Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05813912
Sponsor trial ID:	NN1436-4910
Official title of study:	A single arm study investigating the glycaemic control and safety of adding semaglutide to insulin icodec in participants with type 2 diabetes qualifying for treatment intensification.
Document date:	28 August 2024

Protocol

Protocol Title:

A single arm study investigating the glycaemic control and safety of adding semaglutide to insulin icodec in participants with type 2 diabetes qualifying for treatment intensification.

Short Title:
A research study to see how a new weekly insulin, insulin icodec when given along with semaglutide helps in reducing the blood sugar level in patients with type 2 diabetes

Substance name: Insulin icodec

Protocol Version Number: Version 4.0

Protocol Version Applicability: Global

Universal Trial Number: U1111-1281-4752

EU CT Number: 2022-502717-28-00

IND Number: 137406

Study Phase: 3b

Development Phase: Pivotal stage

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 4.0	28 August 2024	All
Protocol version 3.0	05 October 2023	All
Protocol version 2.0	26 July 2023	Poland and Czech Republic
Original protocol version 1.0	24 March 2023	All

Protocol version 4.0 (28 August 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 16 April 2014.

Overall rationale for preparing protocol, version 4.0:

Version 4.0 of the protocol was prepared to add intestinal obstruction as an important identified risk for semaglutide.

Section # and name	Description of change	Brief rationale
1.2 flow chart	Footnote added for drug dispensing at V28	To clarify that drug must not be dispensed to participants who do not meet criteria for intensification
1.2 flow chart	Cross-references to main sections for SMPG amended	Correction
Table 2-1	Row added for 'intestinal obstruction'	To add intestinal obstruction as an important identified risk for semagluitde, in alignment with recent updates in the Minimum Mandatory Safety Text.
Table 6-1	Instructions regarding administration to opposite sides of the body amended	To remove a contradiction between the protocol and the instructions provided to participants in the Injection Site Training Poster.
Table 6-2	Addition of Accu-Chek® Instant to BG meters	Accu-Chek® Instant is also used in this trial
10.5 Hepatic Safety: Suggested actions and follow-up assessments	Change from central to local laboratory for follow-up of hepatic events	Correction of a typing error. Follow-up is to be performed locally.

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

Protocol attachment II Country list of key staff and relevant departments

1 Protocol summary

1.1 Synopsis

This is an interventional, multi-national, multi-centre, treat-to-target, single-arm and open-label study. The study is designed to investigate the glycaemic control of adding semaglutide subcutaneous (s.c.) to insulin icodec in subjects with type 2 diabetes (T2D) qualifying for intensification.

Rationale:

This is a 52-week single arm study designed to investigate the clinical usability, glycaemic control, and safety of intensification of once-weekly (OW) insulin icodec with OW semaglutide (s.c.) injection. The study will include participants with T2D inadequately controlled with basal insulin. With combined use of OW basal insulin icodec and semaglutide, improved glycaemic control is expected.

Objectives, endpoints and estimand:

Primary objective

To investigate the glycaemic control of intensification of insulin icodec with semaglutide in patients with T2D.

Primary endpoint

Endpoint title	Timeframe	Unite
Change in glycated haemoglobin (HbA_{1c})	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	%-point

Primary estimand

The primary clinical question of interest is: What is the glycaemic control in terms of change in HbA_{1c} 26 weeks after insulin icodec treatment intensification with semaglutide in T2D patients treated with insulin icodec in need for treatment intensification had patients been able to adhere to both treatments and tolerate semaglutide treatment?

The following intercurrent events will be handled by the hypothetical strategy:

- Discontinuation of insulin icodec treatment
- Discontinuation of semaglutide treatment including discontinuation due to gastrointestinal (GI) side effects.

The following intercurrent events will be handled by the treatment policy strategy:

- Initiation of bolus insulin for more than two weeks

- Participants take lower than planned semaglutide dose, either if never titrated to one of the maintenance doses (0.5 or 1 mg) or if the dose is temporarily or permanently decreased during the study.

Overall design:

This is a 52-week single arm study designed to investigate the clinical usability, glycaemic control, and safety of intensification of OW insulin icodec with OW semaglutide s.c. injection. The study will include participants with T2D inadequately controlled with basal insulin.

The study consists of:

- an up to 2-week screening period
- a 26-week run-in period with insulin icodec
- a 26-week intensification period with insulin icodec and semaglutide
- a 5-week 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 run-in period receiving insulin icodec at the run-in visit (V2) for 26 weeks (V2-V28). Participants meeting intensification criteria will proceed to the 26-week treatment period (V28-V54) adding semaglutide to insulin icodec therapy. The end of treatment visit (V54) will be one week after the last dose of insulin icodec and/or semaglutide followed by 2 follow-up visits (V55 and V56). Participants not meeting the intensification criteria after 26 weeks (V28) of run-in on insulin icodec will discontinue the trial product and proceed directly to the follow-up (V55, V56).

Number of participants:

- Number of participants planned to be screened: 197
- Number of participants planned to enter-run-in period: 148
- Number of participants planned to receive intensification with semaglutide: 68

Participant characteristics:

The participants will be female/male aged 18 years at the time of signing informed consent who met the following key 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 7.5%-10.5% (58-91 mmol/mol) (both inclusive).
- Treated with once daily or twice daily basal insulin (minimum of 0.25 IU/kg/day or 20 IU/day) without concomitant glucagon-like peptide-1 receptor agonists (GLP-1 RA) ≥ 90 days prior to the day of screening with or without any of the following antidiabetic 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).

Key exclusion criteria

- Presence or history of pancreatitis (acute or chronic) within 180 days before screening.
- Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening and between screening and initiation.
- Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.
- Planned coronary, carotid or peripheral artery revascularisation.
- 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 initiation. 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 Visit	Run-in (Insulin Icodec Only)					Intensification visit	Treatment (Icodec+Semaglutide)				EOT Follow-up	
Visit		V1	V2	V3	V4	V12	V20	V27	V28 [e, f]	V32	V36	V46	V54 [g]	V55	V56
Weekly Phone Contact	1.2.1				P5-P11	P13-P19	P21-P26		P29-P31	P33-P35	P37-P45	P47-P53			
Timing of Visit (Weeks)		−2	0	1	2	10	18	25	26	30	34	44	52	28/54 [e]	31/57 [e]
Visit Window (Days)		+14	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3
SUBJECT RELATED INFORMATION AND ASSESSMENTS															
Informed Consent	App 1	X													
Demography	8	X													
Eligibility Criteria	5.1, 5.2, 5.5	X	X	X	X	X	X	X	X						
Discontinuation Criteria	7.1			X	X	X	X	X	X	X	X	X			
Medical History/Concomitant Illness	8.2	X	X												
Concomitant Medication	6.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	8.2.5	X							X				X		
Eye Examination [b]	8.2.4	X							X				X		
Physical Examination	8.2.2	X							X				X		
Pregnancy Test [i]	8.2.7, 10.4	X	X						X				X		X
Women of child-bearing potential	10.4	X													
Tobacco Use	5.3.2	X													

PROCEDURE	Protocol Section	Screening	Run-in Visit	Run-in (Insulin Icodec Only)					Intensification visit	Treatment (Icodec+Semaglutide)				EOT Follow-up	
Visit		V1	V2	V3	V4	V12	V20	V27	V28 [e, f]	V32	V36	V46	V54 [g]	V55	V56
Weekly Phone Contact	1.2.1				P5-P11	P13-P19	P21-P26		P29-P31	P33-P35	P37-P45	P47-P53			
Timing of Visit (Weeks)		−2	0	1	2	10	18	25	26	30	34	44	52	28/54 [e]	31/57 [e]
Visit Window (Days)		+14	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3
Vital Signs	8.2.3	X							X				X		
Hypoglycaemia Unawareness	8.2.6	X													
TRIAL MATERIAL	6														
Drug Dispensing			X			X	X		X[k]		X	X			
Body Measurements	8.2.2	X	X						X		X	X	X		
BMI		X	X						X		X	X	X		
Body Weight		X	X						X		X	X	X		
Height		X													
Waist Circumference			X						X		X	X	X		
REMINDERS															
Attend Visit Fasting									X	X	X	X	X		
End of Treatment									X[e]				X		
Training in Trial Product, Pen-handling			X						X[d]			X			
Hand Out and Instruct on Devices			X												
Hand Out and Instruct in Paper Diary [a]								X		X		X			

PROCEDURE	Protocol Section	Screening	Run-in Visit	Run-in (Insulin Icodec Only)					Intensification visit	Treatment (Icodec+Semaglutide)				EOT Follow-up	
Visit		V1	V2	V3	V4	V12	V20	V27	V28 [e, f]	V32	V36	V46	V54 [g]	V55	V56
Weekly Phone Contact	1.2.1				P5-P11	P13-P19	P21-P26		P29-P31	P33-P35	P37-P45	P47-P53			
Timing of Visit (Weeks)		−2	0	1	2	10	18	25	26	30	34	44	52	28/54 [e]	31/57 [e]
Visit Window (Days)		+14	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3
Make Appointment for Eye Examination							X					X			
Last dose of the trial product [c]								X				X			
SAFETY	8.3														
Adverse Event [h]	8.3			X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic Episodes	10.7			X	X	X	X	X	X	X	X	X	X	X	X
Technical Complaints	10.6			X	X	X	X	X	X	X	X	X	X		
Laboratory Assessments	10.2														
HbA_{1c}	8.1.1, 10.2	X				X	X	X	X	X	X	X	X		
FPG	8.1.2, 10.2								X	X	X	X	X		
Fasting C-peptide	10.2								X				X		
Self Assessments	10.28.1.2														
Plasma Glucose	10.28.1.2		X	X	X	X	X	X	X	X	X	X	X	X	X
7-Point SMPG Profile [j]	8.1.2								X		X		X		

[a]: Paper diary for 7-point SMPG profile

[b]: Eye exam should be performed between V20 and V27 and the results should be available by V28 for the investigator to access the eligibility of the participant for the intensification phase

[c]: Participants should be reminded about the last dose of trial product one week prior to V28 and V54.

[d]: Only participants who meet intensification criteria should receive training on second phase of study (intensification phase-insulin icodec and semaglutide).

[e]: For participants who complete the run-in period (V28) but do not meet intensification criteria, proceed directly to the follow-up visits V55 and V56

[f]: For participants who discontinue the study during run-in period, proceed to V28 and thereafter proceed to follow-up visits V55 and V56.

[g]: For participants who discontinue the study during intensification period, proceed directly to V54 and thereafter proceed to follow-up visits V55 and V56.

[h]: AEs must be collected from first administration of investigational intervention and until the end of study visit

[i]: Applicable only for women of child-bearing potential

[j]: On V28, V36 and V54, participants will collect the pre-breakfast PG (to be included in ePID) which will be also transferred as pre-breakfast SMPG (to be included in paper diary)

[k]: Do NOT dispense study drug to participants who do not meet intensification criteria.

