP-1/GIP RA combination products.
- Body mass index (BMI) ≤ 40.0 kg/m^2.

Key exclusion criteria

- Any episodes of diabetic ketoacidosis within 90 days prior to the day of screening.
- Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.
- Chronic heart failure classified as being in New York Heart Association Class IV at screening.
- Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g., treatment with orlistat, thyroid hormones, or corticosteroids).
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

Data monitoring committee:

No

1.2 Flowchart

Procedure	Protocol Section	Screening	Run-in with CGM			Randomisation	Intervention period								Follow-up		Discontinuation follow-up
Visit		V1	V2	V3	V4	V6	V7	V8	V10	V16	V24	V28	V30	V32	V33	V34	V32A
Weekly Phone Contacts number (P; for details see separate flowchart 1.3)					P5			P9	P11-P15	P17-P23	P25-P27	P29	P31				
Timing of Visit (Weeks)		≤-6	-4	-3	-2	0	1	2	4	10	18	22	24	26	28	31	26
Visit Window (Days)		+14	±3	±3	±3	±0	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3
Informed Consent	10.1.3	X															
Demography	8	X															
Eligibility Criteria	5.1, 5.2, 5.5	X	X	X	X	X											
Concomitant Medication	6.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History/Concomitant Illness	8.2	X	X	X	X	X											
Tobacco Use	5.3.2	X															
Childbearing Potential	10.4	X															
Pregnancy Test	8.3.5, 10.4	X				X										X	
Body Measurements	8.2.2	X				X					X			X			X
Body weight	8.2.2	X				X					X			X			X
Vital Signs	8.2.3	X												X			
Physical Examination	8.2.2	X												X			

Procedure	Protocol Section	Screening	Run-in with CGM			Randomisation	Intervention period								Follow-up		Discontinuation follow-up
Visit		V1	V2	V3	V4	V6	V7	V8	V10	V16	V24	V28	V30	V32	V33	V34	V32A
Weekly Phone Contacts number (P; for details see separate flowchart 1.3)					P5			P9	P11-P15	P17-P23	P25-P27	P29	P31				
Timing of Visit (Weeks)		≤-6	-4	-3	-2	0	1	2	4	10	18	22	24	26	28	31	26
Visit Window (Days)		+14	±3	±3	±3	±0	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3
ECG	8.2.5	X												X			
Eye Examination	8.2.4	X												X			
Hypoglycaemia Unawareness	8.2	X															
Blinded CGM	8.1.3		X	X	X	X	X	X	X			X	X	X			
CGM fitting	8.1.3		X	X	X	X	X	X				X	X				
CGM data upload	8.1.3			X	X	X	X	X	X				X	X			
Self-Measured Plasma Glucose	8.1.2					X	X	X	X	X	X	X	X	X	X	X	
Adverse Event	8.3						X	X	X	X	X	X	X	X	X	X	X
Technical Complaints	8.3.6					X	X	X	X	X	X	X	X	X			
Laboratory Assessments	10.2	X				X				X	X			X			X
HbA_{1c}	10.2	X				X				X	X			X			X
Hypoglycaemic episodes	10.7						X	X	X	X	X	X	X	X	X	X	
Clinical Outcome Assessments	8.1.4					X								X			
Diabetes Treatment Satisfaction Questionnaire status version (DTSQs)	8.1.4					X								X			

Procedure	Protocol Section	Screening	Run-in with CGM			Randomisation	Intervention period								Follow-up		Discontinuation follow-up
Visit		V1	V2	V3	V4	V6	V7	V8	V10	V16	V24	V28	V30	V32	V33	V34	V32A
Weekly Phone Contacts number (P; for details see separate flowchart 1.3)					P5			P9	P11-P15	P17-P23	P25-P27	P29	P31				
Timing of Visit (Weeks)		≤-6	-4	-3	-2	0	1	2	4	10	18	22	24	26	28	31	26
Visit Window (Days)		+14	±3	±3	±3	±0	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3	±3
Patient Global Impression of Status (PGI-S)	8.1.4					X								X			
Treatment-Related Impact Measure for Diabetes (TRIM-D)	8.1.4					X								X			
Drug Dispensing	6.1					X			X	X	X	X					
Training in Trial Product, Pen-handling	6.1					X			X	X	X	X					
Training in eDiary	8					X											
End of Intervention	4.1, 6													X[a]			
End of Study	4.4, 7															X	X[b]

[a]The last dose of insulin icodec must be administered 1 week before end of intervention due to its longer half-life. The last dose of insulin glargine U100 must be administered at end of intervention (V32). For participants taking insulin glargine U100 in the evenings, the last dose of trial product should be taken the evening prior to end of intervention.

[b]Applies only to participants who have discontinued investigational intervention.

Abbreviations: CGM = continuous glucose monitoring; DTSQs = Diabetes Treatment Satisfaction Questionnaire status version; ECG = electrocardiogram; HbA1c = glycosylated haemoglobin; P = phone contact; PGI-S = Patient Global Impression of Status; TRIM-D = Treatment-Related Impact Measure for Diabetes; V = visit.

1.3 Flowchart – phone contacts

Phone contacts during the intervention period (P) Time shown in site visit flow chart	**Protocol section**	**P5**	**P9**	**P11-P15**	**P17-P23**	**P25-P27**	**P29**	**P31**
Timing of Phone Contact (Weeks)		-1	3	5-9	11-17	19-21	23	25
Visit window (days)		±3	±3	±3	±3	±3	±3	±3
Blinded CGM	8.1.3	X	X				X	X
CGM fitting	8.1.3	X	X				X	X
Concomitant medication	6.8	X	X	X	X	X	X	X
Self-measured plasma glucose	8.1.2		X	X	X	X	X	X
Adverse event	8.3		X	X	X	X	X	X
Hypoglycaemic episodes	10.7		X	X	X	X	X	X
Last Dose of Trial product Insulin icodec	4.1, 6.1							X[a]

[a]The last dose of insulin icodec must be administered 1 week before end of intervention due to its longer half-life. The last dose of insulin glargine U100 must be administered at end of intervention (V32). For participants taking insulin glargine U100 in the evenings, the last dose of trial product should be taken the evening prior to end of intervention.

Abbreviations: CGM = continuous glucose monitoring; P = phone contact.

2 Introduction

Diabetes mellitus is a metabolic disorder characterised by the presence of hyperglycaemia due to defective insulin secretion, insulin action or both. The chronic hyperglycaemia of diabetes mellitus is associated with significant long-term complications, particularly damage, dysfunction, and failure of various tissues – especially the kidney, eye, nerves, heart, and blood vessels.[2] Diabetes is generally classified according to aetiological factors, in which 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), 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.[3]

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 injection. For people 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[4] compared to once- or twice-daily basal insulin administration. The aim of the ONWARDS development programme for insulin icodec was to improve clinical outcomes for adults with diabetes by limiting the burden associated with insulin treatment.

In a phase 2 study with insulin-experienced adults with T2D, NN1436-4466, switching from a daily basal insulin to insulin icodec without a one-time additional dose, the participants displayed similar glycaemic control after 16 weeks compared to once-daily insulin glargine U100.[5] In the phase 3a study, NN1436-4478 (ONWARDS 2), it was demonstrated to be safe and effective for insulin-experienced participants with T2D to switch to insulin icodec on a unit-to-unit base (seven times pre-study daily basal insulin dose) while adding a one-time additional dose of 50% the first week.[6] As with all basal insulins, insulin icodec is recommended to be dosed in accordance with the individual person's needs at the discretion of the treating physician. For some individuals, switching from a daily basal insulin to insulin icodec without administering the one-time additional dose of 50% at the first injection may be preferable. Therefore, the aim of this study is to confirm the efficacy and safety of insulin icodec, switched unit-to-unit from a daily basal insulin, in adults with T2D on a background of non-insulin anti-diabetic drugs.

2.1 Study rationale

This is a 26-week study designed to investigate the effect and safety of once-weekly insulin icodec, switched unit-to-unit from a daily basal insulin, in comparison to once-daily insulin glargine U100, both treatment arms with or without non-insulin anti-diabetic drugs, in adults with T2D.

Overall, the results of the present study will be important for evaluating the effect and safety of insulin icodec, switched unit-to-unit from a daily basal insulin, in adults with T2D. The study will also generate data to guide the treating physicians in tailoring their dosing decisions to the needs of each patient.

2.2 Background

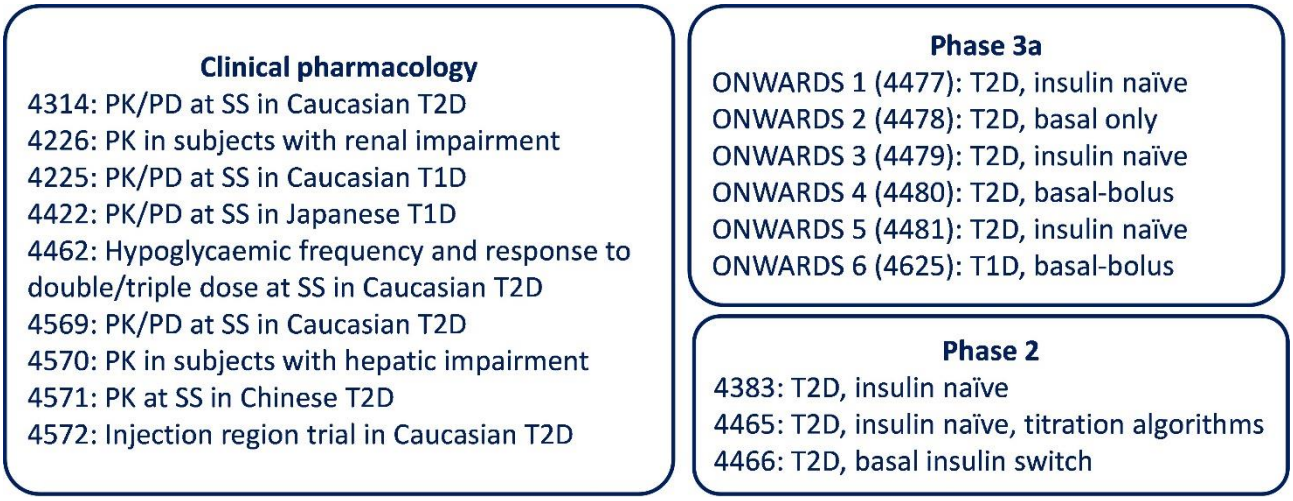
Diabetes mellitus

T2D is characterised by insulin resistance, impaired insulin secretion, increased hepatic glucose output due to glucagon dysregulation resulting in chronic hyperglycaemia.[7] The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors.[8] 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.[9] On average, after failure of diet and exercise alone, people with T2D require a new intervention with glucose-lowering agents every 3-4 years in order to obtain/retain good glycaemic control.[10] Clinical inertia, often resulting from a resistance to insulin initiation and intensification, is a major contributing factor to people with T2D who are not achieving recommended glycaemic targets.[11, 12] 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 1 week, supporting once-weekly dosing. 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 phase 3a programme for insulin icodec has been completed, and the phase 3b programme is currently ongoing.

The clinical development programme for insulin icodec consisted of 18 studies, which have all been completed:



Results from the phase 2 studies were used in the development of the insulin icodec titration guideline used in the phase 3a studies (Appendix 8 [Section 10.8]). Throughout the development

programme, use of insulin icodec was safe and provided effective glycaemic control. A comprehensive review of results from the non-clinical and clinical studies of insulin icodec can be found in the current edition of the investigator's brochure (IB).[13]

Insulin glargine U100

For further details on insulin glargine U100, please refer to the current EMA summary of product characteristics for insulin glargine U100 (Lantus®),[14] the US prescribing information for insulin glargine U100 (Lantus®),[15] or any locally approved label.

Study population

The study population will consist of participants with T2D on basal insulin therapy with or without non-insulin anti-diabetic drugs ensuring a study population representative of a broad T2D population. In the phase 3a programme, insulin-experienced participants with T2D in the insulin icodec treatment arm received a one-time additional dose of 50% when switching from once-daily basal insulin. Therefore, the same population was selected to evaluate the safety and efficacy of insulin icodec administered without the one-time additional dose of 50%.

Eligible participants will be identified by the investigator within the normal clinical practice setting. For more information on the study population, see Section 5, and 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 of insulin icodec may be found in the IB.

2.3.1 Risk assessment

Table 2-1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Study intervention (insulin icodec)		
Identified risk: Hypoglycaemia	Hypoglycaemia is an anticipated undesirable effect related to the pharmacological mechanism of insulin	Exclusion criteria in clinical studies with participants at increased risk of hypoglycaemia: • Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8 (Section 5.25.2), • Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
		Frequent blood glucose measurements will be made throughout drug exposure and will prevent worsening of hypoglycaemia by early detection and administration of carbohydrates and medical treatment, if necessary. The risk of hypoglycaemia is addressed in the SI/IC and IB. Participants are provided with a guidance on hypoglycaemia awareness and rescue actions.
Identified risk: Injection site reactions	Injection site reactions may occur with all injectable drugs. Injection site reactions were reported in the insulin icodec clinical phase 1, phase 2 and completed phase 3 studies.	Participants are instructed by the investigators on the most appropriate injection techniques. Recommendations on rotation of the site of injection are included in the study protocol and SI/IC. Investigators and participants 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 and SI/IC.
Identified risk: Hypersensitivity	Hypersensitivity reactions may potentially occur following injection of therapeutic proteins. Reactions have been observed in previous insulin icodec studies.	Known or suspected hypersensitivity to trial product(s) or related products is an exclusion criterion in the clinical study. Participants and investigators will be instructed in signs and symptoms of hypersensitivity reactions and participants 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 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 study participants treated with insulin icodec.	Participants and investigators will be instructed in signs and symptoms of peripheral oedema. Risk of peripheral oedema is described in the IB and SI/IC.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Potential risk: Immunological events – formation of insulin antibodies	Antibodies to exogenously delivered insulin are common with insulin treatment but are not often clinically significant. In NN1436-4478, -4479, -4480 and -4625 the number of participants that developed anti-insulin icodec antibodies at any time during the study 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, -4480, and -4625 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. No apparent relationship between antibody titres and change in HbA_{1c} or weekly insulin dose was observed.	Investigators will closely monitor the glycaemic control of each participant throughout the study. In case lack of clinical effect is observed, rescue medication will be provided if deemed necessary and participant 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 and SI/IC. For more information on study discontinuation, please refer to Section 7.1.
Study procedures		
Potential risk: COVID-19 infection in relation to participation in study	Participants 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 minimise the risk as much as possible, the following measures have been taken: • Cautious subject recruitment planning ensures controlled subject enrolment in countries where the COVID-19 pandemic is evaluated to be sufficiently under control, and at sites where health care resources are evaluated to be adequate. On-site visits will be well-prepared and as short as possible. Physical contact between participants and site staff will be limited to the extent possible, and protective measures will be implemented (e.g., use of masks, sanitisers, no aerosol-generating procedures, etc., according to the local practice).
Other		

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Device medication error	If the pen-injector is damaged or used differently than described in the directions for use or in the current EMA summary of product characteristics[14] and the US prescribing information for insulin glargine U100,[15] a risk of overdose or underdose of investigational intervention exists. This may cause hypoglycaemia due to overdose or hyperglycaemia due to underdose.	Training in injections and use of devices and guidance materials for investigator, site staff and participants will be provided.
For more information regarding the known and expected benefits and risks of insulin glargine U100, please refer to the insulin glargine U100 IB, the EMA SmPC,[16] the US PI,[17] or any locally approved label.		