Abbreviations: AE = adverse event; BG = blood glucose; BMI = body mass index; ECG = electrocardiogram; EOT = end of treatment; FPG = fasting plasma glucose; HbA_{1c} = glycated haemoglobin; SMPG = self-measured plasma glucose

1.2.1 Phone Visits

Table 1-1 Phone visits during the study

	Run-in (Insulin Icodec Only)			Treatment (Icodec+Semaglutide)			
Visit	P5-11	P13-19	P21-26	P29-31	P33-35	P37-45	P47-53
Timing of Visit (Weeks)	3-9	11-17	19-24	27-29	31-33	35-43	45-51
Visit Window (Days)	±3	±3	±3	±3	±3	±3	±3
PARTICIPANT RELATED INFORMATION AND ASSESSSMENTS							
Eligibility Criteria	X	X	X				
Discontinuation Criteria	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X
EFFICACY							
Self Measured Plasma Glucose	X	X	X	X	X	X	X
REMINDERS							
Last dose of the trial product [a]							X
SAFETY							
Adverse Event	X	X	X	X	X	X	X
AE Requiring Additional Data	X	X	X	X	X	X	X
Hypoglycaemic Episodes	X	X	X	X	X	X	X
Technical Complaint	X	X	X	X	X	X	X

[a]: Participants should be reminded last dose of trial product should occur one week prior to V28 and V54.

2 Introduction

Diabetes mellitus is a metabolic disorder characterised by the presence of hyperglycaemia due to defective insulin secretion, insulin action or both. The chronic hyperglycaemia of diabetes mellitus is associated with significant long-term complications, particularly damage, dysfunction and failure of various tissues – especially the kidney, eye, nerves, heart and blood vessels.[1] Diabetes is generally classified according to aetiological factors, where type 1 diabetes (T1D) and T2D constitute the vast majority of cases. In the latest edition of the International

Diabetes Federation's Diabetes Atlas (2021),[2] the estimated worldwide diabetes prevalence was 537 million, with a prediction that the prevalence of diabetes will have increased to 643 million by 2030 and 783 million by 2045.

2.1 Study rationale

This is a 52-week single arm study designed to investigate the clinical usability, glycaemic control, and safety of intensification of OW insulin icodec with OW semaglutide s.c. injection.

The combination of basal and bolus insulins has been the golden standard regimen used for insulin intensification. Currently, other simpler alternatives like the combination of GLP-1 RA with basal insulin and oral antidiabetic agent (OAD(s)) is approved and is being implemented in clinical practise, with data available to support its broad clinical benefits.[3] Currently data is available on adding semaglutide s.c. to commercially available basal insulins (SUSTAIN 5 (NN9535-3627)[4] and SUSTAIN 11 (NN9535-4386)[5]) and data is generated on adding insulin icodec to commercially available GLP1-RA.[6,7]

Overall, the findings of the current study will be important for providing clinical guidance for add on of semaglutide to insulin icodec when intensification with semaglutide is needed.[8]

2.2 Background

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) treatment guidelines recommend a stepwise approach reflecting the progressive nature of T2D. First-line therapy depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification.

The combination of GLP-1 RA with basal insulin and OAD(s) is approved and is being implemented in clinical practise, with data available to support its broad clinical benefits.[3]

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 s.c. injection. Insulin icodec has a terminal elimination half-life of approximately 196 hours. The molecule consists of a peptide backbone and a fatty acid-containing side-chain. The peptide backbone is more resistant towards proteolytical degradation compared to human insulin and the side chain gives a strong binding to albumin. Both features contribute to the long action of insulin icodec.

The development programme for insulin icodec is currently ongoing. Three phase 3 trials have recently been completed (NN1436-4478, NN1436-4479 and NN1436-4480). Two of the phase 3 completed trials (NN1436-4478 and NN1436-4480) included a population on basal insulin switching to insulin icodec and allowed the concomitant use of GLP-1 RA during the trial.[6] [7]

Semaglutide

Semaglutide is a potent human GLP-1 analogue that acts as a GLP-1 RA, with a long half-life (approximately 1 week) suitable for OW dosing.[9] The long half-life was obtained by applying the fatty acid acylation technology that provides specific high-affinity albumin binding. Furthermore, semaglutide has full stability against dipeptidyl peptidase-4 (DPP-4) degradation. Semaglutide exhibits GLP-1 receptor mediated effects, leading to lowering of glucose and decreased appetite through physiologically relevant mechanisms. As a result, semaglutide provides strong glycaemic control and weight loss. In addition, the cardiovascular (CV) safety of semaglutide has been confirmed (SUSTAIN 6 (NN9535-3744)).[10] The mechanism of action of semaglutide was characterized in extensive non-clinical and clinical studies.[11-13] In the SUSTAIN clinical development programme, OW semaglutide s.c., demonstrated clinically relevant and superior reductions in HbA_{1c} and body weight as compared to placebo and commonly used marketed products.[12, 13]

In SUSTAIN 5 (NN9535-3627)[5], and SUSTAIN 11 (NN9535-4386)[4], semaglutide has been investigated in add-on to daily basal insulin and proved to be safe and efficient in the currently published results.[14,15,16]

Semaglutide is currently approved for T2D including CV indication as Ozempic® and for obesity as Wegovy®.

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 and semaglutide may be found in the respective investigator's brochure.[17]

2.3.1 Risk assessment

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

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: Hypoglycemia	Hypoglycemia is an anticipated undesirable effect related to the pharmacological mechanism of insulin.	The risk of hypoglycaemia is addressed in the SI-IC and IB.[17] 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 development programme.	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[17] and the SI-IC.
Identified risk: Hypersensitivity	Hypersensitivity reactions may potentially occur following injection of therapeutic proteins. Reactions have been observed in previous insulin icodec trials.	Known or suspected hypersensitivity to trial product(s) or related products is an exclusion criterion in the clinical trial. 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[17] and SI-IC.
Identified risk: Peripheral Oedema	Insulins, including insulin icodec, may cause sodium retention and oedema. In the clinical development programme, events of peripheral oedema were observed in trial 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[17] and SI-IC.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Potential risks: Immunological events – formation of neutralising insulin antibodies	Antibodies to exogenously delivered insulin are common with insulin treatment but are not often clinically significant. In NN1436-4478, -4479, -4480 and -4625 the number of participants that developed anti-insulin icodec antibodies at any time during the trial was between 70.2% and 79.0%, of which the large majority had antibodies cross-reacting with human insulin (67.9% to 77.4% of the total). In N1436-4478, -4479 and -4480 no significant correlation between the change of anti-insulin icodec antibodies titre from baseline to follow up and rate of severe (level 3) or clinically significant (levels 2) hypoglycaemia has been found. Results for NN1436-4625 still pending. No apparent relationship between antibody titres and change in HbA1c or weekly insulin dose was observed.	Investigators will closely monitor the glycaemic control of each participant throughout the trial. In case lack of clinical effect is observed, rescue medication will be provided if deemed necessary and 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[17] and SI-IC. For more information, please refer to Section 7.1
Study intervention (semaglutide)		
Gastrointestinal disorder	Consistent with findings for other GLP-1 RAs, the most frequently reported AEs in clinical studies with semaglutide were gastrointestinal (GI) disorders, including nausea, diarrhoea, and vomiting. In general, these reactions are mild or moderate in severity, of short duration, and dose dependent. In participants treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration. This should be considered when treating adults with impaired renal function as it may cause a deterioration of renal function.	Clinical studies have shown that a low starting dose and gradual dose escalation mitigates the risk of developing GI symptoms. A low starting dose and dose escalation steps has been implemented in the study to mitigate the risk of GI AEs. Participants with GI symptoms are recommended to drink plenty of fluids to avoid volume depletion. Thresholds for renal impairment based on the measured estimated Glomerular Filtration Rate (eGFR) at screening are specified in Section 5.2. Adults exceeding these thresholds will not be enrolled in the study.
Intestinal obstruction	There have been postmarketing cases of intestinal obstruction reported with semaglutide. Intestinal obstruction is a severe form of constipation with blocked passage of food, liquid and stool with additional symptoms such as stomachache, bloating, vomiting, etc. In serious cases, intestinal obstruction can lead to bowel ischaemia and perforation.	Please refer to mitigations of gastrointestinal adverse events. Furthermore, participants should be informed of the characteristic symptoms of intestinal obstruction. If intestinal obstruction is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 RA drug class. In the completed phase 3 trials with semaglutide s.c. and oral semaglutide, both the event rate and the proportion of participants experiencing confirmed pancreatitis were similar with semaglutide and comparator. Few events were confirmed; the events occurred throughout the trial periods and the overall rates were similar to the rates reported in background populations.	Adults with a history of chronic pancreatitis or recent acute pancreatitis will not be enrolled in the study (Section 5.2). Participants should be informed of the characteristic symptoms of acute pancreatitis. In addition, in case of suspicion of acute pancreatitis, study intervention should be promptly interrupted in accordance with Section 7.1. If confirmed, semaglutide should not be restarted.
Hypoglycaemia	Semaglutide and other GLP-1 RAs are in general associated with a low risk of hypoglycaemia because of their glucose-dependent mechanism of action. There is a low risk of hypoglycaemic episodes when semaglutide is used as monotherapy. Adults treated with semaglutide in combination with a sulfonyl urea (SU) or insulin have an increased risk of hypoglycaemia.	The risk of hypoglycaemia can be lowered by reducing the dose of SU or insulin when initiating treatment with semaglutide at the discretion of the investigator (Section 6.7).
Diabetic retinopathy complications	In a 2-year clinical trial with s.c. semaglutide (NN9535-3744) involving 3,297 participants with T2D, high CV risk, long duration of diabetes and poorly controlled blood glucose, EAC-confirmed events of diabetic retinopathy complications occurred in more participants treated with s.c. semaglutide (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among participants with a history of diabetic retinopathy at baseline. In the participants who did not have a documented history of diabetic retinopathy the number of events were similar for s.c. semaglutide and placebo. In the other clinical trials up to 1 year involving 4,807 participants with T2D, AEs related to diabetic retinopathy were reported in similar proportions of participants treated with s.c. semaglutide	As a precaution, participants with a history of uncontrolled and potentially unstable diabetic retinopathy or maculopathy will be excluded from the study, and fundus photography or slitlamp- bio microscopy examination with pharmacologically dilated pupils will be performed according to flowchart (Section 1.2). Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Long-term glycaemic control decreases the risk of diabetic retinopathy. These participants should be monitored closely and treated according to clinical guidelines.
Allergic reactions	As with all protein-based pharmaceuticals, participants treated with semaglutide may evoke allergic reactions, including serious allergic reactions such as angioedema and anaphylactic reactions.	Adults with known or suspected hypersensitivity to semaglutide or related products will not be enrolled in this study

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
		In addition, participants will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the study product occurs.
Pancreatic cancer (potential GLP-1 RA class risk)	Patients with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from non-clinical studies, clinical studies, or post-marketing data that GLP-1 RA-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RAs by regulatory agencies based on the unknown long term effects on β-cell stimulation and α-cell suppression. There is no indication of an increased relative risk in the semaglutide treatment groups vs. comparator, including placebo. The rates of EAC-confirmed events of pancreatic cancer were consistently low across trials.	Adults with presence or history of malignant neoplasm within 5 years prior to screening will not be enrolled in this study (Section 5.2).
Medullary thyroid cancer (MTC) (based on non-clinical data)	Thyroid C-cell tumours were seen in the mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. No C-cell tumours were observed in monkeys after 52 weeks exposure up to 52-fold above the clinical plasma exposure at 14 mg/day. The GLP-1 receptor is not expressed in the normal human thyroid, and therefore the clinical relevance of the findings is considered to be low.	Adults with a family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2) are excluded from the study (Section 5.2).
Study procedure		
COVID-19 infection in relation to participation in trial.	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 minimize the risk as much as possible, the following measures have been taken:

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
		• Cautious participant recruitment planning ensures controlled participant 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, sanitizers, no aerosol-generating procedures etc. according to the local practice).

Abbreviations: AEs = adverse events; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; GLP-1 RAs = Glucagon-like peptide-1 receptor agonist; IB = investigator's brochure; MEN2 = multiple endocrine neoplasia type 2; MTC = medullary thyroid carcinoma; s.c. = subcutaneous; SI-IC = subject information-informed consent; T2D = type 2 diabetes

2.3.2 Benefit assessment

Insulin icodec is currently in development for treatment of diabetes mellitus. In both clinical and non-clinical trials, insulin icodec has shown to have a long and stable pharmacokinetic (PK) and pharmacodynamic (PD) profile, supporting a once-weekly treatment. Currently available long-acting basal insulin products need to be administered once-daily to provide 24-hour coverage. Market research has shown that people with diabetes, put value in reducing the number of insulin injections.[18] Therefore, the treatment adherence and quality of life are expected to increase by introducing a OW basal insulin treatment.

Clinical data on OW semaglutide have demonstrated superior glycaemic control, superior reductions in body weight versus placebo and active comparators, and reduced cardiovascular risk compared to placebo in participants with T2D. Further, OW dosing offers flexibility and fewer injections as opposed to current therapy.

Based on these data, adding semaglutide to insulin icodec is expected to be safe and provide efficacy on HbA_{1c} lowering.

For all participants, the anticipated benefits include improved glycaemic control. To ensure all participants receive adequate treatment, investigators are encouraged to optimise glycaemic control every week throughout the study in accordance with the titration guidelines, see Appendix 8 (Section 10.8). Participants will receive intense medical care by means of weekly contact with the sites.

2.3.3 Overall benefit-risk conclusion

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 and semaglutide are justified by the anticipated benefits that may be afforded to participants with diabetes.

3 Objectives, endpoints and estimands

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
To investigate the effect on glycaemic control of intensification of insulin icodec with semaglutide in patients with T2D	Primary		
	Change in HbA_{1c}	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	%-point
	Supportive secondary		
	Change in mean 7-point SMPG profiles	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	mmol/L
	Change in mean post-prandial glucose increment (over all meals)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	mmol/L
	Change in FPG	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	mmol/L
Secondary	**Title**	**Time frame**	**Unit**
To investigate the safety of intensification of insulin icodec with semaglutide in patients with T2D	Supportive Secondary		
	Number of severe hypoglycaemic episodes (level 3)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 57 (V56)	Number of episodes
	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 57 (V56)	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 (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 57 (V56)	Number of episodes
	Change in body weight	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	Kg
	Relative change in weekly insulin icodec dose	From the week prior to intensification, week 25 (V27) to week 52 (V54)	U

Abbreviations: BG=blood glucose; FPG=fasting plasma glucose; HbA_{1c}=glycated haemoglobin; kg=kilograms; SMPG=self-measured plasma glucose; T2D=type 2 diabetes mellitus; V=visit

Table 3-2 Exploratory endpoints

Title	Time frame	Unit
Exploratory		
Change in mean 7-point SMPG profiles	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28) to week 34 (V36)	mmol/L
Change in mean post-prandial increment (over all meals)	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28) to week 34 (V36)	mmol/L
Change in Fasting C-peptide	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54)	nmol/L
Change in Fasting plasma glucose	From baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 34 (V36)	mmol/L

Abbreviations: SMPG = self-measured plasma glucose; V=visit

Primary estimand

The primary clinical question of interest is: What is the glycaemic control in terms of change in HbA_{1c} 26 weeks after insulin icodec treatment intensification with semaglutide in T2D patients treated with insulin icodec in need for treatment intensification had patients been able to adhere to both treatments and tolerate semaglutide treatment?

The following intercurrent events will be handled by the hypothetical strategy:

- Discontinuation of insulin icodec treatment
- Discontinuation of semaglutide treatment including discontinuation due to GI side effects.

The following intercurrent events will be handled by the treatment policy strategy:

- Initiation of bolus insulin for more than two weeks
- Participants take lower than planned semaglutide dose, either if never titrated to one of the maintenance doses (0.5 or 1 mg) or if the dose is temporarily or permanently decreased during the study.

4 Study design

4.1 Overall design

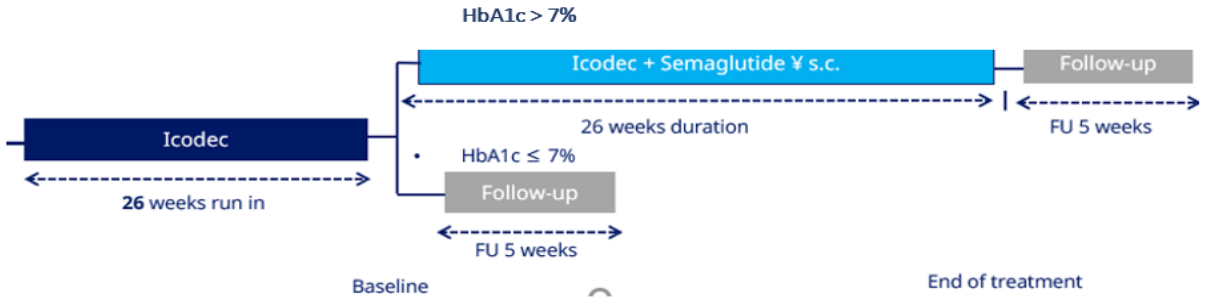
This is an interventional, multi-national, multi-centre, treat-to-target, single-arm and open-label study. The study is designed to investigate the glycaemic control of adding semaglutide (s.c.) to insulin icodec in subjects with T2D qualifying for intensification. The study is planned to enrol 148 participants.

The study duration is approximately 59 weeks and consists of:

- an up to 2-week screening period
- a 26-week run-in period with insulin icodec
- a 26-week treatment period with insulin icodec and semaglutide
- a 5-week follow-up period.

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

Figure 4-1 Study design



The study includes a screening visit (V1) to assess participants eligibility. After screening, all eligible participants will enter the run-in period receiving insulin icodec at run-in visit (V2).

Sulfonylureas and glinides must be discontinued at run-in visit (V2) and DPP-4 inhibitors must be discontinued before intensification visit (V28), when semaglutide is initiated. The dose and dosing frequency of any pre-trial OADs should not be changed during the study, unless due to safety concerns.

Participants will measure daily SMPG throughout the study. 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 dose of trial products will be adjusted in accordance to titration guidelines, Appendix 8 (Section 10.8). The treatment duration with trial products for individual participants is planned for 52 weeks. Participants not meeting the intensification criteria as defined in Section 5.5.2 after 26 weeks (V28) of run-in on insulin icodec will discontinue trial product and proceed directly to end of study follow-up (V55, V56).

Participants meeting intensification criteria will proceed to the 26-week treatment period (V28-V54) adding semaglutide to insulin icodec therapy. The end of treatment visit (V54) will be one week after the last dose of insulin icodec and/or semaglutide.

Two follow-up visits (V55 and V56) will be performed 2 and 5 weeks, respectively, after the end of treatment visit (V28 or V54). This will allow for appropriate wash-out of trial products, following at least 5 half-lives of trial products. After the end of treatment participants will be transferred to a marketed product at the discretion of the investigator.

4.2 Scientific rationale for study design

A 26-week run-in period was included to ensure the dose optimisation of insulin icodec after the transfer of all participants from their pre-trial basal insulin to insulin icodec. The treat-to-target approach has been chosen to ensure optimal titration of insulin icodec based on SMPG values with the aim of improving HbA_{1c} in the run-in period.

Only participants not in adequate glycaemic control after the 26-week run-in period (per central laboratory HbA_{1c} value obtained at the second to last visit and assessed at the last visit during run-in (defined as HbA_{1c} of >7.0% at V27)) are to have their treatment intensified by adding semaglutide to insulin icodec. The intensification phase duration of 26 weeks with semaglutide and insulin icodec is evaluated to be adequate for assessing efficacy on glycaemic control as well as safety.

Potential eligible participants will be identified by the investigator and all eligible participants should be provided the subject information/informed consent (SI-IC) document and asked if they would like to participate in the study. The investigator will have determined the participant eligibility for continued treatment with basal insulin and potential intensification with semaglutide prior to informed consent.

For documenting of glucose levels and for insulin icodec and semaglutide doses, Novo Nordisk will provide all participants with an eDiary. For titration guidance (titration decisions throughout study intervention) see Appendix 8 (Section 10.8).

Throughout the study, the investigator will remind the participants to follow the study procedures and requirements, to ensure participants compliance. The investigator should retrain participants when needed and assess the compliance at each contact (visit or phone) by evaluating the glycaemic control, adherence to the visit schedule and completion of the participant's eDiary, including values for titration, dose, and hypoglycaemia reporting. If a participant is found to be non-compliant, the investigator will remind the participant of the importance of following the instructions given, including taking the study medications as prescribed.

After the end of trial including follow-up visits, participants will be transferred to a marketed product at the discretion of the investigator.

Treatment with sulfonylureas and glinides must be discontinued at V2 in order to minimise the risk of hypoglycaemia. Treatment with DPP-4 inhibitors must be discontinued before V28 because of the initiation of semaglutide and the absence of benefit of combining both treatments.

4.2.1 Patient input into design

Patient input to the design of the current study has not been provided. However, relevant experience and feedback from sites of previous insulin icodec studies has been implemented to the extent possible.

4.3 Justification for dose

Insulin icodec will be switched from the pre-trial basal insulin analogues according to the principles outlined in the titration guideline in Appendix 8 (Section 10.8). A 50% one-time additional dose will be applied to the first dosage of insulin icodec to avoid glycaemic slip during the first few weeks of treatment in the run-in period. No safety concerns have been identified in subjects with T2D, using an one-time additional dose when initiating insulin icodec (studies NN1436-4466[19] and NN1436-4478[6]).

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

The pharmacokinetic/pharmacodynamic (PK/PD) properties of insulin icodec following 5 weeks of once-weekly dosing in participants with T2D (study NN1436-4314) showed that insulin icodec exposure was well distributed across the dosing interval, with a PK profile suitable for once-weekly dosing. Insulin icodec was well tolerated in participants with T2D and no unexpected safety concerns were identified after multiple once-weekly dosing in the dose range of 12−24 nmol/kg (2-4 U/kg).

Semaglutide should be initiated at a dose of 0.25 mg weekly. This initial dose of semaglutide has been used in the SUSTAIN clinical development programme. The planned target dose of semaglutide in this trial is 1 mg with an escalation from 0.25 mg to 0.5 mg and 1 mg every 4 weeks.

Initiation and titration of insulin icodec and semaglutide should be conducted in accordance with the titration guideline, see Appendix 8 (Section 10.8).

4.4 End of study definition

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

A participant is considered to have completed the study if he/she has completed all periods of the study (run-in and treatment period) including the last visit.

The primary endpoint is evaluated at V54 (week 52). The primary completion date (PCD) is defined as the date of V54 (week 52) 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 V54. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to Food and Drug Administration Amendment Act (FDAAA) (Section 10.1.7).