Abbreviations: COVID-19 = Coronavirus Disease of 2019; EMA = European Medicines Agency; HbA_{1c} = glycosylated haemoglobin; IB = investigator's brochure; PI = package insert; SI/IC = subject information/informed consent; SmPC = Summary of Product Characteristics.

Risk assessment has been conducted for the PDS290 icodec clinical pen-injector for insulin icodec in accordance with ISO 14971:2019.

All identified risks (see Table 2-1) associated with using the PDS290 icodec clinical pen-injector for insulin icodec according to the clinical procedures specified in this protocol have been reduced as far as possible and are acceptable, taking into account the current state of the art. The use of the PDS290 icodec clinical pen-injector for insulin icodec in this study is therefore considered to be of non-significant risk.

2.3.2 Benefit assessment

Insulin icodec is currently in development for treatment of diabetes mellitus. In both clinical and non-clinical studies, 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.[18] Therefore, the treatment adherence and quality of life are expected to increase by introducing a once-weekly basal insulin treatment.

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

2.3.3 Overall benefit-risk conclusion

Insulin icodec is efficacious at clinically relevant doses. The titration guidance used in the phase 3a studies aimed to achieve good glycaemic control without increasing the risk of hypoglycaemic events. In NN1436-4478 (ONWARDS 2), insulin icodec use in insulin-experienced participants with T2D was demonstrated to be safe and effective. Switching to insulin icodec from a daily basal insulin may increase the time to glycaemic target by an estimated 1-2 weeks compared to adding a one-time additional dose of 50%. However, the overall safety and efficacy profile of insulin icodec is not expected to change.

No new significant safety information that changes the current benefit-risk profile of insulin icodec emerged from the completed clinical studies. The safety profile of insulin icodec remains in line with the cumulative experience. As an overall assessment, Novo Nordisk evaluates that the benefit-risk balance of insulin icodec remains favourable. Taking into account the measures taken to minimise risk and burden to participants in this study, the potential risks identified in association with insulin icodec are justified by the anticipated benefits that may be afforded to participants with T2D.

More detailed information about the known and expected benefits and risks of insulin icodec can be found in the IB.[13]

3 Objectives, endpoints and estimands

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
To demonstrate the effect on glycaemic control of once-weekly insulin icodec, switched unit-to-unit from a daily basal insulin, with or without non-insulin anti-diabetic drugs, in participants with T2D treated with basal insulin. This includes comparing the difference in change from baseline in HbA_{1c} between insulin icodec and insulin glargine U100 after 26 weeks of treatment to a non-inferiority margin of 0.3%-point.	Primary endpoint:		
	Change in HbA_{1c}	From baseline week 0 (V6) to week 26 (V32)	%-point
Secondary	**Title**	**Time frame**	**Unit**
To compare parameters of glycaemic control, patient-reported outcomes and safety of once-weekly insulin icodec, switched unit-to-unit from a daily basal insulin, compared to once-daily insulin glargine U100, both treatment arms with or without non-insulin anti-diabetic drugs, in participants with T2D treated with basal insulin.	Supportive secondary endpoints:		
	Secondary efficacy endpoints:		
	Change in time in range 3.9–10.0 mmol/L (70–180 mg/dL)[a]	From baseline week -4–0 (V2–V6) to week 22–26 (V28–V32)	% of time
	Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire status version) total treatment satisfaction	From baseline week 0 (V6) to week 26 (V32)	Score of 0–36. 6 items scored on a scale of 0 to 6. The higher the score the greater the satisfaction with treatment.
	Secondary safety endpoints:		
	Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V6) to week 31 (V34)	Number of episodes
	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V6) to week 31 (V34)	Number of episodes
	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V6) to week 31 (V34)	Number of episodes

Objectives	Endpoints		
	Time spent < 3.0 mmol/L (54 mg/dL)[a]	During week 22–26 (V28–V32)	% of time
	Change in time spent > 10.0 mmol/L (180 mg/dL)[a]	From baseline week -4–0 (V2–V6) to week 22–26 (V28–V32)	% of time
	Mean weekly insulin dose	From week 24 (V30) to week 26 (V32)	U
	Change in body weight	From baseline week 0 (V6) to week 26 (V32)	kg
	Exploratory endpoints:		
	Change in TRIM-D (Treatment-Related Impact Measure for Diabetes) total	From baseline week 0 (V6) to week 26 (V32)	Score of 28–140. 28 items scored on a scale of 1 to 5 across 5 different domains. Transformed to a 0–100 scale with higher scores indicating a better health state.

[a]Using continuous glucose monitoring (CGM) system, Dexcom G6.
Abbreviations: BG = blood glucose; DTSQs = Diabetes Treatment Satisfaction Questionnaire status version; HbA_{1c} = glycosylated haemoglobin; T2D = type 2 diabetes; TRIM-D = Treatment-Related Impact Measure for Diabetes; V = visit.

Primary estimand

The primary clinical question of interest is:

What is the treatment difference between once-weekly insulin icodec, switched unit-to-unit from a daily basal insulin, and once-daily insulin glargine U100, both treatment arms with or without non-insulin anti-diabetic drugs, in terms of change in HbA_{1c} from baseline to week 26 in participants with T2D treated with basal insulin, regardless of initiation of bolus insulin treatment for more than 2 weeks and discontinuation of investigational intervention?

The primary estimand is described by the following five attributes:

- Treatment condition: The investigational interventions, both treatment arms with or without non-insulin anti-diabetic drugs, regardless of initiation of bolus insulin treatment for more than 2 weeks and discontinuation of investigational intervention
- Population: Participants with T2D treated with basal insulin
- Endpoint: Change in HbA_{1c} from baseline to week 26
- Remaining intercurrent events: None. The two intercurrent events are captured under treatment condition and handled as follows:

- Initiation of bolus insulin treatment for more than 2 weeks by the treatment policy strategy
- Discontinuation of investigational intervention by the treatment policy strategy

- Population-level summary: Difference in mean changes between treatment conditions

The rationale for the primary estimand is that this estimand captures both the efficacy and safety of the investigational interventions, both treatment arms with or without non-insulin anti-diabetic drugs, regardless of initiation of bolus insulin treatment for more than 2 weeks and discontinuation of investigational intervention and, thus, aims to reflect clinical practice.

4 Study design

4.1 Overall design

This is an interventional, multi-national, multi-centre, randomised, 26-week, parallel-group, treat-to-target, open-label, active-comparator study. The study is designed to investigate the effect on glycaemic control, safety and PROs of once-weekly insulin icodec, switched unit-to-unit from a daily basal insulin, versus once-daily insulin glargine U100, both treatment arms with or without non-insulin anti-diabetic drugs, in adults with T2D treated with basal insulin.

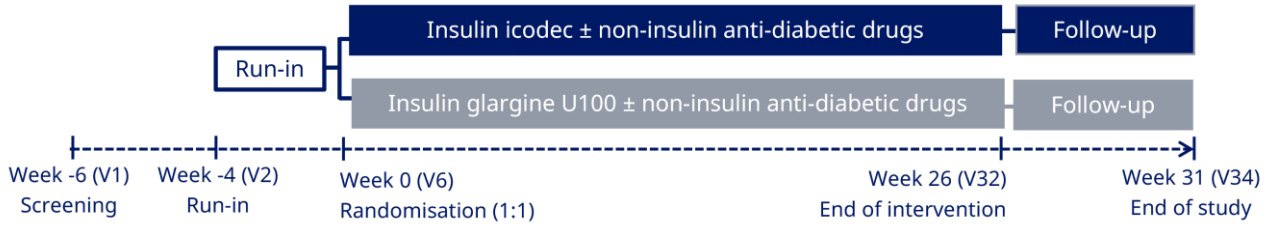
The study consists of:

- an up to 2-week screening period
- a 4-week run-in period with CGM
- a 26-week intervention period
- a 5-week safety follow-up period

The study includes a screening visit (V1) to assess participants eligibility. After screening, all eligible participants will enter the blinded CGM run-in period at the run-in visit (V2). Participants are to remain on their pre-study basal insulin during the run-in period with CGM. After the run-in period, participants will be randomised (1:1) to receive once-weekly insulin icodec or once-daily insulin glargine U100 at the randomisation visit (V6).

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

Figure 4-1 Study design



With exception from sulfonylureas and glinides that must be discontinued at the randomisation visit (V6), the dose and dosing frequency of any pre-study non-insulin anti-diabetic drugs should not be changed during the study, unless due to safety concerns.

Participants will measure daily self-measured plasma glucose (SMPG) throughout the 26-week intervention period (V6–V32) and the 5-week safety follow-up period (V33–V34). The SMPG measurements will be evaluated by the investigator at the weekly contact, either as site visits, by phone or video call.

At the weekly contacts, the dosing will be adjusted according to titration guidelines (Appendix 8, Section 10.8). The treatment duration with investigational interventions for individual participants is planned for 26 weeks.

After the 26 weeks of treatment, participants will come in for an end-of-intervention visit (V32), in which data for the primary endpoint will be collected. The visit at week 26 (V32) will be one week after the last dose of insulin icodec and on the day of or the day after the last dose of insulin glargine U100.

To evaluate the effect on glycaemic control, participants will have CGM profiles collected at baseline and during the first 4 weeks and the end of the intervention period, as specified in the flowchart (Section 1.2).

Two safety follow-up visits (V33 and V34) will be performed 2 and 5 weeks, respectively, after the end-of-intervention visit (V32), meaning 3 and 6 weeks, respectively, after the last dose of insulin icodec. This will allow for appropriate wash-out of investigational interventions, following at least 5 half-lives thereof. After the end of intervention, participants will be transferred to a marketed product at the discretion of the investigator. See also Appendix 8 (Section 10.8).

Overall, the measures taken to ensure participant's safety, includes weekly contacts with site staff, a 5-week safety follow-up period, training of investigators and other site staff, safety surveillance and titration surveillance. In addition, in accordance with GCP, it is the investigators responsibility to assess participant's safety and at their discretion act accordingly.

4.2 Scientific rationale for study design

The study is designed in alignment with the objectives (Section 3) to investigate the effect on glycaemic control, safety and PROs of once-weekly insulin icodec, switched unit-to-unit from a daily basal insulin, versus once-daily insulin glargine U100 in participants with T2D during 26 weeks of treatment.

Currently, basal insulins are dosed once or twice daily. In order to compare to well-established and widely used basal insulin analogues with once-daily dosing, insulin glargine U100 has been chosen as comparator.

The treatment arms will be open-label as it was not considered feasible to blind the two treatments due to the PRO assessments of treatment satisfaction and other PRO domains. In addition, a double-blind, double-dummy study would increase the treatment complexity and therefore increase the burden on the participants.

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 optimising the basal insulins. The treat-to-target approach has been chosen to ensure optimal titration of both treatment arms based on SMPG values with the aim of improving HbA_{1c} in the intervention period.

Titration of insulin icodec and insulin glargine U100 will be based on pre-breakfast SMPG values and follow the principles outlined in the titration guideline, see Appendix 8 (Section 10.8). CGM values will be collected at baseline (week -4–0), after initiation of the investigational intervention (week 0–4) and at end of treatment period (week 22–26). The CGM data collected at baseline and end of study will be used to evaluate the change from baseline in CGM-based glycaemic control. The CGM data collected after initiation of the investigational intervention will be used to evaluate the glycaemic control in the first initial period after switching to a once-weekly insulin without the one-time additional dose of 50%. CGM data for all three data collection periods will be included in the reporting phase.

Participants included in the study will already be on basal insulin treatment with or without non-insulin anti-diabetic drugs ensuring a study population representative of a broad T2D population. To minimise the risk of hypoglycaemia, sulfonylureas and glinides must be discontinued at randomisation.

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

The end-of-study visit is planned six weeks after the last weekly dose of insulin icodec, which corresponds to at least 5 half-lives of insulin icodec and allows enough time for wash-out of the investigational intervention.

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

4.3 Justification for dose

Insulin glargine U100 will be either switched from the pre-study basal insulins according to local label or continued in those participants that were already on glargine U100 before the study. Insulin icodec will be initiated according to the principles outlined in the titration guideline in Appendix 8 (Section 10.8). Based on modelling data, switching unit-to-unit to insulin icodec from a daily basal insulin may increase the time to reach glycaemic target by an estimated 1–2 weeks compared to initiating insulin icodec treatment by including a one-time additional dose of 50% as done in ONWARDS 2 (NN1436-4478). However, no changes in the overall safety and efficacy profile of insulin icodec are anticipated.

One unit of insulin icodec has similar glucose lowering effect to one unit of insulin glargine U100, and therefore once-weekly dosing corresponds to seven times the daily dose of the once-daily comparator.

The PK/PD properties of insulin icodec following five weeks of once-weekly dosing in 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 units/kg).[19]

After randomisation, participants should start once-daily insulin glargine U100 or once-weekly insulin icodec injections on the same day as the randomisation. Due to the longer half-life of insulin icodec, the last dose of insulin icodec will be administered 25 weeks after randomisation, while the last dose of once-daily insulin glargine U100 will be administered 26 weeks after randomisation. The follow-up period for both insulin icodec and insulin glargine U100 will be the 5 weeks from end-of-intervention visit (V32) until the end of the study (V34).

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

4.4 End of study definition

The end of the study is defined as the date of the last scheduled procedure shown in the flowchart for the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure shown in the flowchart.

The primary endpoint is evaluated at the visit at week 26 (V32/V32A). The primary completion date (PCD) is defined as the date of the visit at week 26 (V32/V32A) 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 the visit at week 26 (V32).

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 participant 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. Male or female.
3. Age 18 years or above at the time of signing the informed consent.
4. Diagnosed with T2D ≥ 180 days prior to the day of screening.
5. HbA_{1c} from 7.0–10.0% (53.0-85.8 mmol/mol), both inclusive, at screening confirmed by central laboratory analysis.
6. Treated with once-daily or twice-daily basal insulin (Neutral Protamine Hagedorn insulin, insulin degludec, insulin detemir, insulin glargine 100 U/mL, or insulin glargine 300 U/mL) ≥ 90 days prior to the day of screening with or without any of the following anti-diabetic drugs/regimens with stable doses ≥ 90 days prior to screening:
   - Metformin
   - Sulfonylureas
   - Meglitinides (glinides)
   - DPP-4 inhibitors
   - SGLT2 inhibitors
   - Thiazolidinediones
   - Alpha-glucosidase inhibitors
   - Oral combination products (for the allowed individual oral anti-diabetic drugs)
   - Oral or injectable GLP-1 RAs
   - Injectable GLP-1/GIP RA combination products
7. BMI ≤ 40.0 kg/m^2.