5 Study population

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

Pre-screening is defined as review of the 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. Age above or equal to 18 years at the time of signing informed consent.
3. Diagnosed with T2D ≥180 days prior to the day of screening.
4. HbA_{1c} from 7.5%-10.5% (58-91 mmol/mol) (both inclusive) at screening confirmed by central laboratory analysis.
5. Treated with once daily or twice daily basal insulin (minimum of 0.25 IU/kg/day or 20 IU/day) without concomitant GLP-1 RAs ≥ 90 days prior to the day of screening with or without any of the following antidiabetic 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)
6. Body mass index (BMI) ≤ 40.0 kg/m^2
7. The need and willingness to undergo treatment intensification with the treatments investigated in this study with the aim to reach an HbA_{1c} of 6.5% to 7.5% (48 mmol/mol to 58 mmol/mol) (both inclusive), as assessed by the investigator.
8. Ability and willingness to adhere to the protocol including performance of SMPG profiles according to the protocol.

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 highly effective 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 of diabetic ketoacidosis within 90 days prior to the day of screening[a]
7. Presence or history[a] of pancreatitis (acute or chronic) within 180 days before screening.
8. Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening and between screening and initiation.
9. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.
10. Planned coronary, carotid or peripheral artery revascularisation.
11. Renal impairment with estimated Glomerular Filtration Rate (eGFR) value of eGFR <30 mL/min/1.73m^2.[20]
12. Impaired liver function, defined as Alanine Aminotransferase (ALT) ≥2.5 times or Bilirubin >1.5 times upper normal limit at screening.
13. Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8[21] (Section 8.2).
14. Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator.
15. Inadequately treated blood pressure defined as systolic ≥180 mmHg or diastolic ≥110 mmHg at screening.
16. 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.
17. 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).
18. 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 initiation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.
19. Presence or history 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.
20. Use of any medication with unknown or unspecified content within 90 days before screening.
21. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.

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

5.3 Lifestyle considerations

To ensure alignment of performance of assessments across participants and study sites, the below restrictions apply.

5.3.1 Meals and dietary restrictions

Participants must attend the visits fasting, if indicated, according to the flowchart.

Fasting is defined as at least 8 hours overnight before the visit, without food or liquids, except for water. Trial products and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood samples have been obtained.

If the participant is not fasting as required, the participant should be called in for a new visit within the visit window to have the fasting procedures done. Procedures requiring participant to fast include blood sampling of lipids.

5.3.2 Caffeine, alcohol and tobacco

Participants should avoid caffeine and tobacco use at least 30 minutes prior to measuring the blood pressure.

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

5.3.3 Activity

Not applicable for this study.

5.3.4 Other restrictions

Not applicable for this study.

5.4 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently eligible for participation according to the inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, eligibility criteria, results of laboratory analyses, and any serious adverse event (SAE).

A screen failure must be registered in the Randomisation and Trial Supplies Management (RTSM).

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 exclusion criteria and intensification criteria

If any of the run-in exclusion criteria or intensification criteria related to laboratory parameters were not met, 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).

5.5.1 Run-in exclusion criteria

In addition to the discontinuation criteria listed in Section 7, the participant must be withdrawn from the study during the run-in period, if the following applies after screening and before or at semaglutide initiation.

1. Any of the following: Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack
2. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV
3. Planned coronary, carotid or peripheral artery revascularisation
4. Initiation of any medication for the indication of diabetes or obesity (other than the trial product). However, short-term bolus insulin treatment periods for a maximum of 14 days are allowed.
5. Included in the study in violation of the inclusion and/or exclusion criteria.

For description of discontinuation visit schedule and procedures, refer to Section 7. A run-in failure must be registered in RTSM.

5.5.2 Intensification criteria

To be eligible to the intensification by adding semaglutide to insulin icodec, all following allocation criteria must be answered "yes".

1. HbA_{1c} of >7.0% to ≤10.5% measured at V27 (week 25).
2. The need and willingness to undergo treatment intensification with the treatments investigated in this study with the aim to reach an HbA_{1c} of 6.5% to 7.5% (both inclusive), as assessed by the investigator at allocation (V28)
3. No appearance of uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within 8 weeks prior to the intensification visit (V28). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.
4. Discontinuation of DPP4-inhibitors before V28

5.6 Stand-by participants

Not applicable to this study.

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, semaglutide and non-investigational medicinal products (NIMPs). BG meter is not considered study intervention.

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 semaglutide are considered as investigational interventions. During the run-in period insulin icodec alone and during intensification period the combination of insulin icodec and semaglutide, both are referred as 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 semaglutide. NIMPs are not considered as trial products.

6.1 Study intervention(s) administered

Investigational medicinal products (IMP)

Table 6-1 provides an overview of the investigational medicinal products.

Table 6-1 Investigational medicinal products

Intervention name	Insulin icodec	Semaglutide
Intervention type	IMP, test product	IMP, test product
Pharmaceutical form	Solution for injection	Solution for injection
Route of administration	Subcutaneous (into the thigh, upper arm or side of the abdomen on one side of the body)	Subcutaneous (into the thigh, upper arm or side of the abdomen on the other side of the body)
Trial product strength	700 U/mL	1.34 mg/mL

Intervention name	Insulin icodec	Semaglutide
Dose and dose frequency	Once weekly dosing for 26 weeks during run-in. Once weekly dosing for 26 weeks during treatment period. For dose titration, refer to Appendix 8 (Section 10.8).	Once weekly dosing for 26 weeks starting from baseline at a dose of 0.25 mg. After 4 weeks, the dose should be increased to 0.5 mg. The dose could be increased to 1 mg after at least 4 weeks to further improve glycaemic control, at the investigator's discretion. Dose reduction from the dose of 1 mg to 0.5 mg is allowed in case of safety concern or unacceptable intolerability. For dose titration, refer to Appendix 8 (Section 10.8).
Dosing instructions and administration [a]	Administer insulin icodec OW, on the same day each week, at any time of the day. The day of weekly administration can be changed if necessary, by up to 3 days. A minimum of 4 days between injections should always be kept. A rotation of injection site is recommended between right thigh, right upper arm or right side of abdomen.	Administer semaglutide OW, on the same day each week, at any time of the day. A rotation of injection site is recommended between left thigh, left upper arm or left side of abdomen.
Transfer from other therapy	At run-in visit(V2), participants were transferred from their pre-trial basal insulin treatment to insulin icodec	Not applicable
Sourcing	Manufactured and supplied by Novo Nordisk A/S	Manufactured and supplied by Novo Nordisk A/S
Packaging and labelling Container/device constituent	• 3 mL PDS290 prefilled pen-injector • Labelled and packaged by Novo Nordisk A/S • Labelled in accordance with EU CTR Annex VI,[22] local regulations and study requirements.	• 1.5 mL pre-filled PDS290 pen-injector • Labelled and packaged by Novo Nordisk A/S • Labelled in accordance with EU CTR Annex VI,[22] local regulations and study requirements.

[a] It is advised that both insulin icodec and semaglutide are taken on the same day for better adherence and effect

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) at the first dispensing visit (as specified in the flowchart, Section 1.2). Participants should be instructed to use one pen injector for the full in-use time period. The participants should change the pen-injector only if the in-use time is passed or a full dose can no longer be given.

Non-investigational medicinal products (NIMP)

After run-in visit (V2), the participants should continue their pre-trial OAD medication throughout the entire study, the dose and dosing frequency of which should not be changed, unless due to safety concerns.

In addition, the pre-trial OAD:

- is considered to be NIMP
- 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.

As stated in Section 4.1, DPP-4 inhibitors can be continued throughout the run-in period (must be discontinued before intensification visit (V28)), is also considered as a NIMP.

Auxiliary supplies comprise supplies other than trial products and are listed in Table 6-2. Auxiliary supplies are not under scope of investigation in this study.

Table 6-2 Auxiliary supplies

Auxiliary	Model	Details	Manufacturer
Needles	NovoFine® needles or similar according to local requirements	Only needles with a maximum length of 6 mm provided and approved by Novo Nordisk must be used for administration of treatment. Please refer to TMM.	Novo Nordisk
BG meter (including auxiliaries)	Roche Accu-Chek® Guide / Instant	At run-in visit (V2) 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.
eDiary	Electronic Patient Interaction Device (ePID)	Participant Mobile App in Study Phone, HCP web portal in study tablet, & Cloud Service. Please refer to the eDiary site guide.	Novo Nordisk

Abbreviations: BG = blood glucose; DFU = direction for use; HCP = healthcare professional; V=visit

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

6.2 Preparation, handling, storage and accountability

Only participants enrolled in the study may administer study intervention. Each site will be supplied with sufficient trial products for the study on an ongoing basis according to recruitment, run-in and enrolment.

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).

Trial product accountability must be performed at item level within a DUN as returned either as used/partly used, unused or lost. Trial product accountability must also be performed in RTSM.

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 Randomisation and trial supplies management

All participants will be screened and assigned treatment using the RTSM. This is an open-label, non-randomised study; however, the specific investigational intervention for a participant will be assigned using RTSM. The site will access the RTSM system before the start of investigational intervention administration for each participant.

6.4 Study intervention compliance

Drug treatment compliance

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

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

- Accountability information; counting returned trial product, visual inspection of pens
- Review of dosing diaries
- Questioning of participants
- Other

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

Compliance with other interventions

Not applicable for this study.

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.

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.

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[17] and semaglutide IB.[23]

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 (V56) must be recorded as concomitant medication along with:

- Trade name or generic name
- Primary indication
- Dates of administration including start and stop dates or continuation

- Relevant for participants in COVID-19 studies: Type of study and type of drug

Concomitant medication (diabetes)

Any anti-diabetic medication other than the trial product that the participant receives from screening (V1) until end of trial visit (V56) must be recorded in a separate concomitant medication (diabetes) form in the eCRF. The following information must be recorded for oral antidiabetic drug (OADs), GLP-1 RAs, and insulin products including post-treatment insulin in the follow-up period:

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

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

6.8.1 Rescue medicine

Not applicable for this study.

7 Discontinuation of study intervention and participant discontinuation/withdrawal

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

7.1 Discontinuation of study intervention

Study intervention may be discontinued at any time during the study at the discretion of the participant or at the discretion of the investigator for safety, behavioural, 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 discontinue study intervention as soon as possible to attend the discontinuation visit, V28 (if participants exit the study during run-in period) or V54 (if participants exit the study during intensification period) to collect the data. Discontinuation of either insulin icodec or semaglutide during the intensification period should be considered as discontinuation of the study intervention. All participants should attend the 2 follow-up visits (V55 and V56), irrespective of when the study intervention was discontinued.

Only participants who withdraw consent will be considered as withdrawn from the study. Participants must be informed about the continued scientific importance of their data, even if they discontinue study intervention.

The study 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. Confirmation of acute pancreatitis
6. Lack of efficacy, defined as fulfilment of ALL criteria (a, b and c) below :
   - a. Mean of pre-breakfast SMPG values (on the two days before and on the day of visit) of 3 consecutive weeks are above 15 mmol/L (270 mg/dL), and
   - b. no treatable intercurrent cause for the hyperglycaemia (e.g. non-compliance) has been identified.
   - c. In such case, the participant must be called for a confirmatory FPG measurement as soon as possible. A confirmatory FPG must be obtained and analysed by the central laboratory. If this FPG exceeds 15 mmol/L (270 mg/dL), participant fulfils the lack of efficacy criteria.

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

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

7.1.1 Temporary discontinuation of study intervention

The temporary discontinuation of the study intervention is allowed only 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 hepatic events, defined as:

- ALT (or AST) > 3 x upper limit of normal (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 UNL with the appearance of fatigue, nausea, vomiting, anorexia, abdominal pain or tenderness, fever, rash, and/or eosinophilia (>5%).

**Please note that such an event must 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. Temporary discontinuation and restart of the study intervention must be registered in RTSM.

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).

7.1.2 Rescue criteria

Not applicable for this study.

7.2 Participant discontinuation/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 after run-in visit (V2) and before V28, the investigator must ask the participant if he/she is willing, as soon as possible, to have assessments performed according to V28.

If a participant withdraws consent or is withdrawn by the investigator after the intensification visit (V28), the investigator must ask the participant if he/she is willing, as soon as possible, to have assessments performed according to V54. See the flowchart for data to be collected.

All participants should attend the 2 follow-up visits (V55 and V56), irrespective of when the participant withdraws consent or is withdrawn by the investigator.

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.

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

7.3 Lost to follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, at least three telephone calls and, if necessary, a certified letter to the 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 enrolled in the study, 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.

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

All run-in exclusion criteria must be reviewed at each of the visits during the run-in period (V2 (week 0) to V28 (week 26)).

At the intensification visit (V28), run-in exclusion criterion and intensification criteria must be assessed prior to other assessments.

Adherence to the study design requirements, including those specified in the flowchart, is essential and required for study conduct.

Review of diaries (paper and eDiary), 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 paper diary or 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

Participants will be provided with a BG meter including auxiliaries.

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 '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.

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

Pre-breakfast daily self measured glucose

Participants should be instructed to measure their pre-breakfast SMPG daily from week 0 (V2) to last follow up visit (V56) and to transfer the measured SMPG values into the eDiary.

Selected titration data (e.g. certain SMPGs and dose data) from the eDiary will be used during the 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 10.1.10).

7-point SMPG profile

All participants will be instructed to perform 7-point SMPG profiles in the week prior to V28, V36 and V54. This profile is collected in a paper diary. The 7-point profile is used to measure glycaemic variability over a day.

Participants should be instructed in how to record the results of the SMPG values in the paper diaries. The record of each SMPG value should include date, time and value. All data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone, and a discrepancy is later detected, the values in the eCRF must be corrected.

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

The 7-point profile includes a day's time points as listed below:

- Before breakfast
- 90 minutes after the start of breakfast
- Before lunch
- 90 minutes after the start of lunch

- Before main evening meal (dinner)
- 90 minutes after the start of main evening meal (dinner)
- At bedtime

SMPG values measured before breakfast, lunch, main evening meal and at bedtime should be performed before any insulin injection and just before the start of the meal (breakfast, lunch or main evening meal). SMPG values measured before breakfast should be performed in a fasting condition. The measurements will be used to evaluate the glucose profile.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the flowchart (Section 1.2) and in Appendix 2 (Section 10.2).

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 the eCRF.

As part of the medical history, information on the following will be collected:

- History of diabetes
- History of cardiovascular disorder and procedure
- History of non-alcoholic fatty liver disease (NAFLD)
- COVID-19 vaccines

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.[21] 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 Dose

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

The investigator must record the first and last date of insulin icodec and semaglutide in the eCRF.

Starting at run-in (V2), participants must be instructed to report date, actual dose applied and time of once weekly insulin icodec in the eDiary. Starting at the intensification visit (V28) participants must be instructed to report date, actual dose applied, and time of semaglutide in the eDiary.

8.2.2 Physical examinations

A physical examination will include assessments of:

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

Body measurements (e.g., height and weight and waist circumference) will also be measured and recorded as specified in the flowchart.

- Body weight should be measured in pounds (lb) or kilograms (kg) 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 will be calculated and recorded in the participants medical records.
- The weight circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest and will be measured using a non-stretchable measuring tape. The measurement of the waist circumference should be performed and recorded in the eCRF to the nearest ½ cm or ¼ inch using the same measuring tape throughout the study. The waist circumference should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The participant should be standing with arms down their side and feet together. The tape should touch the skin but not compress soft tissue. The participant should be asked to breathe normally, and the measurement should be taken when the participant is breathing out gently.

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

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 (V1), V28, and end of treatment (V54).

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.

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.

8.2.4 Eye examination

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

Results of an eye examination performed by an ophthalmologist or another suitably qualified health care provider (e.g., optometrist) possibly aided by diagnostic artificial intelligence algorithms approved by FDA and/or CE-marked must be available and evaluated by the investigator before run-in visit (V2) 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-centered, one disc-centered 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 run-in visit (V2) 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.

Eye examination required at V28 (week 26) can be performed within 8 weeks before the visit. Eye examinations required at the visit at V54 (week 52) can be performed within 2 weeks before the visit, if results are available for evaluation at the visit. The investigator should examine the outcome of each eye examination. Relevant findings before run-in must be recorded as concomitant illness/medical history. While relevant findings occurring after run-in should be reported as an AE, please refer to Section 8.3 and Appendix 3 (Section 10.3).

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, QT 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 but at the latest at run-in (V2). The results must be interpreted by the investigator before initiation of insulin icodec in order to determine the eligibility of the participant.

The ECG required at the visits at week 26 (V28) and week 52 (V54) 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. At the following visits, any new abnormal, clinically significant findings or clinically significant deteriorations after initiation of the study intervention should be reported as an AE, see Appendix 3 (Section 10.3).

8.2.6 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the flowchart (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 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 10 (Section 10.10).

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. All AEs and SAEs must be collected from the run-in period (V3) and until the end of trial visit at the time points specified in the flowchart (1.2).

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 events are listed below in Table 8-1 and other events requiring collection of additional information.

Table 8-1 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[a]	X	
Hypoglycaemic episodes		X

[a]See further guidance in Section 10.3.3, if using the hepatic event form in connection with mandatory AE reporting.

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 investigator's brochure 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 pregnancy outcome and 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 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable for this study.

8.3.7 Adverse event of special interest

Not applicable for this study.

8.3.8 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.

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.

8.8 Immunogenicity assessments

Not applicable for this study.

8.9 Human biosamples for future research

Not applicable for this study

9 Statistical considerations

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

9.1 Statistical hypotheses

For the primary estimand with primary endpoint, change from baseline (defined as time of treatment initiation with insulin icodec and semaglutide (week 26, V28)) to week 52 (V54) in HbA_{1c}, the following 1-sided hypothesis will be tested.

Formally, let D be the change from baseline (week 26) to week 52 in HbA_{1c}. The null-hypothesis of no decrease in HbA_{1c} will be tested against the alternative hypothesis of a decrease in HbA_{1c} as given by

$$H0: D \geq 0\% \text{ against } HA: D < 0\%$$

Operationally the hypothesis will be evaluated by a 2-sided test.

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 participants allocated to the intensification phase
Safety analysis set	All participants who are exposed to investigational intervention (s)

The following data points sets are defined:

Defined data points set	Description
Run-in-in-study	All observed data during the run-in period: • From the run-in visit (V2) until the day before the intensification visit (V28) for participants continuing for the intensification period. • From the run-in visit (V2) until last participant contact for participants not being assigned to semaglutide treatment at the end of the run-in period or discontinuing insulin icodec treatment during the run-in period.
Run-in-on-treatment	All observed data during the run-in period while on insulin icodec treatment: • From the first dose of insulin icodec until the day before the intensification visit (V28) for participants continuing for the intensification period. • All data from the first dose until 6 weeks after last dose of insulin icodec for participants not being assigned to semaglutide treatment at the end of the run-in period or discontinuing insulin icodec treatment during the run-in period.
Treatment-phase-in-study	All observed data from time of the intensification visit (V28) until last participant contact.

Defined data points set	Description
Treatment-phase-on-treatment	All observed data from time of the intensification visit (V28) until 6 weeks after last date of either insulin icodec or semaglutide treatment (whichever comes last).
On-intensification	Observed data at planned visits from time of the intensification visit (V28) until the end of treatment visit (V54), i.e., for participants who permanently discontinue either insulin icodec or semaglutide treatment, post-discontinuation observations will not be included.

The on-treatment data points sets represent data collected in the period in which a participant is considered exposed to assigned treatment(s).

V2 is always included in the run-in-in-study and run-in-on-treatment data point sets. Information on V28 will be included while presenting descriptive statistics for run-in-in-study and run-in-on-treatment data point sets. Baseline (V28) is always included in the treatment-phase-in-study, treatment-phase-on-treatment, on-intensification data point sets.

FAS and on-intensification are used for efficacy evaluations and specifically to estimate the primary estimand.

Safety data will be presented separately for run-in-on-treatment and treatment-phase-on-treatment periods based on the safety analysis set (SAS). SAEs will also be presented based on the SAS and run-in-in-study and treatment-phase-in-study, respectively.

9.3 Statistical analyses

9.3.1 General considerations

Presentation of results from a statistical analysis will include the estimated mean presented together with the two-sided 95% confidence interval and the corresponding two-sided p-value. The nominal significance threshold is 5%.

Baseline is defined as the time of treatment intensification with semaglutide (week 26, V28).

9.3.2 Primary endpoint analysis

9.3.2.1 Definition of endpoint

The primary endpoint is change in HbA_{1c} from baseline (week 26, V28) to week 52 (V54).

9.3.2.2 Main analytical approach

The primary endpoint will be analysed by a mixed model for repeated measurements (MMRM) with an unstructured covariance matrix. The model will include visit as fixed factor and baseline HbA_{1c} as a covariate. Interactions between visit and baseline HbA_{1c} will also be included in the model. All post-intensification values obtained at planed visits that are in the on-intensification data points set will be included in the analysis.

9.3.2.3 Sensitivity analysis

Not applicable for this study.

9.3.2.4 Supplementary analysis

Not applicable for this study.

9.3.3 Secondary endpoints analysis

Two endpoints from the 7-point SMPG profile will be defined:

- Mean of the 7-point profile, defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time.
- Mean post-prandial PG increment over all meals will be derived as the mean of all available meal increments (from before meal to 90 min after for breakfast, lunch and dinner).

Change in mean 7-point SMPG, change in mean postprandial glucose increment (over all meals) in 7-point SMPG, change in body weight and relative change in weekly insulin icodec dose from the week prior to intensification V27 (week 25) to V54 (week 52) will be analyzed similarly to the primary endpoint except a multiplicative model will be used, i.e., the endpoint will be log-transferred before analysis. Further details will be provided in the statistical analysis plan.

Other secondary endpoints will be presented descriptively only.

9.3.4 Exploratory endpoints analysis

Exploratory endpoints will be presented descriptively only.

9.3.5 Safety analyses

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

9.3.6 Other analyses

For other analyses, please refer to the SAP.

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 to detect a change from baseline in HbA_{1c} at week 52 of 0.4%-point as being statistically significantly different from 0% in participants eligible for treatment intensification.

In previous IDegLira studies evaluating an insulin/GLP-1 RA combination product in previous insulin users, the standard deviation (SD) for IDegLira treated subjects ranged from 0.8 to 1.0 %-point (Table 9-1), i.e., an SD of 1.0 is assumed for this study.

Table 9-1 HbA_{1c} results - IDegLira studies

Study id	Study description	Study duration	SD
NN9068-3912	IDegLira vs. IDeg	26 weeks	1.0
NN9068-3952	IDegLira vs. IGlar	26 weeks	0.8
NN9068-4184	IDegLira vs. IDeg in Japanese	26 weeks	0.8
NN9068-4166	IDegLira vs. IDeg in Chinese	26 weeks	0.9

Abbreviations: IDeg=insulin degludec; IDegLira=insulin degludec/liraglutide; IGlar=insulin glargine; SD=standard deviation

Intercurrent events are expected to have a negligible effect on the estimated change in HbA_{1c} from baseline to week 52 (V54) as the majority will be events of treatment discontinuation which are handled by the hypothetical strategy.