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 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 screening in the current study.
5. Any disorder, except for conditions associated with T2D, which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.
6. Any episodes[a] of diabetic ketoacidosis within 90 days prior to the day of screening.
7. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.
8. Chronic heart failure classified as being in New York Heart Association Class IV at screening.
9. Planned coronary, carotid or peripheral artery revascularisation.
10. Renal impairment with estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73m^2 at screening[20] by central laboratory analysis.
11. Impaired liver function, defined as Alanine Aminotransferase ≥ 2.5 times or Bilirubin >1.5 times upper normal limit at screening.
12. Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8[21] (Section 8.2).
13. Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator.
14. Inadequately treated blood pressure defined as systolic ≥180 mmHg or diastolic ≥110 mmHg at screening.
15. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days prior to the day of screening.
16. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g., treatment with orlistat, thyroid hormones, or corticosteroids).
17. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening (V1) and until the start of run-in (V2). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.
18. Presence or history[a] of malignant neoplasms 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 [PIN]) within 5 years before screening.
19. Anticipated change in lifestyle affecting glucose control (e.g., eating, exercise or sleeping pattern) during the study.
20. Use of any medication with unknown or unspecified content within 90 days prior to the day of screening.

[a]As declared by the participant or in the medical records.

5.3 Lifestyle considerations

5.3.1 Meals and dietary restrictions

~~Not applicable for this study.~~ For all scheduled activities, meal and dietary restrictions are not applicable. In the case of potential lack of efficacy as described in Section 7.1, participants attend an unscheduled visit in a fasting state for blood sampling. Fasting is defined as at least 8 hours without food and drink intake, except for water and other prescription medications. Trial product and other glucose lowering agents should be withheld on the day of the fasting visit until blood sampling has been performed. All other prescription medication should be taken as usual. If the participant attends this visit in a non-fasting state, the blood sampling is to be rescheduled.

5.3.2 Caffeine, alcohol and tobacco

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

5.3.3 Physical activity

Not applicable for this 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, eligibility criteria, results of laboratory analyses, and any serious adverse event (SAE).

A screen failure must be registered in the Systems used for Randomisation and Trial Supplies Management/Interactive Web Response System (RTSM/IWRS).

Individuals who do not meet the criteria for participation in this study may not be rescreened. If the individual 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 sample), re-sampling is allowed for the affected parameter(s).

5.5 Run-in criteria

The blinded CGM should only be initiated after all inclusion (Section 5.1) and exclusion criteria (Section 5.2) have been assessed.

5.5.1 Run-in Exclusion Criteria

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

1. Pregnancy
2. Intention of becoming pregnant
3. 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.

4. Included in the run-in period in violation of the inclusion and/or exclusion criteria
5. Initiation of bolus insulin for more than 14 days after screening
6. Other conditions that, at the discretion of the investigator, make the participant unsuitable for continued study participation.

To be randomised, 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 be randomised to investigational intervention (i.e., has met one of the run-in exclusion criteria).

A screen failure must be registered 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.

6 Study intervention(s) and concomitant therapy

Study intervention is defined as all pre-specified investigational and auxiliary medicinal products, medical devices and other intervention(s) (e.g., surgical and behavioural), intended to be administered to the study participants during the study conduct according to the study protocol. In this study, study interventions comprise insulin icodec, insulin glargine U100 and auxiliary medicinal products (AxMPs). Blood glucose (BG) meter and CGM are not considered study interventions.

Investigational interventions are a subset of study interventions that are being tested or used as a control (e.g., placebo or active control). In this study, insulin icodec and insulin glargine U100 are considered investigational interventions.

The term 'trial product' is used in the protocol when referring to specific actions to be taken (e.g., actions related to shipping and storage), that only apply for these products. In this study, 'trial products' comprise investigational medicinal products (IMPs), i.e., insulin icodec and insulin glargine U100.

6.1 Study interventions administered

Investigational medicinal products (IMP)

Table 6-1 provides an overview of all IMPs.

Table 6-1 Investigational medicinal products

Intervention	Icodec treatment arm	Comparator treatment arm
Intervention name	Insulin icodec	Insulin glargine
Intervention type	IMP, test product	IMP, reference therapy
Investigational or non-investigational	Investigational intervention	Investigational intervention
Pharmaceutical form	Solution for injection	Solution for injection
Route of administration	Subcutaneous (into the thigh, upper arm or abdomen)	Subcutaneous (into the thigh, upper arm or abdomen)
Trial product strength	700 U/mL	100 U/mL
Dose and dose frequency	Once-weekly dosing for a total of 26 weeks during intervention period. For dose titration, refer to Appendix 8 (Section 10.8).	Once-daily dosing for a total of 26 weeks during intervention period. For dose titration, refer to Appendix 8 (Section 10.8).
Dosing instructions and administration	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] A minimum of 4 days between injection should always be kept. Rotation of injection site is recommended.	Administer insulin glargine U100 once daily, at any time of the day but at the same time every day throughout the study. Rotation of injection site is recommended.
Transfer from other therapy	At randomisation visit (V6), participants must be transferred from their pre-study basal insulin treatment to insulin icodec as described in the titration guideline (Appendix 8 [Section 10.8])	At randomisation visit (V6), participants must be transferred from their pre-study basal insulin treatment to insulin glargine U100 as described in the titration guideline (Appendix 8 [Section 10.8])
Sourcing	Manufactured and supplied by Novo Nordisk A/S	Manufactured by Sanofi A/S. Supplied by Novo Nordisk A/S.
Packaging and labelling	Labelled and packaged by Novo Nordisk A/S. Labelled in accordance with EU CTR Annex VI,[22] local regulations and study requirements. Trial product is provided in 3 mL PDS290 pre-filled pen-injector.	Labelled and packaged by Novo Nordisk A/S. Labelled in accordance with EU CTR Annex VI,[22] local regulations and study requirements. Trial product is provided in 3 mL SoloSTAR pre-filled pen-injector.

[a]It is advised that insulin icodec is taken on the same day for better adherence and effect.
Abbreviations: CTR = Clinical Trials Regulation; IMP = investigational medicinal product; V = visit.

The investigator must document that directions for use (DFU) was given to the participant verbally and in writing as a DFU document (supplied in the eDiary for insulin icodec and paper for insulin glargine U100) at the first dispensing visit (as specified in the flowchart, Section 1.2).

- At randomisation visit (V6) participants should administer insulin icodec or insulin glargine U100 at site.
- Participants should be instructed to discard the needle after each injection and store the pen-injector without a needle attached.
- Instructions on missed doses can be found in the titration guideline in Appendix 8 (Section 10.8).
- It is not allowed to split a dose between two pens.
- Information about the PDS290 pre-filled pen-injector can be found in the eDFU.
- Information about the SoloSTAR pre-filled pen-injector can be found in the printed DFU.

Auxiliary medicinal products (AxMP)

After randomisation visit (V6), participants should continue their pre-study non-insulin anti-diabetic medication throughout the entire study except from sulfonylureas and glinides, which must be discontinued at randomisation. The dose and dosing frequency of pre-study non-insulin anti-diabetic medication should not be changed, unless due to safety concerns.

In addition, the pre-study non-insulin anti-diabetic medication:

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

Other study supplies including non-investigational medical device(s)

Other study supplies consist of non-medicinal products, including non-investigational medical device(s). Table 6-2 provides an overview of all other study supplies.

Table 6-2 Other study supplies

Study supply	Model	Details	Manufacturer
Needles	NovoFine® needles	Only needles with a maximum length of 6 mm provided and approved by Novo Nordisk must be used for administration of treatment. Please refer to TMM.	Novo Nordisk A/S
BG meter (including auxiliaries)	Roche Accu-Chek® Guide/Guide Me/Instant	At randomisation visit (V6) participants must be instructed in how to use the BG meter and the BG meter should be linked to the eDiary as described in the eDiary site guide. Please refer to the Roche manufacturer's guide.	Roche Diabetes Care Inc.
CGM system	Dexcom G6®	At first run-in visit (V2) participants must be instructed in handling of the CGM. Please refer to the Investigator CGM Manual provided.	Dexcom Inc.
eDiary	ePID	Participant Mobile App in Study Phone, HCP web portal in study tablet, & Cloud Service. Please refer to the eDiary site guide.	Novo Nordisk A/S
Abbreviations: BG = blood glucose; CGM = continuous glucose monitoring; ePID = electronic patient interactive device; HCP = healthcare professional; TMM = tactical medical module; V = visit.			

Only needles and prefilled pen-injectors provided by Novo Nordisk must be used for administration of trial product.

For a description of device components and materials in contact with tissues or body fluids, please refer to the BG meter manufacturer's guide and Investigator CGM Manual.

6.1.1 Investigational medical device

The study-provisioned CGM is used according to its approved indication for use in Bulgaria, Germany, Japan, Poland, South Africa, Spain and USA.

The CGM is not currently approved for use in India.

For the countries where the CGM is not approved and/or is not being used according to its approved indication for use, the study-provisioned CGM is regarded as an investigational medical device. Please refer to Appendix 9 (Section 10.9.1) for further information, including additional requirements for reporting of adverse events and technical complaints.

6.2 Preparation, handling, storage and accountability

Only participants enrolled in the study may use study intervention and only delegated site staff may supply study intervention.
Each site will be supplied with sufficient trial product(s) for the study on an ongoing basis according to recruitment and randomisation.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.

All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.

The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any 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 6 (Section 10.6)) must be stored separately from non-allocated trial products. No temperature monitoring is required.

Non-allocated trial products, including expired or damaged products, must be accounted by the site and reconciled by the monitor, at the latest at closure of the site.

6.3 Measures to minimise bias: Randomisation and blinding

All participants will be screened and centrally randomised using the RTSM/IWRS and assigned to the next available treatment according to the randomisation schedule. Investigational intervention will be allocated by the RTSM/IWRS and dispensed by the investigator at the study visits summarised in the flowchart.

This is an open-label study; however, the specific investigational intervention for a participant will be assigned using RTSM/IWRS. The site will access the RTSM/IWRS system before the start of

investigational intervention administration for each participant. Potential bias will be reduced by central randomisation.

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:

- Drug accountability information
- Review of eDiaries including SMPG profiles, insulin dose and hypoglycaemia reporting
- Evaluating glycaemic control and adherence to the visit schedule

Trial product start and stop dates will be recorded in the eCRF.

6.5 Dose modification

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

6.6 Continued access to study intervention after end of study

When discontinuing investigational intervention, the participant should be transferred to a suitable marketed product at the discretion of the investigator or treating physician. The post-study treatment should be recorded in the concomitant medication form, as described in Section 6.8.

If the switch to post-study treatment includes a new insulin treatment, please refer to the titration guideline in Appendix 8 (Section 10.8).

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/SAEs and laboratory abnormalities until the blood glucose is normalised and/or signs/symptoms have been relieved.

A specific overdose for insulin icodec and insulin glargine U100 cannot be defined; however, hypoglycaemia may develop over sequential stages if the doses administered are too high relative to the participant's requirements.

Mild hypoglycaemia can be treated by oral administration of glucose or sugary products.

Severe hypoglycaemia in which the participant 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, by other drugs for the indication of treatment hypoglycaemia in accordance with local guidelines, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously if the participant does not respond to glucagon within 10-15 minutes. If the participant has been unconscious, administration of oral carbohydrates is recommended for the participant 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 or insulin glargine U100 IB.

6.8 Concomitant therapy

Any medication that the participant is receiving at the time of the screening visit (V1) or receives until end-of-study visit (V34), or until discontinuation follow-up visit (V32A) for participants discontinuing investigational intervention, must be recorded as concomitant medication along with:

- Select predefined medication. If not listed, enter trade name or generic name.[a]
- Primary indication
- Dates of administration including start and stop dates
- For antidiabetic medication and concomitant medications related to SAEs: Doses and frequency
- Relevant for participants participating in COVID-19 studies: Type of study and type of drug

[a]Combination drugs should be split and reported as their individual components using generic drug names.

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

For information regarding restrictions to antidiabetic medication other than investigational intervention, see Section 6.1.

For information regarding collection of concomitant medication for participants who discontinue investigational intervention, see Section 7.1.

6.8.1 Rescue Medicine

Not applicable for this study. In case of lack of efficacy, please refer to Section 7.1.

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, or compliance reasons.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention.

Efforts should be made to have the participants who permanently discontinue investigational intervention attend the end-of-intervention visit (V32) as soon as possible to collect the required data for the analysis of the primary endpoint. Two safety follow-up visits (V33 and V34) should be performed after discontinuation of investigational intervention. These safety follow-up visits should be conducted 3 and 6 weeks, respectively, after discontinuation of once-weekly insulin icodec and 2 and 5 weeks, respectively, after discontinuation of once-daily insulin glargine U100. It is stressed that the visit window for both V33 and V34 is plus 3 days.

Further, it is important that discontinued participants come in for the discontinuation follow-up visit (V32A) 26 weeks after randomisation visit (V6). V32A will be the last visit for discontinued participants.

Participants who prematurely discontinue investigational intervention should keep and use the eDiary during the safety follow-up period (V32–V34) and return it at the second safety follow-up visit (V34).

The investigator should change participant’s status in the HCP web portal to 'In Follow-up' at the end-of-intervention visit (V32) to ensure that the participant is no longer prompted to report insulin dose.

The investigator should change participant’s status in the HCP web portal to ‘End of Participation’ at the last safety follow-up visit (V34).

After discontinuation of investigational intervention, the investigator and participant should continue to collect, record and report AEs as described in Section 8.3. AEs and anti-diabetic medication should be collected and recorded in the eCRF until the discontinuation follow-up visit (V32A) for discontinued participants; no other concomitant medication will be collected. Refer to Section 6.6 for treatment after end of intervention.

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

Participants must be informed about the continued scientific importance of their data, even if they discontinue investigational intervention. Only participants who withdraw consent will be considered as withdrawn from the study (see Section 7.2). The site should stay in contact with the participants who discontinue investigational intervention by phone, video call and/or site visits to motivate the participants to attend the safety follow-up visits (V33 and V34) and the visit at week 26 (V32A). Site contacts should be documented in the medical record.

The investigational intervention must be discontinued, if any of the following applies for the participant:

1. Pregnancy
2. Intention of becoming pregnant
3. 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.
4. Safety concern related to trial product or unacceptable intolerability
5. Lack of efficacy, defined as fulfilment of ALL 4 criteria below:
   a. No reduction in HbA_{1c} measured by central laboratory from randomisation (V6) to V16, or to V24,
      AND
   b. The pre-breakfast SMPG readings on 3 consecutive days higher than 240 mg/dL (13.3 mmol/L) within the last two weeks period despite appropriate dose adjustments
      AND
   c. A confirmatory fasting plasma glucose exceeding 240 mg/dL (13.3 mmol/L) measured by central laboratory. The participant should come in for an unscheduled visit as soon as possible (within one week), the next scheduled visit should not be awaited
      AND
   d. No treatable intercurrent cause (e.g., non-compliance) for the hyperglycaemia at the investigator's judgment.

See the flowchart for data to be collected at the time of discontinuation of investigational intervention (early discontinuation visit) and follow-up and for any further evaluations that need to be completed.

The primary reason for discontinuation of investigational intervention must be specified in the eCRF, and final trial product accountability must be performed. Discontinuation of treatment must be registered in the RTSM/IWRS.

7.1.1 Temporary discontinuation of study intervention

The participant should adhere to the treatment to the extent possible, with the exception of any adverse events or safety concerns, at the discretion of the investigator. Participants who have

temporarily discontinued investigational intervention are allowed to restart study intervention, unless any of the discontinuation criteria in Section 7.1 apply.

The temporary discontinuation of the investigational intervention is allowed if hepatic events with the following criteria are reported.

7.1.1.1 Hepatic events requiring temporary discontinuation of study intervention

Temporary discontinuation of study intervention is required for:

- ALT or AST > 8 x upper limit of normal (ULN)
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT (or AST) > 3 x ULN and total bilirubin > 2 x ULN (> 35% direct bilirubin) or ALT (or AST) > 3 x ULN and international normalised ratio (IRN) > 1.5 (if IRN measured), which may indicate severe liver injury (potential Hy's law)**
- ALT (or AST) > 3 x ULN with the appearance of fatigue, nausea, vomiting, anorexia, abdominal pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

For some patient populations with elevated baseline liver enzymes and liver function tests, these thresholds can be subject to change as justified and documented by sound scientific evidence.

**Please note that such an event much be reported as a SAE using the important medical event criterion if no other seriousness criteria are applicable (as described in Appendix 3 (Section 10.3)).

Temporary discontinuation of study intervention is also required in case of abnormal liver laboratory values not meeting protocol-specified discontinuation criteria, if the investigator deems that it is in the best interest of the participant.

Study intervention can be restarted only if an alternative aetiology is definitively identified, and liver blood parameters have returned to pre-event levels. If an alternative aetiology is not definitively defined and/or liver blood parameters have not returned to pre-event levels, drug-induced liver injury (DILI) cannot be excluded, and study intervention must be permanently discontinued.

Please see Appendix 5 (Section 10.5) for follow-up information on hepatic safety.

Please also see the criteria for an AE and Hepatic Event form in Appendix 3 (Section 10.3.3).

7.2 Participant withdrawal from the study

A participant may be withdrawn from the study at any time at the discretion of the investigator for safety, behavioural, or compliance reasons.

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 randomisation (V6), he/she will not be asked to have any follow-up assessments performed. The following data must be collected: Demography, available eligibility criteria, date of informed consent, date of screening and the date when participant's participation ended. The end of study form must be completed.

If a participant withdraws consent or is withdrawn by the investigator after randomisation (V6), the investigator must ask the participant if he/she is willing, as soon as possible, to have assessments performed according to end-of-intervention visit (V32). See the flowchart for data to be collected. The investigator should also ask the participant if he/she is willing to attend the two safety follow-up visits (V33 and V34). Refer to 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. Discontinuation of treatment must be registered 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; the investigator must document this in the medical record and notify the sponsor as soon as possible.

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 participant's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the eCRF.

7.2.1 Replacement of participants

If a participant discontinues investigational 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 participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's 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 randomised, 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.

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, is essential and required for study conduct.

Assessments should be carried out according to the clinic's standard of practice unless specified in the current section. Efforts should be made to limit the bias between assessments.

All run-in exclusion criteria must be reviewed at each of the visits during the run-in period (V2 [week -4] to V6 [week 0]).

The suggested order of the assessments and procedures at randomisation visit (V6) is as follows:

- Evaluation of whether the participant meets any of the run-in exclusion criteria
- Blood sample collection
- Randomisation in RTSM/IWRS
- Treatment Related Impact Measure for Diabetes (TRIM-D; Paper PRO)
- CGM fitting and training
- The investigator should create a participant profile and record administrative information (e.g., subject ID, year of birth and sex) and treatment arm in the ePID HCP web portal
- Participants should be provided with an eDiary and instructed in how to use it
- The BG meter should be connected with the eDiary
- SMPG should be measured using the BG meter
- Diabetes Treatment Satisfaction Questionnaire status version (DTSQs; ePRO)
- Patient Global Impression of Status (PGI-S; ePRO)
- Dispensing and Dosing of trial product, see titration guideline (Appendix 8, Section 10.8)

For information regarding the eDiary and HCP web portal please refer to the ePID site guide.

Please refer to Section 6.4 for drug treatment compliance.

All data entered in the eDiary is considered source data. The investigator should review all the data for the participants through the HCP web portal, before or during each visit/phone contact. The investigator should also review for missing data, e.g., missing BG measurements.

Source data of clinical assessments performed and recorded in the eCRF must be available and will usually be in the participant's medical records. Additional recording to be considered source data includes, but is not limited to; laboratory reports, BG meter, CGM, pictures, electrocardiogram (ECG) recordings, and paper PRO questionnaires.

The investigator should ensure that the electronic PRO questionnaires are completed by the participant in the eDiary.

Review of eDiary, ePROs and paper PROs, ECG, laboratory reports, etc., must be documented in the source documents or the participant's medical record. If clarification of entries or discrepancies in the eDiary is needed, the participant must be questioned, and a conclusion made in the participant's source documents. Care must be taken not to bias the participant. In case of detection of an AE, this should be reported as applicable.

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 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.

8.1.2 Self-measured glucose

When using BG meters, the measurement is performed with capillary blood calibrated to plasma equivalent glucose values, i.e., the measurement is performed on blood while the value is reported as plasma; therefore 'PG' or 'self-measured plasma glucose' (SMPG) are the terms to use as descriptor for the value.

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 required in the protocol.

A baseline SMPG value should be collected using the BG meter at randomisation (V6).

Pre-breakfast daily SMPG

Participants should be instructed to measure their pre-breakfast SMPG daily from week 0 (V6) to the last safety follow-up visit (V34). Participants must be instructed in how to transfer the results of the SMPG values daily into the eDiary.

Selected titration data (e.g., certain SMPG values and dose data) from the eDiary will be used during the study for central titration surveillance, to ensure compliance with the titration guideline in Appendix 8 (Section 10.8). All data will be stored by Novo Nordisk (see Appendix 1, Section 10.1).

8.1.3 Continuous glucose monitoring

Participants will be equipped with a study CGM device during the run-in (week -4–0), after initiation of the investigational intervention (week 0–4) and at end-of-intervention period (week 22–26). The CGM system used in this study will be the Dexcom G6®.

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

Participants using a personal real-time CGM device are allowed to continue using this during the study CGM periods. If they choose to do so, it will be in addition to the study-provisioned CGM. Only the study-provisioned CGM can be used to generate study data.

If a participant withdraws consent during the study at a timepoint when wearing the study-provisioned CGM, a site visit should be scheduled in order to remove the study-provisioned CGM sensor and to ensure data upload.

CGM fitting and training

The site staff will closely supervise and assist the fitting of the sensor and transmitter during the site visits (Table 8-1). The site staff is responsible for providing appropriate training to the participant at the relevant visits, enabling the participants to change the sensor by themselves during the phone visits P5, P9, P29, and P31. For information on fitting and changing of the CGM components/sensor, please refer to the provided Investigator's CGM manual and participant CGM guide.

Participants must be instructed to remove the CGM sensor prior to an X-ray, magnetic resonance imaging, computed tomography scan or diathermy (high-frequency electrical heat) treatment.

Table 8-1 CGM fitting and CGM data upload schedule

	Fit new CGM	Remove CGM	Upload CGM data
CGM period 1	V2	V3	V3
CGM period 2	V3	V4	V4
CGM period 3	V4	P5	V6
CGM period 4	P5	V6	V6
CGM period 5	V6	V7	V7
CGM period 6	V7	V8	V8
CGM period 7	V8	P9	V10
CGM period 8	P9	V10	V10
CGM period 9	V28	P29	V30
CGM period 10	P29	V30	V30
CGM period 11	V30	P31	V32
CGM period 12	P31	V32	V32

CGM sensor check

The CGM sensor has an in-use period of 10 days. The sensor will automatically stop recording data exactly 10 days after sensor start. This should be considered when scheduling the site visits within the visit windows.

The site staff should ensure that the participant has fitted the sensor correctly and that the CGM receiver is working. This will be done during the site visit. In cases where the sensor is dislodged prematurely, the participants must be fitted with a new sensor as soon as possible.

CGM data upload

CGM data must be uploaded at the site by the site staff via the CGM software following the instruction provided to the sites. The upload will be documented by the system directly.

8.1.4 Clinical outcome assessments

Clinical outcome assessments must be completed by the participant as specified in the flowchart (see Section 1.2).

The PRO questionnaires are to be completed by the participants without assistance of the site personnel. Explanations of item intent or explanation of terms from the study staff is a source of bias that should be avoided. It takes approximately ten minutes to complete the questionnaires.

The completed questionnaire must be reviewed for potential AEs and missing data while the participant is still at the site. Timely review of the paper PRO questionnaire (TRIM-D) should be documented in the medical record. Timely review of the ePID PRO questionnaires should be documented in the HCP web portal or in the medical records.

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

- Diabetes Treatment Satisfaction Questionnaire status version (DTSQs)[23-25]
  - DTSQs measures the satisfaction with diabetes treatment regimens in people with diabetes. The measure consists of 8 items, of which 6 items contribute to 1 global score. Higher scores on the global score indicate greater satisfaction with treatment.
  - Global score (score range): Total Treatment Satisfaction (0-36)
  - Data collection mode: eDiary
  - Approximate completion time: 3–5 minutes
- Patient Global Impression of Status (PGI-S)
  - PGI-S is a single-item global rating PRO measure used to establish a threshold for what would constitute a meaningful within-patient change in score for the target COA for the target patient population.
  - The PGI-S Diabetes Treatment Satisfaction measure will be used in this study.
    - Target COA: DTSQs total treatment satisfaction.
  - Data collection mode: eDiary
  - Approximate completion time: 1 minute
- Treatment-Related Impact Measure for Diabetes (TRIM-D)[26, 27]
  - TRIM-D measures impact of diabetes treatment. The measure consists of 28 items yielding 5 domain scores and a total score. Higher scores indicate a better health state (less negative impact).
  - Domain scores (score range): Treatment Burden (0–100), Daily Life (0–100), Diabetes Management (0–100), Compliance (0–100), Psychological Health (0–100)
  - Total score (0–100)
  - Data collection mode: paper PRO questionnaire
  - Approximate completion time: 3 minutes
  - Recall/Observation Period: 2 weeks

8.2 Safety assessments

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

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

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 in the eCRF.

Information on hypoglycaemia unawareness will be recorded according to Clarke's questionnaire, question 8.[28] The investigator must ask the participant in the following way: "To what extent can you tell by your symptoms that your blood glucose is low?" Participants answering ‘never, rarely or sometimes’ are considered to have impaired awareness of hypoglycaemia, whereas those answering ‘often or always’ are not.

8.2.1 Insulin dose

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

During the study, starting at randomisation (V6), participants must be instructed to report date, dose taken and time of once-weekly insulin or once-daily insulin in the eDiary. In the follow-up period, if the participant switches to a new basal insulin, the investigator must also report date, dose and time of the new basal insulin in the eCRF.

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

The investigator must record the following in the eCRF:

- Date of first and last dose of trial product

For dosing of anti-diabetic medication prescribed in the follow-up period please see Section 6.8.

8.2.2 Physical examinations

A physical examination will include assessments of the cardiovascular, respiratory, gastrointestinal, musculoskeletal, central and peripheral neurological system, the skin, as well as the head, ears, eyes, nose, throat, and neck.

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

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

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

- Body weight should be measured in kilogram (kg) or pounds (lb) without coat and shoes wearing only light clothing. Body weight will be recorded to one decimal.
- Body weight should be assessed with the same equipment throughout the study, if possible.
- Height should be measured in centimetres (cm) or inches (in) without shoes. Height will be recorded to the nearest whole number.

From the body weight and height, the BMI should be calculated at screening visit (V1) and recorded in the participant's medical records to evaluate inclusion criteria 7 and recorded in the participant's medical record.

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 last 2 systolic and last 2 diastolic blood pressure measurements should be recorded in the eCRF.
- The mean systolic blood pressure and diastolic blood pressure values are calculated automatically based on the last 2 measurements.

Pulse rate will be measured in connection to the blood pressure measurements.

- The pulse rate for the last 2 measurements should be recorded in the eCRF.
- The mean pulse rate value is calculated automatically based on the last 2 pulse rate measurements.

All readings should be recorded in the medical record.

8.2.4 Eye examination

Participants with uncontrolled and potentially unstable diabetic retinopathy or maculopathy are not eligible (Section 5.2) 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) possibly aided by diagnostic artificial intelligence algorithms approved by FDA and/or CE-marked 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., 3-field 45-degree, 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). The use of 3 fields of 45-degree diameter, one fovea-centred, one disc-centred and one at a comparable distance temporal of the fovea, is a good substitute for two 60-degree fields. In addition, an Optical Coherence Tomography (OCT) should be performed. Pharmacological pupil-dilation is a

requirement unless using a digital fundus photography camera specified for non-dilated examination. If diagnostic artificial intelligence algorithms are used an additional eye examination may be necessary if indicated so by the algorithm.

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 randomisation an eye examination must be performed according to above as per protocol flowchart (Section 1.2). An eye examination performed within 2 weeks prior to the applicable visits is acceptable, provided that no clinical symptoms suggestive of eye disease have occurred in the meantime, in which case a new examination must be completed. The investigator should indicate the outcome of each eye examination.

8.2.5 Electrocardiograms

12-lead ECG will be obtained as outlined in the flowchart using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT_c intervals. The ECG should be preceded by at least 5 minutes of rest for the participant in a supine/sitting position in a quiet setting without distractions (e.g., no use of television, cell phones).

The ECG must be interpreted, signed and dated by the investigator to verify that the data has been reviewed.

The ECG required at screening can be obtained within two weeks before run-in (V2) but at the latest at the start of run-in (V2). The results must be interpreted by the investigator before initiation of the CGM in order to determine the eligibility of the participant.

The ECG required at the visit at week 26 (V32) can be obtained within two weeks before the visit. The results must be available for evaluation at the visit.

Abnormal, clinically significant findings at screening should be recorded as concomitant illness in the eCRF. Abnormal, clinically significant findings after randomisation should be recorded as AEs at the investigator's discretion.

8.2.6 Clinical safety laboratory assessments

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

8.2.7 Pregnancy testing

Women of childbearing potential (WOCBP) should only be included after a negative, highly sensitive urine or serum 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 11 (Section 10.11).

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

Some AEs require additional data collection on a specific event form. The relevant event(s) are listed below in Table 8-2, together with other events requiring collection of additional information.

Table 8-2 AEs requiring additional data collection and other events requiring collection of additional information

Event type	AE requiring additional data collection	Other events requiring collection of additional information
Medication error	X	
Misuse and abuse	X	
Hepatic events	X	
Elevated liver enzymes		X
Hypoglycaemic episodes		X

Abbreviations: AE = adverse event.

Definitions and reporting timelines for the events mentioned in the above table can be found in Appendix 3 (Section 10.3) and Appendix 7 (Section 10.7) for hypoglycaemic episodes.

8.3.1 Time period and frequency for collecting AE information

All AEs and SAEs must be collected from first administration of investigational intervention and until the end-of-study visit 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 conditions identified during screening or identified during other study-related procedures performed before exposure to investigational intervention, 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 without undue delay but not later than within 24 hours of obtaining knowledge of the events. Similarly, the investigator must submit any updated

SAE data to Novo Nordisk or designee without undue delay, but not later than within 24 hours of obtaining knowledge of the information.

Investigators are not obligated to actively seek for AEs or SAEs in former study participants. However, if the investigator learns of any SAE with a suspected causal relationship to the IMP or to study participation, occurring after a participant has discontinued/completed the study, the investigator must notify Novo Nordisk without undue delay.

8.3.2 Method of detecting AEs

The method of recording, evaluating, and assessing causality of AEs and SAEs 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 an investigational intervention 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, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSARs).

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, occurring between first exposure to IMP and until the newborn is one month of age in female participants. For details regarding collection and reporting of pregnancy information, please refer to Appendix 4 (Section 10.4).