Based on the above assumptions, 68 participants will need to be intensified with semaglutide treatment at week 26, in order to have 90% power to detect a change in HbA_{1c} from baseline (week 26) to week 52 (V54) of 0.4 %-point as being statistically significantly different from 0 %-point.

This number of participants being intensified with semaglutide treatment appears to be reasonable also under deviations from the assumed standard deviation and change in HbA_{1c} as illustrated in the figures below. Figure 9-1 illustrates the power for various changes in HbA_{1c} and SDs with a sample size of 68 participants in need for treatment intensification. Figure 9-2 displays the required number of participants to be intensified for various changes in HbA_{1c} and SDs to achieve a power of 90%.

Figure 9-1 Power as function of change in HbA_{1c} and SD with 68 participants being intensified

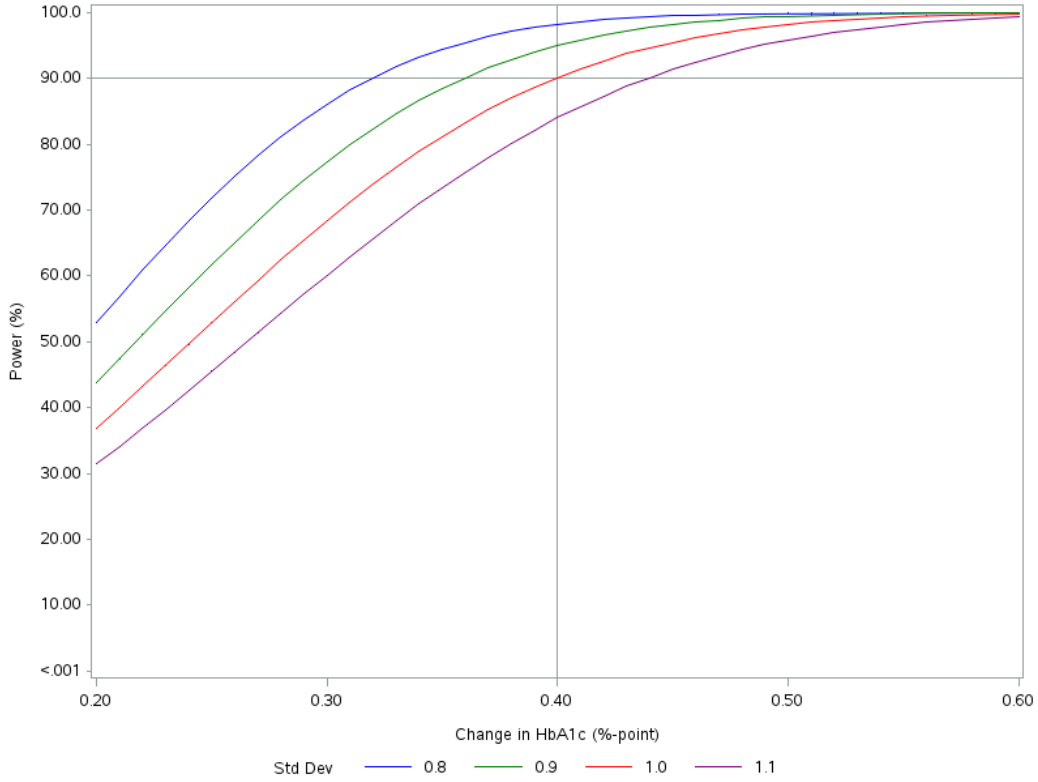
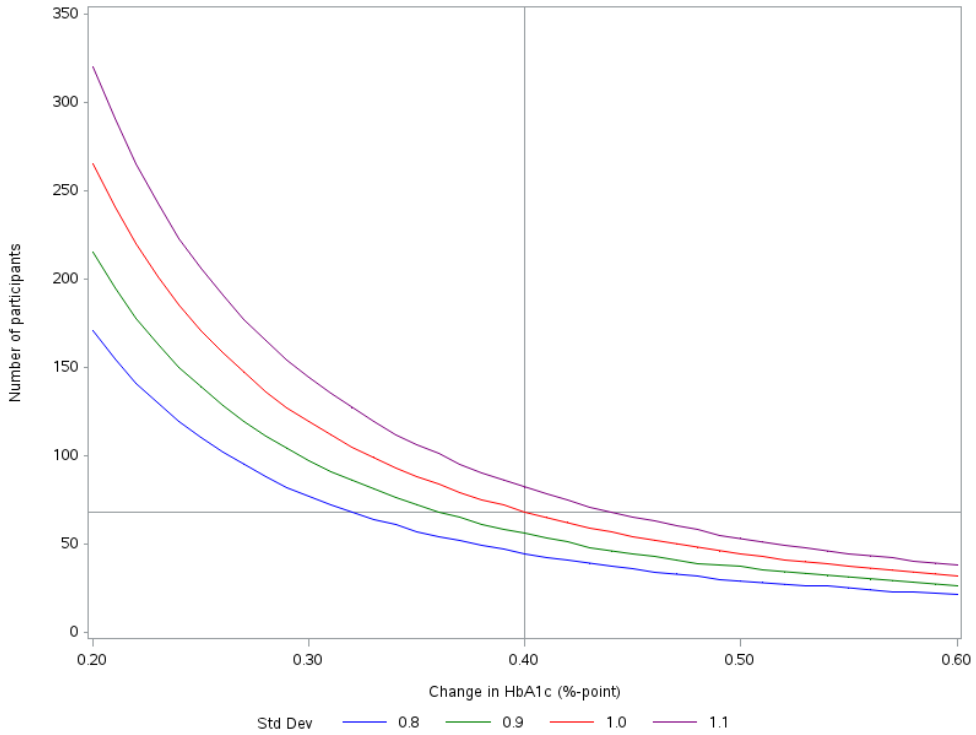


Figure 9-2 Sample size to be intensified as function of change in HbA1c and SD to achieve a power of 90%



In a recent insulin icodec study in previously insulin treated T2D patients (NN1436-4478) with a similar titration target, 153 out of 263 (60%) of the completing insulin icodec treatment and had not achieved adequate glycaemic control at week 26 as determined by a HbA_{1c} >7.0%. Two percent did not have an HbA_{1c} assessment at week 26 in NN1436-4478 and to further allow for the variability in this proportion and for participants meeting the run-in exclusion criteria, it is assumed that 46% of participants in this study will complete insulin icodec treatment and being eligible for treatment intensification at week 26. Hence, it is estimated that approximately 148 participants should enter the run-in phase to obtain approximately 68 available for treatment intensification.

Assuming 25% screening failures, approximately 197 patients will be screened to achieve approximately 148 participants for the run-in and subsequently approximately 68 participants eligible for treatment intensification.

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[24] and applicable ICH Good Clinical Practice (GCP) Guideline[25].
-
- Applicable laws and regulations

The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.

Regulatory authorities will receive the clinical trial application, protocol amendments/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.

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.

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[25] guidelines, Declaration of Helsinki,[24] 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, 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,[24] the International Committee of Medical Journal Editors (ICMJE),[26] the Food and Drug Administration Amendment Act (FDAAA),[27] European Commission Requirements[28-30] 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 eCRF on a regular basis during the conduct of the study as well as at the end of the study, as described in the eCRF completion guideline.

All participant data relating to the study will be recorded on eCRFs unless transmitted electronically to Novo Nordisk or designee (e.g., laboratory and eDiary) data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The following will be provided as paper eCRFs.

- 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 to be used to report complaints on study intervention not yet allocated to a participant

Corrections to the eCRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF 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 eCRF, the eCRF must be signed and dated again by the investigator.

The investigator must ensure that data is recorded in the eCRF 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 eCRF 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[25], 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 CRF or via listings from the study database.

10.1.9 Source documents

All data entered in the eCRF must be verifiable in source documentation other than the eCRF, except for the following data that should be recorded directly in the eCRFs and will be considered source data:

- For e.g. eDiary, data in the service providers' database is considered source data.
- Source documents provide evidence for the existence of the 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 eCRF 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, eCRF and other participant data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by Novo Nordisk. Site-specific eCRFs 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.

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.[31]

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned publication.

Where required by the journal, the investigator from each site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

10.1.14.3 Site-specific publication(s) by investigator(s)

For a multicentre clinical 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 additional data 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 / glycaemic control	HbA_{1c} V1, V12, V20, V27, V28, V32, V36, V46, V54
	FPG [a] V28, V32, V36, V46, V54
[a]: An FPG result < 3.9 mmol/L (70 mg/dL) in relation to planned fasting visits should not be reported as a hypoglycaemic episode but as an AE at the discretion of the investigator (Appendix 3, Section 10.3).	

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology V1, V12, V20, V28, V36, V46, V54	Haemoglobin Leucocytes
Biochemistry[a] V1, V12, V20, V28, V36, V46, V54	Alanine Aminotransferase (ALT) Albumin Alkaline phosphatase Aspartate Aminotransferase (AST) Bilirubin Creatinine Potassium Sodium

Laboratory assessments	Parameters
Lipids V1, V28, V54	Cholesterol High density lipoprotein (HDL) cholesterol Low density lipoprotein (LDL) cholesterol Triglycerides Free fatty acids
Pregnancy Testing[b] V1, V2, V28, V54, V56	Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test
Other tests V1	eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation, eGFR is for screening purposes only.
Notes: [a] Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 3 (Section 10.3) (Hy's Law) and Section 7.1. [b] For women of childbearing potential, as needed, local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC, see Appendix 4 (Section 10.4).	

Table 10-3 Other assessments

Laboratory assessments	Parameters
Others	Fasting c-peptide V28, V54

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 UNL and total bilirubin >2x UNL 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 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

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

Other events requiring collection of additional information

Hypoglycaemic episodes

- All hypoglycaemic episodes must be recorded by the participant in the hypoglycaemic episode form which is a part of 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.

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 investigator's brochure of semaglutide and insulin icodec, 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):

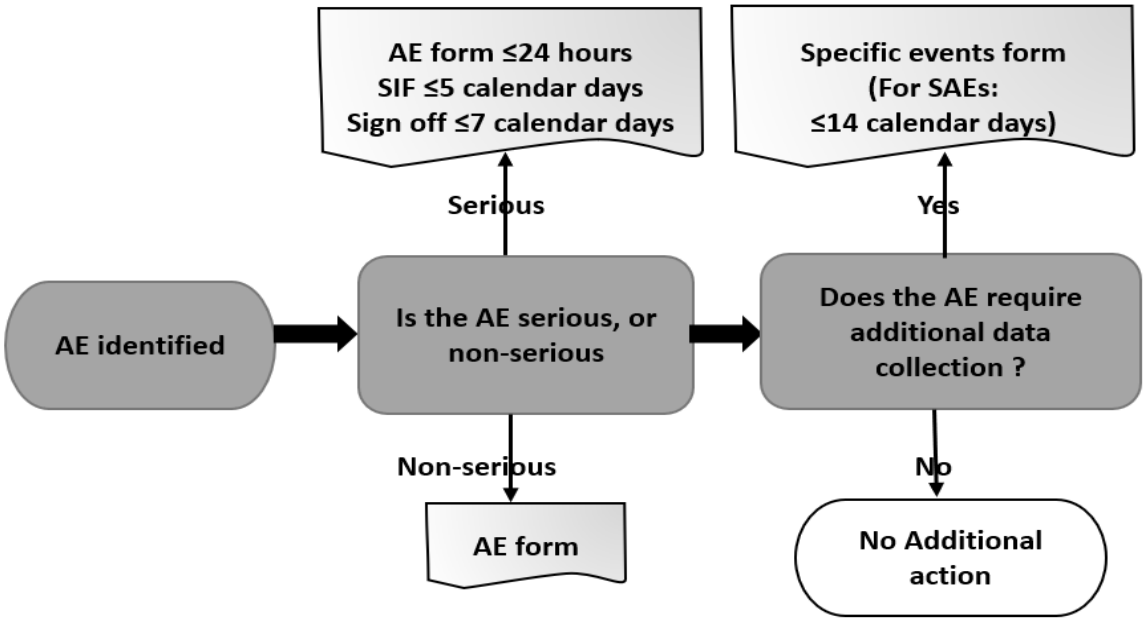
- AE form without undue delay, but not later than within 24 hours.
- Safety information form within 5 calendar days.
- Both the AE and the safety information form must be signed within 7 calendar days after first knowledge by the investigator.
- Specific event form within 14 calendar days.