8.3.6 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form on a continuous basis. Follow up should be made regularly during the intervention period, to make sure all technical complaints are captured.

Technical complaints on study-provisioned CGM Dexcom G6 in India should be reported as mentioned in Appendix 11 (Section 10.11).

Instructions for reporting technical complaints can be found in Appendix 6 (Section 10.6).

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

Not applicable for this study.

8.5 Pharmacodynamics

Not applicable for this study.

8.6 Genetics

Not applicable for this study.

8.7 Biomarkers

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 including primary and secondary endpoints.

9.1 Statistical hypotheses

The primary hypothesis to be tested is that insulin icodec is non-inferior to insulin glargine U100 in terms of change in HbA_{1c} from baseline week 0 to week 26.

Formally, let D be the mean treatment difference 'insulin icodec' minus 'insulin glargine U100' of the change in HbA_{1c} from baseline week 0 to week 26. The null hypothesis will be tested against the alternative hypothesis of non-inferiority as given by

$$H_0: D \geq 0.3\% \text{ against } H_A: D < 0.3\%$$

The non-inferiority margin of 0.3%-point is chosen based on the recommendation of health authority guidance for industry on developing drugs for treatment of diabetes.[10, 29] Also, this margin is considered to provide sufficient assay sensitivity based on the below considerations:

- The margin does not represent an unacceptable loss of efficacy with insulin icodec relative to treatment with a basal insulin.
- It represents less than 50% of a suitably conservative estimate of insulin glargine U100's treatment effect on HbA_{1c} in a placebo-controlled study; the treatment effect of glargine U100 versus placebo in a basal insulin treated population is unknown, but in a similar progressed T2D population of participants already treated with liraglutide, degludec was shown to be superior to placebo (estimated treatment difference: -0.92%-point [-1.00; -0.75]95%CI)[30] and other basal insulin analogues have previously been shown to yield similar reduction in HbA_{1c} compared to insulin degludec.

9.1.1 Multiplicity adjustment

Not applicable for this study.

9.2 Analysis sets

The following participant analysis sets are defined:

Participant analysis set	Description
Full analysis set	All randomised participants. Participants will be included in the analyses according to the planned investigational intervention.
Safety analysis set	All randomised participants who are exposed to investigational intervention. Participants will be included in the analyses according to the investigational intervention they actually received.

The following data points sets are defined:

Data points set	Description
In-study	All data points obtained at or after randomisation until last participant contact
On-treatment	All data points obtained while the participant is considered exposed to investigational intervention, i.e., data points collected from first dose of investigational intervention until 5 weeks after end of last dosing interval

Baseline assessments are always included in the in-study and on-treatment data points sets.

In exceptional cases, participants or observations may be excluded from the analysis sets or the data points sets. In such case the reasons for their exclusion will be documented before unblinding. The participants and observations excluded from efficacy analyses, and the reason for this, will be described in the clinical study report.

The full analysis set and the in-study data points set will be used to estimate the primary estimand.

In general, all efficacy, all PROs and all CGM metrics will be evaluated using the full analysis set and the in-study data points set. Safety will be evaluated using the on-treatment data points set with descriptive statistics being based on the safety analysis set and statistical analyses being based on the full analysis set unless otherwise specified.

9.3 Statistical analyses

9.3.1 General considerations

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

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

- Randomised treatment: Once-weekly insulin icodec, Once-daily insulin glargine U100
- Region: Asia, Europe, North America, Africa
- Personal CGM/FGM device: Yes, No

The regions will be defined as follows:

- Asia: India, Japan
- Europe: Bulgaria, Germany, Poland, Spain
- North America: United States
- Africa: South Africa

Baseline is defined as information collected at week 0 (V6). In case a measurement is not available at week 0 (V6) the most recent measurement prior to week 0 (V6) will be used as baseline.

The number 541024 will be used as the seed for all imputations.

9.3.2 Primary estimand analysis

9.3.2.1 Definition of endpoint

The primary endpoint is change in HbA_{1c} from baseline week 0 to week 26.

9.3.2.2 Main analytical approach

The estimand (see Section 3) will be estimated based on the full analysis set using the in-study data points set which includes all HbA_{1c} measurements obtained at the week 26 visit, especially measurements from participants experiencing intercurrent events. Missing HbA_{1c} values at the week 26 visit (regardless of treatment completion status) will be imputed from participants who discontinue investigational intervention and have a measurement at the week 26 visit in the following way:

- First, one thousand (1000) copies of the dataset will be generated for HbA_{1c}.
- Second, for participants who discontinue investigational intervention and have an HbA_{1c} measurement at the week 26 visit, the change in HbA_{1c} from last available planned on-treatment (LAOT-) value to the week 26 visit will be analysed for each dataset copy using an analysis of variance (ANOVA) model with randomised treatment as fixed factor. The estimated parameters, and their variances, from the model will be used to impute missing HbA_{1c} values for the change from LAOT- to the week 26 visit and subsequently derive the missing HbA_{1c} values at the week 26 visit.
- For each of the complete data sets, the primary endpoint will be analysed using an ANCOVA model with randomised treatment, region and personal CGM/FGM device (yes/no) as fixed factors, and baseline HbA_{1c} as a covariate. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.[31]

This analysis has the underlying assumption that participants with missing data behave similarly as participants who discontinue investigational intervention.

Non-inferiority is confirmed if the upper bound of the two-sided 95% confidence interval is strictly below 0.3%.

9.3.2.3 Sensitivity analysis

The following sensitivity analysis evaluating the robustness of the assumptions about the missing data will be carried out:

For the primary endpoint, a two-dimensional tipping point analysis will be performed where participants having imputed HbA_{1c} measurement at the week 26 visit are assumed to have a worse outcome in the insulin icodec arm and a better outcome in the insulin glargine U100 arm compared to what was imputed in the primary analysis. This is done by adding or subtracting values Δ_i to the imputed HbA_{1c} values before analysing the data. The value of Δ_i will be varied independently in the two treatment arms. The non-inferiority margin of 0.3% will be among the Δ_i values investigated. The plausibility of the values of Δ_i where the conclusion of the primary analysis changes will be evaluated to assess the robustness of the primary analysis result.

9.3.3 Secondary estimands analysis

9.3.3.1 Supportive secondary estimands

Supportive secondary estimands related to supportive secondary endpoints have the following attributes. Population attributes are the same as specified for the primary estimand, and endpoint attributes are the corresponding supportive secondary endpoint. Treatment condition attribute and intercurrent events for change in body weight are the same as specified for the primary estimand. For all other supportive secondary endpoints, treatment condition attributes are the investigational interventions regardless of initiation of bolus insulin treatment for more than 2 weeks and had participants not discontinued investigational intervention with the former intercurrent event handled by the treatment policy estimand and the latter intercurrent event handled by the hypothetical strategy, though, except for hypoglycaemic episodes, participants are assumed to return to baseline. Population-level summary attributes would instead be rate ratio for hypoglycaemic episodes, and treatment ratio for time spent < 3.0 mmol/L (54 mg/dL) and mean weekly insulin dose.

9.3.3.1.1 Supportive secondary efficacy estimands

The following subsections describe how the supportive secondary estimands related to supportive secondary efficacy endpoints (see Section 3) will be estimated. The subsections refer to the corresponding supportive secondary endpoint.

Change in time in range 3.9–10.0 mmol/L (70–180 mg/dL) from baseline week -4–0 (V2–V6) to week 22–26 (V28–V32)

The supportive secondary estimand regarding change in time in range 3.9–10.0 mmol/L (70–180 mg/dL) (TIR) from baseline week -4–0 to week 22–26 will be estimated using a multiple imputation model as described below.

Missing TIR during week 22–26 (regardless of treatment completion status) for both treatment arms will be imputed with baseline value adding a random error term. The random error term is normally distributed with a standard deviation set equal to the estimated residual standard deviation of an ANCOVA analysis on the LAOT values. Specifically, the imputations and analyses will be carried out as follows:

- First, an ANCOVA model with randomised treatment, region and personal CGM/FGM device (yes/no) as fixed factors, and a baseline value as a covariate will be fitted to the LAOT values.
- Second, the estimated residual standard deviation, *s*, from this model will be used to impute missing values by the baseline value, adding a random normally distributed term with mean 0 and standard deviation *s*. This will be done 1000 times.
- For each of the completed data sets, the endpoint will be analysed using an ANCOVA model with randomised treatment, region and personal CGM/FGM device (yes/no) as fixed factors, and a baseline value as a covariate. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.[31]

Change in DTSQs total treatment satisfaction score from baseline week 0 (V6) to week 26 (V32)

The supportive secondary estimand regarding change in DTSQs total treatment satisfaction score from baseline week 0 to week 26 will be estimated using a model similar to the analysis for change in TIR substituting DTSQs total treatment satisfaction score for TIR.

9.3.3.1.2 Supportive secondary safety estimands

The following subsections describe how the supportive secondary estimands related to supportive secondary safety endpoints (see Section 3) will be estimated.

Hypoglycaemic episodes

The supportive secondary estimands regarding the following supportive secondary safety endpoints will be analysed separately to the extent data allows using the method described below:

- Number of severe hypoglycaemic episodes (level 3) from baseline week 0 (V6) to week 31 (V34)
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) from baseline week 0 (V6) to week 31 (V34)
- Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) from baseline week 0 (V6) to week 31 (V34)

For participants who discontinued their randomised treatment, the number of episodes in the missing period (time of follow-up 2 visit (V34) to planned end of the on-treatment data points set) will be imputed using a multiple imputation technique, assuming that the event rate pre-follow-up 2 visit (V34) follows the respective treatment arms rate whilst post-follow-up 2 visit (V34) event rate is the rate of the comparator arm. The imputation will be done as follows:

- First, a Bayes negative binomial model with log-link function will be fitted to the event rate data to obtain the posterior distribution of model parameters. The model will include randomised treatment, region and personal CGM/FGM device (yes/no) as fixed factors, and the logarithm of the period for the on-treatment data points set as offset.
- Second, based on the estimated parameters for the comparator arm in this model, the number of episodes in the missing period will be imputed for participants who discontinued their randomised treatment. Multiple copies (1000 copies) of a complete data set will be generated by sampling from the estimated distribution.
- For each of the complete data sets, the number of episodes will be analysed using a negative binomial model with log-link function, fixed factors and the logarithm of the period for the on-treatment data points set plus the missing period for which the number of episodes have been imputed as offset. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.[31]

The endpoints are defined as described in Protocol Appendix 7 (Section 10.7).

Time spent < 3.0 mmol/L (54 mg/dL) during week 22–26 (V28–V32)

The supportive secondary estimand regarding time spent < 3.0 mmol/L (54 mg/dL) (time below range [TBR]) during week 22–26 will be estimated using a negative binomial model on the number of recorded measurements below range with a log-link function and the logarithm of the total number of recorded measurements as an offset. The model will include randomised treatment, region and personal CGM/FGM device (yes/no) as factors and baseline number of recorded measurements below range as a covariate.

Change in time spent > 10.0 mmol/L (180 mg/dL) from baseline week -4–0 (V2–V6) to week 22–26 (V28–V32)

The supportive secondary estimand regarding change in time spent > 10.0 mmol/L (180 mg/dL) (time above range [TAR]) from baseline week -4–0 to week 22–26 will be estimated using a model similar to the analysis for change in TIR substituting TAR for TIR.

Mean weekly insulin dose from week 24 (V30) to week 26 (V32)

The supportive secondary estimand regarding mean weekly insulin dose from week 24 to week 26 will be estimated using a model similar to the analysis for change in TIR substituting change in TIR with log-transformed mean weekly insulin dose from week 24 to week 26 and using the log-transformed pre-randomisation (baseline) weekly insulin dose as a covariate. The imputation will also be done on log-transformed values, i.e., missing values will be imputed by the log-transformed baseline value adding a random error term. The random error term will be normally distributed with a standard deviation set equal to the estimated residual standard deviation of an ANCOVA analysis on the log-transformed LAOT values.

Change in body weight from baseline week 0 (V6) to week 26 (V32)

The supportive secondary estimand regarding change in body weight from baseline week 0 to week 26 will be estimated based on the in-study data points set using a model similar to the primary analysis above substituting body weight for HbA_{1c}.

9.3.4 Exploratory endpoint analysis

Details on exploratory endpoint analysis will be included in the SAP.

9.3.5 Other safety analyses

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

Details on other analyses will be included in the SAP.

9.4 Interim analysis

Not applicable for this study.

9.5 Sample size determination

The sample size is determined in order to have 90% power for meeting the primary hypothesis.

Based on a recent study evaluating insulin icodec with a one-time additional dose in participants with T2D treated with basal insulin (NN1436-4478) the percentage of participants experiencing an intercurrent event is expected to be 3% per 6 months in an open-label study in participants with T2D treated with basal insulin. Titration of insulin icodec without the one-time additional dose did not lead to excess treatment discontinuation in an earlier study (NN1436-4466).

It is assumed that there is no difference in change in HbA_{1c} between the treatment arms for participants not experiencing intercurrent events and a treatment difference of 0.3%-point in favour of the comparator for participants experiencing intercurrent events. Thus, with 3% expected to experience any of the specified intercurrent events before week 26, this leads to an assumption of a mean treatment difference of $0.03 \cdot 0.3\%\text{-point} = 0.009\%\text{-point}$ for the specified primary estimand in the overall population. The standard deviation (SD) is assumed to be 0.9%-point based on results from the aforementioned study (NN1436-4478).

From the above assumptions, 404 randomised participants will ensure a power of 90% for confirming non-inferiority using a non-inferiority margin of 0.3%-point.

The sample size calculation above is sensitive to the assumptions made for the primary hypothesis. In Figure 9-1 and Figure 9-2 the sample size and power are presented, respectively, for different assumptions.

Figure 9-1 Sample size as function of treatment difference and SD to achieve 90% power

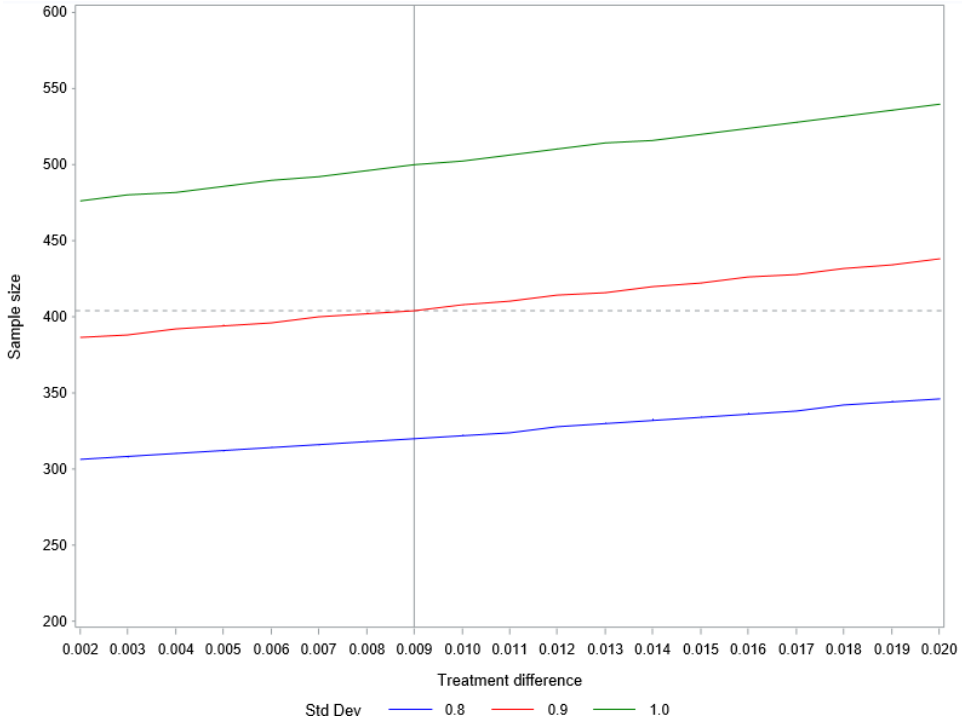
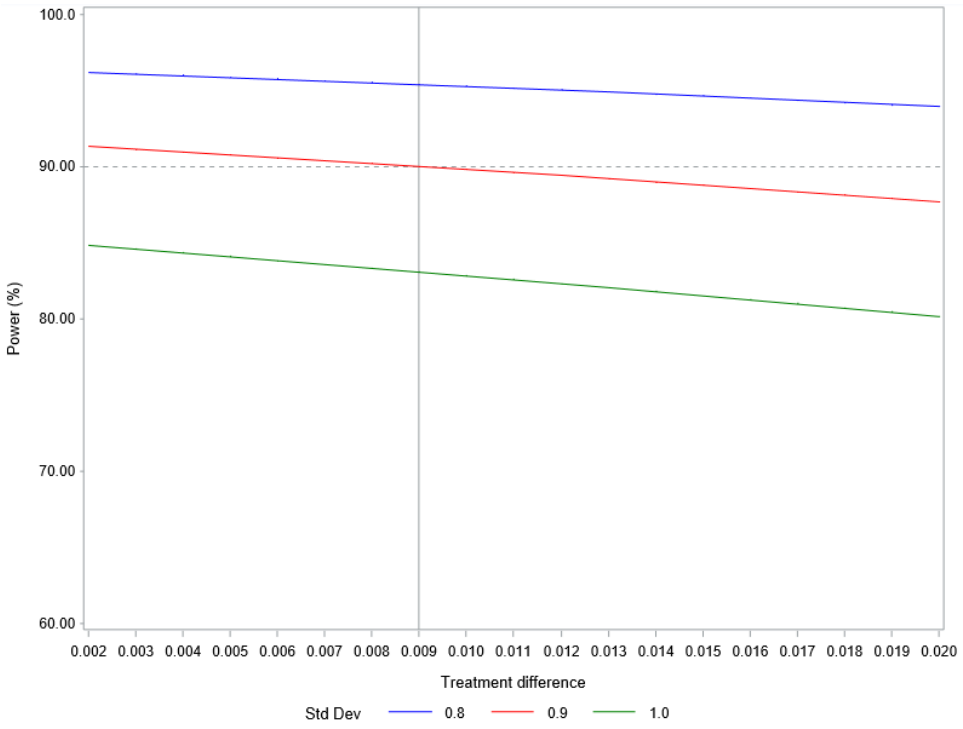


Figure 9-2 Power as function of treatment difference and SD with 404 participants



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[32] and applicable ICH Good Clinical Practice (GCP) Guideline[33].
- Applicable laws and regulations

The protocol, informed consent form, IB (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/modifications, reports on SAEs, and the CSR according to national requirements.

Any amendments/modifications 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. In case of changes made to eliminate an immediate safety hazard, the actions must be reported to Novo Nordisk immediately.

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 (within 24 hours after discovery). A serious breach is a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of data generated in the clinical study. This includes persistent or systematic non-compliance with ICH GCP E6 and/or the protocol.

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 ('Agreement to take part' form) that meets the requirements of local regulations, ICH GCP[33] guidelines, Declaration of Helsinki,[32] 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 according to sponsor instructions.

A copy of the informed consent form(s) must be provided to the participant.

10.1.4 Recruitment and information to participants during the study

The site will be offered a communication package for the participant during the conduct of the study. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the participants. The written information will be translated and adjusted to local requirements and distributed to the participant 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 clinical study report. 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.

The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organisational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorised disclosure or access.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

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

10.1.6.2 Study safety group

The study safety group must notify the Novo Nordisk safety committee about any significant findings indicating a potential safety signal in the study and ask for further guidance.

10.1.6.3 Data monitoring committee

Not applicable for this study.

10.1.6.4 Event adjudication committee

Not applicable for this study.

10.1.7 Dissemination of clinical study data

This is a multinational study including both EU/EEA and non-EU/EEA sites, and the end of study is defined as the global end of study. The summary of study results and layperson summary of results will be submitted within 12 months after the global end of study, as the planned statistical analyses cannot be performed until data from all sites are available.

Study information will be disclosed at clinicaltrials.gov and novonordisk-trials.com and euclinicaltrials.eu 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,[32] the International Committee of Medical Journal Editors (ICMJE),[34] the Food and Drug Administration Amendment Act (FDAAA),[35] European Commission Requirements[1, 36, 37] 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.

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 CRF 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 CRFs unless transmitted electronically to Novo Nordisk or designee (e.g., laboratory and eDiary 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). Remote access to the source data documents by Novo Nordisk monitors and auditors can be agreed in countries where this is acceptable according to regulatory requirements and national legislation. 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[33], 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 clinical study report.

10.1.8.3 Protocol compliance

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

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

10.1.9 Source documents

All data entered in the CRF must be verifiable in source documentation other than the CRF.

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.

The original of the completed PROs must not be removed from the site, unless they form part of the CRF and a copy is kept at the site.

Data in the service provider's database are considered source data, e.g., laboratory data, CGM ePROs and eDiary.

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 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 participant's medical history in source documents, such as participant's medical record.

The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.

Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical 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/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the study. The investigator must be able to access his/her study documents without involving Novo Nordisk in any way. If applicable, CRF and

other participant data will be provided in an electronic readable format to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. Site-specific CRFs and other 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.

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

10.1.11 Study and site start and closure

First act of recruitment

The start of study is defined as the date when the clinical study will be open for recruitment of participants, i.e., the 'first act of recruitment.' The first act of recruitment is defined as the first site activation in the study.

Study or site termination

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, or 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, dignity 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.

Novo Nordisk accepts liability in accordance with local laws/acts/guidelines. For Poland, Novo Nordisk carries liability for the study exclusively in the scope defined by the local applicable laws. For Spain, Novo Nordisk accepts liability in accordance with Article 10 (Liability regime) of the Royal Decree 1090/2015 of 4 December.

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 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 CSR 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.[38]

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.

Additional tests may be performed at any time during the study as deemed 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 laboratory 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 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.

Clinical laboratory samples will be destroyed no later than at end of study or no later than at finalisation of the CSR.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism V1, V6, V16, V24, V32, V32A	• HbA_{1c}
Abbreviations: HbA_{1c} = glycosylated haemoglobin; V = visit.	

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology V1, V16, V24, V32	• Haemoglobin • Leukocytes
Biochemistry[a] V1, V16, V24, V32	• Alanine Aminotransferase (ALT) • Albumin • Alkaline phosphatase • Aspartate Aminotransferase (AST) • Bilirubin • Creatinine • Potassium • Sodium
Lipids V1, V32	• Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides • Free fatty acids
Pregnancy Testing[b] V1, V6, V34	• 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. eGFR is for screening purposes only. • In the case of suspected lack of efficacy (Section 7.1): Fasting plasma glucose (FPG)[c]

[a]See Section 10.3 (Hy's Law) for details of required actions, and follow-up assessments for increased liver parameters. Discontinuation criteria are given in Appendix 3 (Section 10.3.3) 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).
[c]An FPG result < 3.9 mmol/L (70 mg/dL) should not be reported as a hypoglycaemic episode but as an adverse event at the discretion of the investigator (Appendix 3, Section 10.3).
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; hCG = human chorionic gonadotropin; HDL = high density lipoprotein; LDL = low density lipoprotein; V = visit.

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 an 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.

A 'lack of efficacy' or 'failure of expected pharmacological action' per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.

Events NOT 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 an AE 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 aspartate aminotransferase (AST) >3x ULN and total bilirubin >2x ULN where no alternative aetiology exists (Hy's law)

10.3.3 Description of AEs requiring additional data collection and other events requiring collection of additional information

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.
A specific event form needs to be completed for the following events.

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 Kit ID/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 the 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:

- If a liver related AE is reported the Hepatic Event form must be filled out.

Other events requiring collection of additional information

Hypoglycaemic episodes:
All hypoglycaemic episodes must be recorded by the participant on a hypoglycaemic episode form which is a part of the eDiary (see Appendix 7 (Section 10.7)). 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.

Elevated liver enzymes:
In all cases where one or more results from liver laboratory parameters (ALT, AST or ALP) measured in a central laboratory sample are increased above the limits defined below the Elevated Liver Enzymes form must be completed. Criteria for discontinuation of study intervention may also apply; see Section 7.1.1.1.

- Alanine aminotransferase (ALT): > 3.0 x ULN if baseline was normal; > 3.0 x above baseline if baseline was abnormal
- Aspartate aminotransferase (AST): > 3.0 x ULN if baseline was normal; > 3.0 x above baseline if baseline was abnormal
- Alkaline phosphatase (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 eCRF.

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, see Section 10.1.5.

Please refer to Figure 10-1 for reporting of non-serious AEs. 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 Section 10.3.5.

If an AE is considered to have a causal relationship with a concomitant medication *or AxMP*, it is important that the suspected relationship is reported to Novo Nordisk in e.g., the alternative aetiology section on the safety information form. Novo Nordisk may need to report it 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**: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe**: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  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 consult the IB of insulin icodec and insulin glargine U100 when making the causality 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 eCRF.

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.

  Note: this term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal**: This term is only applicable if the 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., severe 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 eCRF.

The investigator will submit any updated SAE data to Novo Nordisk without undue delay, but not later than within 24 hours of receipt of the information.

10.3.5 Reporting of SAEs

SAE reporting via eCRF

Relevant forms must be completed in the eCRF.

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 Figure 10-1):

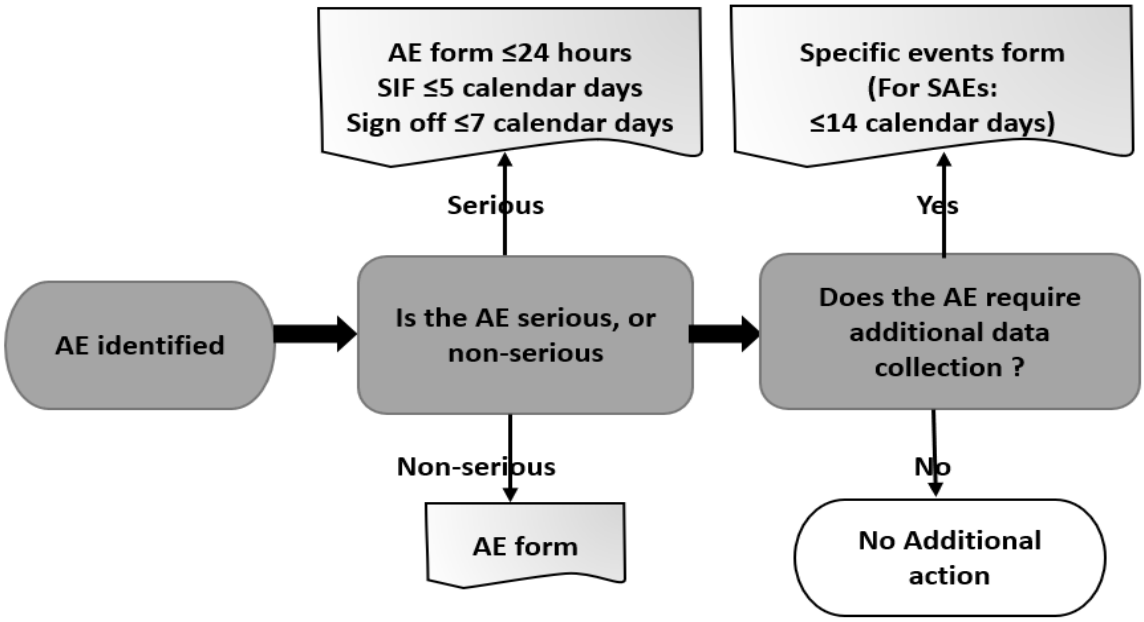
- AE form without undue delay, but not later than within 24 hours.
- Safety information form within 5 calendar days.
- Both the AE and the safety information form must be signed within 7 calendar days after first knowledge by the investigator.
- Specific event form within 14 calendar days.

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 eCRF 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 eCRF will be decommissioned to prevent the entry of new data or changes to existing data. If a new SAE from a participant or updated information on a previously reported SAE needs to be reported after eCRF decommission, a paper AE and safety information form should be used to notify Novo Nordisk.

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 hypoglycaemic episodes form, which is part of the eDiary. If the hypoglycaemic episode fulfils the criteria for an SAE then an 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 eCRF as soon as possible, preferably within 5 working days (see Appendix 1 [Section 10.1]).

Abbreviations: AE = adverse event; eCRF = electronic 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 and in Attachment I of the protocol.

10.3.6 Reporting of AEs for non-Novo Nordisk medical devices and use errors not included in the technical complaint form

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

Additional reporting of AEs considered related to Roche Accu-Chek® Guide/Guide Me/Instant and Dexcom G6®:
All complaints should be reported directly to the manufacturer. AEs considered related to the device should be reported both to Novo Nordisk or designee, and to the manufacturer.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of 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 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 HRT and whose menopausal status is in doubt are considered of childbearing potential and will be required to use one of the highly effective/acceptable contraception methods.

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

10.4.2 Contraceptive guidance

Male participants

No contraception measures are needed for male participants.

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 highly effective and acceptable methods of contraception allowed. Local regulations may apply, see Appendix 16 (Section 10.11).

Highly effective or acceptable contraception should be utilised until the end of treatment.

Table 10-3 Highly effective and acceptable contraceptive methods allowed[39]

Highly effective methods[a] (Failure rate of <1% per year when used consistently and correctly):
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  • oral
  • intravaginal
  • transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation
  • oral
  • injectable
  • implantable
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomised partner
Vasectomised partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
• Sexual abstinence
Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Acceptable methods[c] • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide[d] • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)
Notes: [a]Contraceptive use by men or women should comply with local regulations regarding the use of contraceptive methods for those participating in clinical studies. [b]If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. [c]Considered effective, but not highly effective - failure rate of ≥1% per year. [d]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 (LAM).

10.4.3 Collection of pregnancy information

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 participant's pregnancy (see Figure 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.