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 hyoglycaemic episodes form, which is a part of eDiary. If the hypoglycaemic episodes 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 10.1.8.1).

Abbreviations: AE = adverse events; 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

All complaints should be reported both to the manufacturer and Novo Nordisk.

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 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 10-4 lists the highly effective and acceptable methods of contraception allowed. Local regulations may apply, see Appendix 10 (Section 10.10).

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

Table 10-4 Highly effective and acceptable contraceptive methods allowed[32]

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[b] • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide[c] • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)
Notes: [a]Contraceptive use by men or women should comply with local regulations regarding the use of contraceptive methods for those participating in clinical studies. [b]Considered effective, but not highly effective - failure rate of ≥1% per year. [c]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.

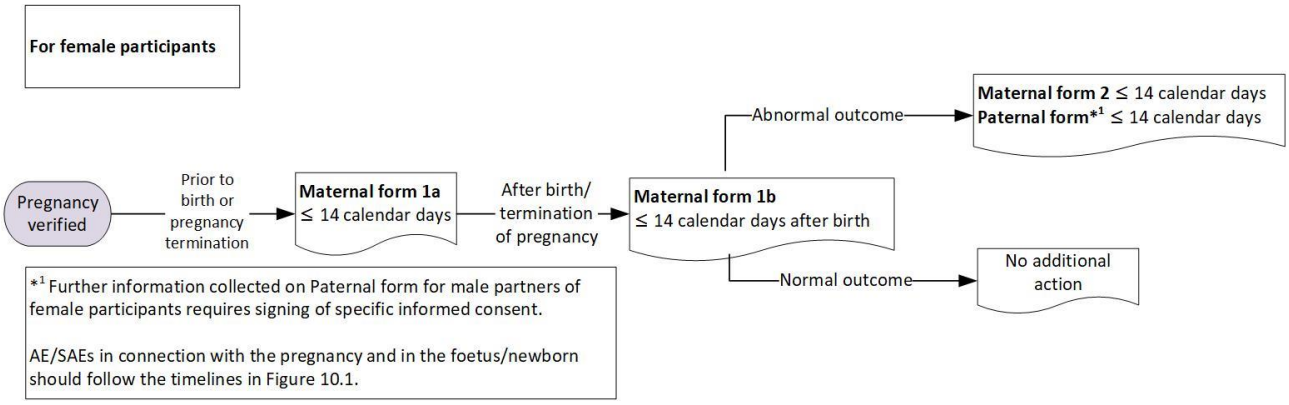
Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

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: Suggested actions and follow-up assessments

For all hepatic events, defined as:

- ALT (or AST) ≥ 3 x upper limit of normal (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 UNL with the appearance of fatigue, nausea, vomiting, anorexia, abdominal pain or tenderness, fever, rash, and/or eosinophilia (>5%),

where no alternative or competing aetiology exists, repeat testing within 48 to 72 hours, follow-up assessments and work-up for alternative aetiologies must be performed, including:

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

Timelines for reporting technical complaints to Novo Nordisk

The investigator must complete and forward the technical complaint form to Customer Complaint Center, Novo Nordisk, 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.

Follow-up of technical complaints

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

Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and all associated parts and notify the monitor within 5 calendar days of obtaining the sample at site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the 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 10-5 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,[33] ADA,[34] ISPAD,[35] type 1 diabetes outcomes program,[36] ATTD.[37] Severe hypoglycaemia as defined by Seaquist[38] and ISPAD.[35]		

Severe hypoglycaemia

[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.[38]

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 a part of 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.

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. 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.

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.[38]

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.[38]

Diary review

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

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

From V2, all participants will receive insulin icodec.

Insulin icodec should be taken once weekly at the same day of the week. All participants should receive a one-time additional dose of insulin icodec at V2 to avoid glycaemic slip, as insulin icodec has a longer half-life. This one-time additional dose consists of total daily basal insulin dose before run-in visit (V2) x 7 + 50% of their total daily basal insulin dose x 7. The following weekly dose (V3) should be the total daily dose x 7 (without the one-time additional dose). In Table 10-6, the weekly V2 and V3 doses for participants receiving from 20U to 100U per day have been calculated. Please, note that the displayed values are rounded off to the nearest dose that is dividable by 10.

The treat-to-target approach will be applied to optimise glycaemic control throughout the study. There are no maximum or minimum insulin doses.

Table 10-6 Insulin Icodec dose titration at V2 and V3

Total daily dose before run-in	V2 insulin icodec dose	V3 insulin icodec dose	Total daily dose before run-in	V2 insulin icodec dose	V3 insulin icodec dose
20	210	140	61	640	430
21	220	150	62	650	430
22	230	150	63	660	440
23	240	160	64	670	450
24	250	170	65	**680**	460
25	260	180	66	690	460
26	270	180	67	700	470
27	280	190	68	710	480
28	290	200	69	720	480
29	300	200	70	740	490
30	320	210	71	750	500
31	330	220	72	760	500
32	340	220	73	770	510
33	350	230	74	780	520

Total daily dose before run-in	V2 insulin icodec dose	V3 insulin icodec dose	Total daily dose before run-in	V2 insulin icodec dose	V3 insulin icodec dose
34	360	240	75	790	530
35	370	250	76	800	530
36	380	250	77	810	540
37	390	260	78	820	550
38	400	270	79	830	550
39	410	270	80	840	560
40	420	280	81	850	570
41	430	290	82	960	570
42	440	290	83	870	580
43	450	300	84	880	590
44	460	310	85	890	600
45	470	320	86	900	600
46	480	320	87	910	610
47	490	330	88	920	620
48	500	340	89	930	620
49	510	340	90	950	630
50	530	350	91	960	640
51	540	360	92	970	640
52	550	360	93	980	650
53	560	370	94	990	660
54	570	380	95	1000	670
55	580	390	96	1010	670
56	590	390	97	1020	680
57	600	400	98	1030	690
58	610	410	99	1040	690
59	620	410	100	1050	700
60	630	420			

Dose adjustment of insulin icodec during the run-in period V4-V27

From V4 insulin icodec will be adjusted once weekly by the investigator in connection with the scheduled visits/phone contacts as described below.

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

Adjustment of insulin icodec will be done in accordance with Table 10-7.

Table 10-7 Insulin icodec dose adjustment

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

Abbreviation: SMPG=self-measured plasma glucose

Adjustment of insulin icodec at initiation of semaglutide at V28

At V28 eligible participants should initiate semaglutide treatment (see below).

- For participants with a $HbA_{1c} \leq 8.0\%$ at V27, the insulin icodec dose should be reduced by 20% in accordance with Table 10-8.
- Participants with a $HbA_{1c} > 8.0\%$ at V27 will only need to adjust their insulin icodec dose as per the investigator's discretion.

Table 10-8 Insulin icodec dose adjustment at V28 (Participants with HbA1c ≤ 8.0%)

Insulin icodec dose at V27	Insulin icodec dose at V28	Insulin icodec dose at V27	Insulin icodec dose at V28
50	40	380	300
60	50	390	310
70	60	400	320
80	60	410	330
90	70	420	340
100	80	430	340
110	90	440	350
120	100	450	360
130	100	460	370
140	110	470	380
150	120	480	380
160	130	490	390
170	140	500	400
180	140	510	410
190	150	520	420
200	160	530	420
210	170	540	430
220	180	550	440
230	180	560	450
240	190	570	460
250	200	580	460
260	210	590	470
270	220	600	480
280	220	610	490
290	230	620	500

Insulin icodec dose at V27	Insulin icodec dose at V28	Insulin icodec dose at V27	Insulin icodec dose at V28
300	240	630	500
310	250	640	510
320	260	650	520
330	260	660	530
340	270	670	540
350	280	680	540
360	290	690	550
370	300	700	560

From V28 (week 26) to V36 (week 34) the insulin icodec dose can be further decreased at each semaglutide dose escalation as per Investigator's discretion.

In the remaining study period (P37 (week 35) to P53 (week 51)), insulin icodec dose may be adjusted at investigator's discretion and according to pre-breakfast SMPGs per Table 10-7.

Semaglutide

Initiation of semaglutide at V28

Eligible participants should initiate semaglutide with a dose of 0.25 mg.

Dose escalation of semaglutide from intensification visit (V28)

After 4 weeks of treatment with 0.25 mg, the dose should be increased to 0.5 mg. After at least 4 weeks with a dose of 0.5 mg OW, the dose of semaglutide should be increased to 1 mg to further improve glycaemic control. Dose reduction from the dose of 1 mg to the dose of 0.5 mg of semaglutide is allowed in case of safety concern or unacceptable intolerability.

The participant should make at least one attempt to re-escalate to the designated target dose, as per the investigator’s discretion. It is recommended that the investigator consults Novo Nordisk in case of persistent deviations from the planned escalation regimen.

The date, time and dose of trial products administration (insulin icodec and semaglutide) should be recorded in the eDiary.

Missing doses during the study

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

Semaglutide
If a semaglutide dose is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 2 days (≥48 hours). If a dose is missed and the next scheduled

dose is less than 2 days (<48 hours) away, the participant should not administer the missed dose. A missed dose should not affect the scheduled dosing day of the week.

If ≥ 2 consecutive doses of semaglutide are missed, the participant should be encouraged to recommence the treatment if considered safe as per the investigator's discretion. Semaglutide should be continued as early as the situation allows. The missed doses should not affect the scheduled dosing day of the week. The start dose for re-initiation of semaglutide is at the investigator's discretion. In case of questions related to re-initiation of semaglutide, the investigator should consult Novo Nordisk global medical experts. If doses are missed, blood glucose should be more closely monitored if judged necessary by the investigator.

Insulin icodec dose recommendation from end of treatment and during follow up

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

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

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

Deviations from the algorithm

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

Data surveillance

Surveillance of titration data will be performed centrally by Novo Nordisk in an unbiased or, if possible, a blinded manner. The data will be reviewed and significant changes from the titration algorithm will be followed up.

It is important that data regarding dose titration is entered into the ePID. 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 by phone or via on online portal (CONNECT) 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: Mitigations to ensure participant safety and data integrity during an emergency situation

10.9.1 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 lock-down 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 10-9 indicates the minimum requirements for assessments that should be performed during a lock-down, 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.