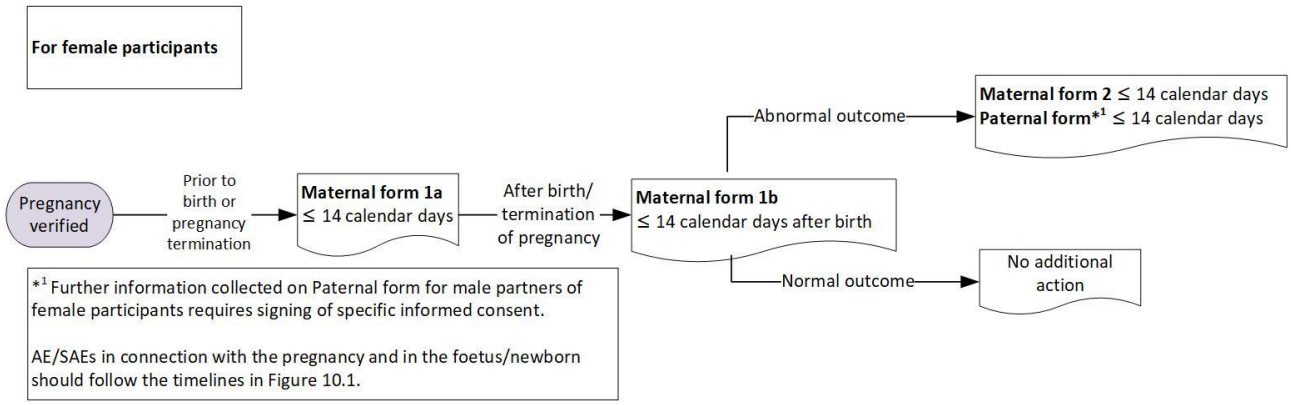
Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

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

Pregnancy outcome should be documented in the participant's medical record. Abnormal pregnancy outcome (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE. In case of abnormal pregnancy outcome, paternal information should be recorded in the appropriate form after obtaining the necessary signed paternal informed consent.

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: Hepatic Safety: Actions and follow-up assessments

For some patient populations with elevated baseline liver enzymes and liver function tests, these thresholds can be subject to change as justified and documented by sound scientific evidence.

For all events, defined as:

- ALT or AST > 8 ULN
- ALT or AST > 5 ULN for more than 2 weeks
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN (> 35% direct bilirubin) or ALT or AST > 3 x ULN and international normalised ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (potential Hy's law)
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, anorexia, abdominal pain or tenderness, fever, rash, and/or eosinophilia (>5%),

The following must be performed:

- Repeat testing within 48 to 72 hours
- Follow-up assessments
- Work-up for alternative aetiology

If no alternative or competing aetiology is identified:

- Complete liver profile including ALT, AST, ALP, total bilirubin, liver function tests (INR/coagulation factors, albumin, PT), performed at the local laboratory. Repeat testing and frequency of retesting should be determined at the discretion of the investigator.
- Detailed clinical information, such as related symptoms, risk factors, medical history, family history, including contributing conditions (e.g., viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, hypoxic/ischemic hepatopathy, hepatobiliary or pancreatic disorders, exposure to environmental chemical agents) should be gathered to seek a possible alternative aetiology of the observed laboratory test abnormalities.
- Evaluation of the need for imaging and other examinations and procedures such as liver biopsy, ultrasonography, computerised tomography (CT) scan, magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), echocardiography.
- History of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, special diets, recent events of food poisoning or excessive physical activity should also be evaluated.
- Referral to hepatologist/gastroenterologist should be considered.

10.6 Appendix 6: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

10.6.1 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.

10.6.2 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 Kit ID/DUN: One technical complaint form must be completed for each affected Kit ID/DUN.
2. For products without Kit ID/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 eCRF within the following timelines of obtaining knowledge of the technical complaint:

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

If the eCRF is unavailable, make sure the related SAEs are reported via paper forms within 24 hours. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

In order to report a technical complaint on a study intervention listed on the technical complaint form but not allocated to a participant, use the paper technical complaint form.

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 Kit ID/DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

The technical complaint sample should contain the batch, code or lot number and, if available, the Kit ID/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 for the technical complaint sample must be done in accordance with the conditions prescribed for the product.

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

Technical complaints on products not included in the technical complaint form should be reported to manufacturing holder.

10.7 Appendix 7: Hypoglycaemic episodes

Table 10-4 Classification of hypoglycaemia

Classification of hypoglycaemia		
Level	Glycaemic criteria	Description
Hypoglycaemia alert value (level 1)	< 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (level 2)	< 3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (level 3)[a]	No specific glucose threshold	[a]Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery
Notes: The Novo Nordisk terms are adapted from IHSG,[40] ADA,[41] ISPAD,[42] type 1 diabetes outcomes program,[43] ATTD.[44] Severe hypoglycaemia as defined by Seaquist[45] and ISPAD.[42]		

Severe hypoglycaemia

[a]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.[45]

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, which is part of the eDiary. 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, see Appendix 3 (Section 10.3.3).

Reporting of hypoglycaemic episodes by BG meters:
Plasma glucose (PG) should always be recorded in the eDiary when a hypoglycaemic episode is suspected. The following should be reported in the eDiary as hypoglycaemic events:

- PG values < 3.9 mmol/L (70 mg/dL)
- Severe hypoglycaemic episodes without confirmed PG values.

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

investigator should still report the hypoglycaemic episode on the hypoglycaemic episodes form. If the participant is not able to fill in the eDiary (e.g., in case of hospitalisation) at time of episode, the participant can report the episode in the eDiary retrospectively.

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

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.[45]

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.[45]

Diary review

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

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.

10.8 Appendix 8: Titration guideline

Titration guidelines have been developed, providing recommended dose adjustments at different PG levels to ensure that participants receive an optimal treatment. However, it is recognised that insulin treatment should be individualised, and the specific titration algorithms may not be applicable in certain clinical situations. Hence, it is important that other information, such as symptoms of hypo/hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the participant's 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 trial products

At randomisation visit (V6), eligible participants will be randomised to receive insulin icodec or to receive insulin glargine U100.

Insulin icodec should be taken once weekly, on the same day each week, at any time of the day. At randomisation visit (V6), all participants should receive a dose that is equivalent to their previous total daily basal insulin dose x 7, rounded off to the nearest dose that is dividable by 10. Table 10-5 displays the insulin icodec V6 dose for the first week for participants receiving from 10U to 100U per day of daily basal insulin prior to randomisation.

Table 10-5 Insulin icodec dose titration at V6

Total daily dose before randomisation (U)	V6 insulin icodec dose (U)	Total daily dose before randomisation (U)	V6 insulin icodec dose (U)
10	70	56	390
11	80	57	400
12	80	58	410
13	90	59	410
14	100	60	420
15	110	61	430
16	110	62	430
17	120	63	440
18	130	64	450
19	130	65	460
20	140	66	460
21	150	67	470
22	150	68	480
23	160	69	480
24	170	70	490
25	180	71	500
26	180	72	500
27	190	73	510
28	200	74	520
29	200	75	530
30	210	76	530
31	220	77	540
32	220	78	550
33	230	79	550
34	240	80	560

35	250	81	570
36	250	82	570
37	260	83	580
38	270	84	590
39	270	85	600
40	280	86	600
41	290	87	610
42	290	88	620
43	300	89	620
44	310	90	630
45	320	91	640
46	320	92	640
47	330	93	650
48	340	94	660
49	340	95	670
50	350	96	670
51	360	97	680
52	360	98	690
53	370	99	690
54	380	100	700
55	390		
Abbreviations: V = visit.			

Insulin glargine U100 should be taken once daily, at any time of the day but at the same time every day throughout the study. Switching from another basal insulin should be in accordance with local label.

The treat-to-target approach will be applied to both treatment arms to optimise glycaemic control throughout the study.

There are no maximum or minimum insulin doses.

Dose adjustment of trial products during the study

After the randomisation visit (V6), the trial products will be adjusted once weekly by the investigator in connection with the scheduled visits/phone contacts as described in Table 10-6.

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

If one of the SMPG values is below target (< 4.4 mmol/L or 80 mg/dL), the insulin dose should be reduced in accordance with Table 10-6, regardless of the mean value.

If none of the SMPG values are below target (< 4.4 mmol/L or 80 mg/dL), the mean of the values should be calculated. If the mean is within the range (4.4–7.2 mmol/L or 80–130 mg/dL), the dose should remain unchanged. If the mean is above target (7.2 mmol/L or 130 mg/dL), the insulin dose should be increased in accordance with Table 10-6.

Table 10-6 Insulin adjustment

Pre-breakfast SMPG			**Insulin icodec**	**Insulin glargine U100**
Value to use	**mmol/L**	**mg/dL**	**U**	**U**
Lowest of the SMPG values	<4.4	<80	-20	–3
Mean of the SMPG values	4.4–7.2	80–130	0	0
	>7.2	>130	+20	+3
Abbreviations: SMPG = self-measured plasma glucose.				

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 HCP web portal by the investigator as applicable.

Missing insulin icodec dose guidance

If an insulin icodec dose is missed for ≤ 3 days after the planned dosing day, the participant should inject the planned dose as soon as possible. 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

Insulin icodec arm

Last dose of insulin icodec is taken at P31 (week 25). If it is decided that a participant should continue on daily insulin after end of intervention (V32, week 26), it is recommended that the participant is switched from insulin icodec to any available basal insulin at the discretion of the investigator. The initial post-study basal dose is estimated as follows:

- Calculate the new daily basal insulin by dividing the latest weekly insulin icodec dose by 7 rounded off to the closest value dividable by 7
- Initiate the new daily basal insulin two weeks after the latest insulin icodec dose, i.e., at week 27
- Continue to measure pre-breakfast SMPGs daily
- If the pre-breakfast SMPG exceeds 10 mmol/L (180 mg/mL) before week 27, the daily basal insulin dose can be initiated at this day. E.g., if the pre-breakfast SMPG = 11.4 mmol/L (205 mg/dL) eight days after the last dose of insulin icodec, the daily insulin should be initiated at this day.
- Consider titrating the basal insulin once or twice weekly according to the pre-breakfast SMPG values and the local label of the chosen insulin

Insulin glargine U100 arm

If it is decided that a participant should continue on daily insulin after end of intervention (V32, week 26), it is recommended that the participant is switched from insulin glargine U100 to any other available basal insulin at the discretion of the investigator.

Data Collection

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

- Date, dose and time of insulin icodec or insulin glargine U100 injections
- Daily SMPG values with an indication of "pre-breakfast" or "other"
- Hypoglycaemic episodes as described in Appendix 3 (Section 10.3) and Appendix 7 (Section 10.7)

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

- Insulin icodec or insulin glargine U100 doses prescribed at the weekly contacts
- Reasons for deviation from the titration algorithm, 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 changes from the titration algorithm will be followed up.

It is important that data regarding dose titration is entered into the eDiary and HCP dashboard in a timely manner. If delays occur, action cannot be taken in due time before the participant's 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 via CONNECT or by 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.

10.9 Appendix 9: Continuous glucose monitoring

10.9.1 Continuous glucose monitoring

Targets for CGM metrics as guidance for the investigator are not applicable for this study due to the blinded nature of the CGM data.

10.9.2 CGM being used as investigational medical device

For India, where the study-provisioned CGM is not approved at the time of the final protocol, the CGM is regarded as an investigational medical device and will be labelled for investigational use only. The CGM has been selected to provide the best data accuracy and to be consistent in the global clinical programme.

Technical complaints for the study-provisioned CGM must be reported to IQVIA on a technical complaint paper form received from IQVIA for the device. Timelines for reporting, from the study site obtaining knowledge of the technical complaint:

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

AE and SAEs related to the technical complaint must be reported both on the technical complaint paper form and in the eCRF. In addition, they must be reported in accordance with the standard protocol requirements for AE and SAE reporting as described in Appendix 3 (Section 10.3). At the end of study, the study-provisioned CGM must be collected by the investigator.

If the study-provisioned CGM is approved in India during the study conduct, the procedures above are not applicable anymore in the said country and technical complaints reporting should follow the standard vigilance procedures.

10.10 Appendix 10: Mitigations to ensure participant safety and data integrity during an emergency situation

10.10.1 Definition and scope of appendix

A major emergency is defined as a situation that causes substantial restrictions to study site access for participants and/or sponsor representatives.

In case local restrictions due to a major emergency lead to lockdown of a site, the site must contact Novo Nordisk to allow for implementation of mitigations mentioned in this appendix based on mutual agreement.

According to local regulation, health authorities and independent ethics committees should be notified in case elements of the emergency appendix are activated.

Table 10-7 indicates the minimum requirements for assessments that should be performed during a lockdown, but sites should always try to follow the assessments outlined in the original flowchart (Section 1.2) to the extent possible. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.

Alternative visit formats are examples of the mitigations that can be implemented:

- Home Visits: visits to be performed at the participant's home
- Off-site visits: visits to be performed at a place other than the site or the participant's home

Alternative visit formats and all other mitigations mentioned in this appendix can be implemented only if allowed and deemed feasible according to local regulations, requirements and/or guidelines at the sites and countries and should be performed by the site-staff. As a pre-requisite, sites need to ensure that the study site staff is covered by workers' compensation insurance, also when performing home and off-site visits.

Sites should comply with local regulations, requirements and/or guidelines if they are issued.

10.10.2 Visits

Screening (V1), run-in (V2) and randomisation (V6) should always be performed as on-site visits. If a site is unable to perform these visits on-site, screening and randomisation of new participants at that site should be on hold until on-site visits are possible.

Visits V3, V4, V7, V8, V10, V16, V24, V28, and V30 should be performed as on-site visits, if in any way possible. If not, assessments can be conducted remotely video, phone or similar or as home or off-site visits.

On-site visits V33 and V34 can be converted to remote visits (video, phone or similar) or home or off-site visits.

If the end of intervention visit (V32) and discontinuation follow-up visit for participants discontinuing investigational intervention (V32A) cannot be performed on-site, using remote

(video, phone or similar) or home or off-site visits within the given visit window, the visit window for the assessment can be extended for up to 28 days.

At each visit, the investigator must indicate in the CRF how the visit was performed and specify the reason for the preferred assessment method.

10.10.3 Assessments

Assessments used for safety endpoints (i.e., number of severe and clinically significant hypoglycaemic events, change in body weight and weekly insulin dose) should be prioritised, as well as CGM. The preferred order for the method of assessment is: on-site, video, phone, home visit.

HbA_{1c} should be prioritised and be performed on-site at least at V1, V6 and V32.

CGM fitting and training at V2 and V28 should be prioritised preferably on-site visit, but if not possible then home and off-site visit can be performed. If not on site, remember to map the CGM Receiver to a given Subject ID at site before meeting the participant for CGM fitting.

The site staff is responsible for providing appropriate training to the participant, enabling the participants to change the sensor by themselves.

CGM fitting at V4, V8 and V30 should be prioritised and preferably be on-site visit, but if not possible then home and off-site visit can be performed. CGM data must be uploaded by the site staff to the CGM software.

The site staff should ensure that the participant has fitted the sensor correctly and that the CGM receiver is working, especially when fitting of the sensor is performed over the phone or as video call.

CGM data upload at V6, V10, and V32 should be prioritised and be performed as on-site visit. CGM data must be uploaded at the site by the site staff to the CGM software.

The site should instruct the participants in manually stopping the sensor in the receiver menu when the CGM period is complete and keep the battery charged. The site staff can collect the receiver from the participant up to 4 weeks later and bring the receiver to the site for the CGM data upload.

Specifications regarding how to perform these assessments using remote visits or as home visits will be provided by Novo Nordisk or the vendor. Specifications will include training for raters performing remote assessments and adoption of modifications for equivalent administration of assessments using remote visits (video, phone or similar).

Local laboratories or diagnostic facilities can be used for haematology, biochemistry and ECG at the investigator's discretion if on-site visits are not possible or in case of temporary lockdown of the central laboratory. Only findings meeting the definition for an AE (refer to Appendix 3 (Section 10.3)) should be reported in the eCRF.

Home measurements of weight, vital signs and CGM can be performed if on-site visits are not possible and if deemed feasible for the participant. Only findings meeting the definition for an AE (refer to Appendix 3 (Section 10.3)) should be reported in the eCRF.

If the assessments indicated in Table 10-7 cannot be performed as on-site visits, remote visits or be analysed at a local laboratory or diagnostic facility, they should be performed at the first possible timepoint following the originally scheduled visit in agreement with Novo Nordisk.

10.10.4 Study intervention

Alternative dispensing methods of study intervention may be implemented, and details will be communicated and documented. The dispensing options will be provided by Novo Nordisk A/S and will be based on options and requirements at country level and if permitted by local regulations.

Table 10-7 Minimum assessments following randomisation

Please refer to Section 1.2 for the full flowchart.

Procedures marked with a **X** should be prioritised and be performed on-site.

Procedures marked with an X can be performed at the participant's home, off-site, via the phone or video call if deemed necessary because of the lockdown.

Abbreviations for visit formats: V = on-site visit; H = home visit; O = off-site visit; R = remote video call; P = phone contact.

Procedure	**Protocol Section**	**Screening**	**Run-in with CGM**			**Randomisation**	**Intervention period**								**Follow-up**		**Discontinuation follow-up**
Visit (preferred visit format)		V1	V2	V3	V4	V6	V7	V8	V10	V16	V24	V28	V30	V32	V33	V34	V32A
Alternative Visit Format			H/O/ R/P	H/O/ R/P	H/O/ R/P		H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P		H/O /R/P	H/O/ R/P	
Timing of Visit (Weeks)		≤-6	-4	-3	-2	0	1	2	4	10	18	22	24	26	28	31	26
Visit Window (Days)		+14	±3	±3	±3	±0	±3	±3	±3	±3	±3	±3	±3	-2/+28	+3	+3	±3
Informed Consent	10.1.3	**X**															
Demography	8	X															
Eligibility Criteria	5.1, 5.2, 5.5	**X**	X	X	X	**X**											
Concomitant Medication	6.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History/Concomitant Illness	8.2	**X**	**X**	**X**	**X**	**X**											
Tobacco Use	5.3.2	X															

Procedure	**Protocol Section**	**Screening**	**Run-in with CGM**			**Randomisation**	**Intervention period**								**Follow-up**		**Discontinuation follow-up**
Visit (preferred visit format)		V1	V2	V3	V4	V6	V7	V8	V10	V16	V24	V28	V30	V32	V33	V34	V32A
Alternative Visit Format			H/O/ R/P	H/O/ R/P	H/O/ R/P		H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P		H/O /R/P	H/O/ R/P	
Timing of Visit (Weeks)		≤-6	-4	-3	-2	0	1	2	4	10	18	22	24	26	28	31	26
Visit Window (Days)		+14	±3	±3	±3	±0	±3	±3	±3	±3	±3	±3	±3	-2/+28	+3	+3	±3
Childbearing Potential	10.4	X															
Pregnancy Test	8.3.5, 10.4	**X**				**X**										**X**	
Body Measurements	8.2.2	**X**				**X**					X			**X**			**X**
Body weight	8.2.2	**X**				**X**					X			**X**			**X**
Vital Signs	8.2.3	**X**												**X**			
Physical Examination	8.2.2	**X**												**X**			
ECG	8.2.5	**X**												**X**			
Eye Examination	8.2.4	**X**												**X**			
Hypoglycaemia Unawareness	8.2	**X**															
Blinded CGM	8.1.3		**X**	X	X	**X**	X	X	X			X	X	**X**			

Procedure	Protocol Section	Screening	Run-in with CGM			Randomisation	Intervention period								Follow-up		Discontinuation follow-up
Visit (preferred visit format)		V1	V2	V3	V4	V6	V7	V8	V10	V16	V24	V28	V30	V32	V33	V34	V32A
Alternative Visit Format			H/O/ R/P	H/O/ R/P	H/O/ R/P		H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P		H/O /R/P	H/O/ R/P	
Timing of Visit (Weeks)		≤-6	-4	-3	-2	0	1	2	4	10	18	22	24	26	28	31	26
Visit Window (Days)		+14	±3	±3	±3	±0	±3	±3	±3	±3	±3	±3	±3	-2/+28	+3	+3	±3
CGM fitting	8.1.3		**X**	X	X	**X**	X	X				**X**	X				
CGM data upload	8.1.3			X	X	**X**	X	X	X				X	**X**			
Self-Measured Plasma Glucose	8.1.2					**X**	X	X	X	X	X	X	X	**X**	X	X	
Adverse Event	8.3						X	X	X	X	X	X	X	**X**	X	X	**X**
Technical Complaints	8.3.6					**X**	X	X	X	X	X	X	X	**X**			
Laboratory Assessments	10.2	**X**				**X**				X	X			**X**			**X**
HbA_{1c}	10.2	**X**				**X**				X	X			**X**			**X**
Hypoglycaemic episodes	10.7						X	X	X	X	X	X	X	X	X	X	
Clinical Outcome Assessments	8.1.4					X								X			

Procedure	Protocol Section	Screening	Run-in with CGM			Randomisation	Intervention period								Follow-up		Discontinuation follow-up
Visit (preferred visit format)		V1	V2	V3	V4	V6	V7	V8	V10	V16	V24	V28	V30	V32	V33	V34	V32A
Alternative Visit Format			H/O/ R/P	H/O/ R/P	H/O/ R/P		H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P		H/O /R/P	H/O/ R/P	
Timing of Visit (Weeks)		≤-6	-4	-3	-2	0	1	2	4	10	18	22	24	26	28	31	26
Visit Window (Days)		+14	±3	±3	±3	±0	±3	±3	±3	±3	±3	±3	±3	-2/+28	+3	+3	±3
Diabetes Treatment Satisfaction Questionnaire status version (DTSQs)	8.1.4					X								X			
Treatment-Related Impact Measure for Diabetes (TRIM-D)	8.1.4					X								**X**			
Patient Global Impression of Status (PGI-S)	8.1.4					X								X			
Drug Dispensing	6.1					**X**			X	X	X	X					
Training in Trial Product, Pen-handling	6.1					**X**			X	X	X	X					
Training in eDiary	8					**X**											
End of Intervention	4.1, 6													**X**			

Procedure	Protocol Section	Screening	Run-in with CGM			Randomisation	Intervention period								Follow-up		Discontinuation follow-up
Visit (preferred visit format)		V1	V2	V3	V4	V6	V7	V8	V10	V16	V24	V28	V30	V32	V33	V34	V32A
Alternative Visit Format			H/O/ R/P	H/O/ R/P	H/O/ R/P		H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P		H/O /R/P	H/O/ R/P	
Timing of Visit (Weeks)		≤-6	-4	-3	-2	0	1	2	4	10	18	22	24	26	28	31	26
Visit Window (Days)		+14	±3	±3	±3	±0	±3	±3	±3	±3	±3	±3	±3	-2/+28	+3	+3	±3
End of Study	4.4, 7															X	X

Abbreviations: CGM = continuous glucose monitoring; DTSQs = Diabetes Treatment Satisfaction Questionnaire status version; ECG = electrocardiogram; HbA_{1c} = glycosylated haemoglobin; PGI-S = Patient Global Impression of Status; TRIM-D = Treatment-Related Impact Measure for Diabetes.

10.11 Appendix 11: Country-specific requirements

For Japan:

- Inclusion criterion 2, Section 5.1: age ≥ 18 years at the time of signing informed consent
- Preparation/Handling/Storage/Accountability, Section 6.2: The head of the trial site or the trial product storage manager assigned by the head of the trial site (a pharmacist in principle) is responsible for control and accountability of the trial products.
- Trial governance consideration: A seal is accepted as signature.
- Exclusion criterion 4, Section 5.2: the footnote, "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 screening in the current study.", is not applicable for Japan.
- Run-in Exclusion criterion 3, Section 5.5.1: the footnote, "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.", is not applicable for Japan.
- Discontinuation criterion 3, Section 7.1: the footnote, "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.", is not applicable for Japan.

For South Africa:

- Exclusion criterion 4, Section 5.2: the footnote, "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 screening in the current study.", is not applicable for South Africa.
- Run-in Exclusion criterion 3, Section 5.5.1: the footnote, "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.", is not applicable for South Africa.
- Discontinuation criterion 3, Section 7.1: the footnote, "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.", is not applicable for South Africa.

For USA:

- Financial disclosure, Section 10.1.2: Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

For Bulgaria:

- Regulatory reporting requirements for SAEs, Section 8.3.4: Novo Nordisk will report SUSARs according to regulation (EU) No 536/2014, article 40 and article 42, to the Eudravigilance database.
- Regulatory and ethical considerations, Section 10.1.1: This study will be conducted in accordance with EU regulation No 536/2014.[46]
- Data protection, Section 10.1.5: Handling of data security breached will be performed in accordance with EU regulation No 536/2014.[46]
- Communication of results, Section 10.1.14.1: The study data will be uploaded to the clinical trial information system (CTIS) within one year after the end of study.
- Visits, Appendix 10.10.2: Home visits are not allowed in Bulgaria and will be completed as regular visits at the site.

For Germany:

- Exclusion criterion 4, Section 5.2: the footnote, "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 screening in the current study.", is not applicable for Germany.
- Run-in Exclusion criterion 3, Section 5.5.1: the footnote, "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.", is not applicable for Germany.
- Discontinuation criterion 3, Section 7.1: the footnote, "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.", is not applicable for Germany.
- Regulatory reporting requirements for SAEs, Section 8.3.4: Novo Nordisk will report SUSARs according to regulation (EU) No 536/2014, article 40 and article 42, to the Eudravigilance database.
- Regulatory and ethical considerations, Section 10.1.1: This study will be conducted in accordance with EU regulation No 536/2014.[46]
- Data protection, Section 10.1.5: Handling of data security breached will be performed in accordance with EU regulation No 536/2014.[46]
- Communication of results, Section 10.1.14.1: The study data will be uploaded to the CTIS within one year after the end of study.

For Poland:

- Regulatory reporting requirements for SAEs, Section 8.3.4: Novo Nordisk will report SUSARs according to regulation (EU) No 536/2014, article 40 and article 42, to the Eudravigilance database.

- Regulatory and ethical considerations, Section 10.1.1: This study will be conducted in accordance with EU regulation No 536/2014.[46]
- Data protection, Section 10.1.5: Handling of data security breached will be performed in accordance with EU regulation No 536/2014.[46]
- Indemnity statement, Section 10.1.13: Novo Nordisk carries liability for the Trial in the scope defined by the applicable law, in particular liability resulting from the Civil Code, the Act on Clinical Trials of Medicinal Products for Human Use (Act on Clinical Trials), the Pharmaceutical Law and all other applicable law. Novo Nordisk and Investigator are liable for damages of the Trial's participants resulting from their actions or omissions. In order to support potential claims for liability attributable to the Trial, Novo Nordisk and Investigator are covered by the Insurance Policy issued according to applicable law.
- Communication of results, Section 10.1.14.1: The study data will be uploaded to the CTIS within one year after the end of study.

For Spain:

- Regulatory reporting requirements for SAEs, Section 8.3.4: Novo Nordisk will report SUSARs according to regulation (EU) No 536/2014, article 40 and article 42, to the Eudravigilance database.
- Regulatory and ethical considerations, Section 10.1.1: This study will be conducted in accordance with EU regulation No 536/2014.[46]
- Data protection, Section 10.1.5: Handling of data security breached will be performed in accordance with EU regulation No 536/2014.[46]
- Indemnity statement, Section 10.1.13: Novo Nordisk accepts liability in accordance with Article 10 (Liability regime) of the Royal Decree 1090/2015 of 4 December.
- Communication of results, Section 10.1.14.1: The study data will be uploaded to the CTIS within one year after the end of study.

For India:

The study-provisioned CGM Dexcom G6® is not approved at the time of the final protocol version 1.0.

The CGM will be regarded as an investigational medical device and will be labelled for investigational use only.

The CGM has been selected to provide the best data accuracy and to be consistent in the global clinical programme.

Technical complaints for the study-provisioned CGM must be reported to IQVIA on a technical complaint paper form received from IQVIA for the device. Timelines for reporting, from the study site obtaining knowledge of the technical complaint:

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

AE and SAEs related to the technical complaint must be reported both on the technical complaint paper form and in the eCRF. In addition, they must be reported in accordance with the standard protocol requirements for AE and SAE reporting as described in Appendix 3 (Section 10.3). At the end of study, the study-provisioned CGM must be collected by the investigator.

If the study-provisioned CGM is approved in India during the study conduct, the procedures above are not applicable anymore in the said country and technical complaints reporting should follow the standard vigilance procedures.

10.12 Appendix 12: Abbreviations

ADA	American Diabetes Association
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATTD	Advanced Technologies & Treatments for Diabetes
AxMP	auxiliary medicinal product
BG	blood glucose
BMI	body mass index
CFR	Code of Federal Regulations
CGM	continuous glucose monitoring
CI	confidence interval
COA	clinical outcome assessment
COVID-19	Coronavirus Disease of 2019
CRF	case report form
CRO	contract research organisation
CSR	clinical study report
CT	computerised tomography
CTFG	clinical trial facilitation group
CTIS	clinical trial information system
CTR	Clinical Trials Regulation
CVOT	cardiovascular outcome trial
DFU	directions for use
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl peptidase 4
DPS	data points set
DRE	disease related event
DTSQs	Diabetes Treatment Satisfaction Questionnaire status version
DUN	dispensing unit number
EAC	Event Adjudication Committee

EAS	event adjudication system
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ePID	electronic patient interactive device
ERCP	endoscopic retrograde cholangiopancreatography
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FGM	flash glucose monitoring
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GIP RA	glucose-dependent insulinotropic polypeptide receptor agonist
GLP-1 RA	glucagon-like peptide 1 receptor agonist
$HbA1_c$	glycated haemoglobin
HCP	healthcare practitioner
HIV	Human Immunodeficiency Virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICE	intercurrent event
ICH	International Council for Harmonisation
IEC	independent ethics committee
IHSG	The International Hypoglycaemia Study Group
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalised ratio
IRB	institutional review board
ISO	International Organization for Harmonization
ISPAD	International Society for Paediatric and Adolescent Diabetes
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhoea method
LAOT	last available planned on-treatment
MDR	Medical Device Regulation

MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
OCT	optical coherence tomography
PAS	participant analysis set
PCD	primary completion date
PD	pharmacodynamic
PG	plasma glucose
PGI-S	Patient Global Impression of Status
PI	package insert
PIN	prostatic intraepithelial neoplasia
PK	pharmacokinetic
PRO	patient-reported outcome
QTL	quality tolerance limits
RNA	ribonucleic acid
RTSM/IWRS	Systems used for Randomisation and Trial Supplies Management (also Interactive Web Response System)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SGLT2	sodium-glucose transporter protein 2
SI/IC	subject information/informed consent
SMPG	self-measured plasma glucose
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
T1D	type 1 diabetes
T2D	type 2 diabetes
TAR	Time Above Range
TBR	Time Below Range
TIR	Time In Range
TMM	Trial Materials Manual
TRIM-D	Treatment-Related Impact Measure for Diabetes
ULN	upper limit of normal
USADE	Unanticipated serious adverse device effect
WOCBP	woman of childbearing potential

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