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

10.9.2 Visits

Screening (V1), run-in visit (V2) and intensification visit (V28) should always be performed as on-site visits. If a site is unable to perform these visits on-site, screening, run-in and intensification visits should be on hold until on-site visits are possible.

Visits 12, 20, 27, 32, 36, 46, 54 should be performed as on-site visits, if in any way possible. If not, assessments can be conducted as home or off-site visits.

On-site visits (Visits 3, 4, 55 and 56) can be converted to remote visits (video, phone or similar) or home or off-site visit*s*.

If the end of intervention visit 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 3 months.

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

10.9.3 Assessments

Assessments used for safety endpoints (i.e., number of severe and clinically significant hypoglycaemic events and change in body weight and weekly insulin icodec dose) should be prioritised. The preferred order for the method of assessment is: on-site, video, phone, home visit. 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, height, waist circumference, vital signs, plasma glucose and 7 point SMPG) 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 10-9 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.

10.9.4 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 10-9 Minimum assessments following initiation of the trial product

PROCEDURE	Protocol Section	Screening	Run-in Visit	Run-in (Insulin Icodec Only)					Intensification visit	Treatment (Icodec+Semaglutide)				EOT Follow-up	
Visit		V1	V2	V3	V4	V12	V20	V27	V28	V32	V36	V46	V54 [g]	V55	V56
Weekly Phone Contact	1.2.1				P5-P11	P13-P19	P21-P26		P29-P31	P33-P35	P37-P45	P47-P53			
Timing of Visit (Weeks)		−2	0	1	2	10	18	25	26	30	34	44	52	28/54	31/57
Visit Window (Days)		+14	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3
SUBJECT RELATED INFORMATION AND ASSESSMENTS															
Informed Consent	App 1	X													
Demography	8	X													
Eligibility Criteria	5.1, 5.2, 5.5	X	X	X	X	X	X	X	X						
Discontinuation Criteria	7.1			X	X	X	X	X	X	X	X	X			
Medical History/Concomitant Illness	8.2	X													
Concomitant Medication	6.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	8.2.5	X							X				X		
Eye Examination	8.2.4	X							X				X		
Physical Examination	8.2.2	X							X				X		
Pregnancy Test	8.2.7, 10.4	X	X						X				X		X
Women of child-bearing potential	10.4	X													
Tobacco Use	5.3.2	X													

PROCEDURE	Protocol Section	Screening	Run-in Visit	Run-in (Insulin Icodec Only)					Intensification visit	Treatment (Icodec+Semaglutide)				EOT Follow-up	
Visit		V1	V2	V3	V4	V12	V20	V27	V28	V32	V36	V46	V54 [g]	V55	V56
Weekly Phone Contact	1.2.1				P5-P11	P13-P19	P21-P26		P29-P31	P33-P35	P37-P45	P47-P53			
Timing of Visit (Weeks)		−2	0	1	2	10	18	25	26	30	34	44	52	28/54	31/57
Visit Window (Days)		+14	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3
Vital Signs	8.2.3	X							X				X		
Hypoglycaemia Unawareness	10.7	X													
TRIAL MATERIAL	6														
Drug Dispensing			X			X	X		X		X	X			
Body Measurements	8.2.2	X	X						X				X		
BMI		X	X						X				X		
Body Weight		X	X						X				X		
Height		X													
Waist Circumference			X						X				X		
REMINDERS															
Attend Visit Fasting									X	X	X	X	X		
End of Treatment									X[e]				X		
Training in Trial Product, Pen-handling			X						X			X			
Hand Out and Instruct on Devices			X												
Hand Out and Instruct in Paper Diary								X		X		X			

PROCEDURE	Protocol Section	Screening	Run-in Visit	Run-in (Insulin Icodec Only)					Intensification visit	Treatment (Icodec+Semaglutide)				EOT Follow-up	
Visit		V1	V2	V3	V4	V12	V20	V27	V28	V32	V36	V46	V54 [g]	V55	V56
Weekly Phone Contact	1.2.1				P5-P11	P13-P19	P21-P26		P29-P31	P33-P35	P37-P45	P47-P53			
Timing of Visit (Weeks)		−2	0	1	2	10	18	25	26	30	34	44	52	28/54	31/57
Visit Window (Days)		+14	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	+3
Make Appointment for Eye Examination							X					X			
Last dose of the trial product [c]								X					X		
SAFETY	8.3														
Adverse Event	8.3		X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic Episodes	10.7		X	X	X	X	X	X	X	X	X	X	X	X	X
Technical Complaints	10.5			X	X	X	X	X	X	X	X	X	X		
Laboratory Assessments	8.1, 10.2														
HbA_{1c}		X						X	X				X		
FPG									X				X		
Fasting C-peptide									X				X		
Self Assessments															
Plasma Glucose		X	X	X	X	X	X	X	X	X	X	X	X	X	X
7-Point SMPG Profile	8.1.2								X		X		X		

Abbreviations: AE = adverse event; BG = blood glucose; BMI = body mass index; ECG = electrocardiogram; EOT = end of treatment; FPG = fasting plasma glucose; HbA_{1c} = glycated haemoglobin; SMPG = self-measured plasma glucose

10.10 Appendix 10: Country-specific requirements

Thailand

Section 5.2, Exclusion criteria

- Adequate contraceptive measures are: diaphragm, condom (by the partner), intrauterine device in place for last three months before trial starts, sponge, cap with spermicide, contraceptive patch, approved hormonal implant (i.e. Norplant), oral contraceptives taken without difficulty for the last three months before trial starts, post-menopausal state or sterilisation.

Serbia

Section 5.2, Exclusion criteria

- **Co-participation in COVID-19-related studies:** Yes

Malaysia

Section 5.2, Exclusion criteria

- Co-participation in COVID-19-related studies: Yes

Poland

Section 8.3.4, Regulatory reporting requirements for SAEs

Novo Nordisk will report SUSARs according to regulation (EU) No 536/2014, article 40 and article 42, to the Eudravigilance database.

Section 10.1.1 Regulatory and ethical considerations

The study will be conducted in accordance with EU regulation No 536/201451[39]

Section 10.1.5 Data protection

In accordance with EU regulation No 536/201451[39]

Section 10.1.13, Indemnity statement

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.

Section 10.1.14.1 Communication of results

The study data will be uploaded to the clinical trial information system (CTIS) within one year after the end of study.

Section 10.4.2 Contraceptive guidance

For participants who have been enrolled in the intensification period, a highly effective or acceptable contraception should be utilised until at least two months after the last dose of semaglutide.

Czech Republic

Section 2.2, Background

- Clinical data from previous development are needed for next trial phase as background for evaluation.
- It is required for study design with run-in period as well, where trial products are not dispensed.

Section 5.2, Exclusion criteria

- Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies. This means use of double barrier methods is not applicable for Czech Republic.

Section 8, Study assessments and procedures

- It is not accepted that some basic assessments leading for subjects treatment (for example determination of TP dose) should be blinded to investigator.
- In case of proof of reproduction toxicity in preclinical trials the monthly pregnancy test for female in fertile age is needed. This information need to be added to Inform.

Section 8.2.7, Pregnancy testing

- Monthly testing with highly sensitive urine pregnancy tests are required for WOCBP.

Section 10.1.3, Informed consent process

- Subject's electronic signature is not permitted.
- Only Year of Birth requirement can be disclosed in the electronic data.

Section 5.2, Exclusion criteria

- **Co-participation in COVID-19-related studies:** Yes

Section 8.3.4, Regulatory reporting requirements for SAEs

Novo Nordisk will report SUSARs according to regulation (EU) No 536/2014, article 40 and article 42, to the Eudravigilance database.

Section 10.1.1 Regulatory and ethical considerations

The study will be conducted in accordance with EU regulation No 536/201451[39]

Section 10.1.5 Data protection

- In accordance with EU regulation No 536/201451[39]

Section 10.1.14.1 Communication of results

The study data will be uploaded to the clinical trial information system (CTIS) within one year after the end of study.

Section 10.4.2 Contraceptive guidance

For participants who have been enrolled in the intensification period, a highly effective or acceptable contraception should be utilised until at least two months after the last dose of semaglutide.

10.11 Appendix 11: Abbreviations

ADA	American Diabetes Association
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BG	blood glucose
CRF	case report form
CRO	contract research organisation
CSR	clinical study report
DFU	directions for use
DMC	Data Monitoring Committee
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1 RA	glucagon-like peptide-1 receptor agonists
HbA_{1c}	glycated haemoglobin
IB	investigator's brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IND	investigational new drug
IRB	institutional review board
ISO	International Organization for Harmonization
LDL	low-density lipoprotein
MMRM	mixed model for repeated measurements
NIMP	non-investigational medicinal product
OAD	oral antidiabetic agent
OW	once weekly

PCD	primary completion date
PG	plasma glucose
RTSM	Systems used for Randomisation and Trial Supplies Management
SAE	serious adverse event
SAP	Statistical Analysis Plan
s.c.	subcutaneous
SI-IC	Subject information-informed consent
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T1D	type 1 diabetes
T2D	type 2 diabetes
TMM	trial master manual
WOCBP	woman of childbearing potential

10.12 Appendix 12: Protocol amendment history

Protocol version 2.0 (26 July 2023), Poland and Czech Republic

This amendment is considered to be non-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 16 April 2014; because it neither substantially impacts the safety or rights of the participants nor the reliability or robustness of the data generated in the study.

Overall rationale for preparing protocol, version 2.0:

Version 2.0 of the protocol was prepared to address requests raised by European Medicines Agency 19 July 2023.

Section # and name	Description of change	Brief rationale
6 Study intervention(s) and concomitant therapy	Quotes have been deleted	To correct a typo
6.1 Study intervention(s) administered	The sentence about auxiliary supplies has been re-phrased	To correct an incomplete sentence
8.3 Adverse events and other safety reporting	A sentence on the AE and SAE collection has been included	To give details on the time frame for AE and SAE collection
8.3.4 Regulatory reporting requirement for SAEs	A sentence on reporting of SUSARs to Eudravigilance database has been included	To describe the procedures for reporting of SUSARs by the sponsor to the Eudravigilance database.
10.1.1 Regulatory and ethical considerations	A sponsor statement describing that the clinical study will be conducted in compliance with EU regulation (Regulation [EU] No 536/2014 Annex I) has been added	To state that the clinical study will be conducted in compliance with EU regulation
10.1.5 Data protection	A reference to EU regulation (Regulation [EU] No 536/2014 Annex I) has been inserted	To state that handling of data security breaches will be in compliance with EU regulation
10.1.14.1 Communication of results	The publication policy has been added in the sentence about public disclosure of the study data	To update protocol with the publication policy of the study data being uploaded to the CTIS database within one year after end of study
10.4.2 Contraceptive guidance	A sentence on the use of contraceptives after the last dose of trial product has been included	To align with the previous and ongoing trials where the use of contraceptives should be 35 days after the last dose of the trial product
10.10 Appendix 10: Country-specific requirements	Additional country-specific information for Poland has been added	To update information for Poland with current regulation

Protocol version 3.0, including versions 1.0 and 2.0 (05 October 2023), global

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 16 April 2014.

Overall rationale for preparing protocol, version 3.0:

Version 3.0 of the protocol was prepared to address requests raised by European Medicines Agency 30 August 2023.

Section # and name	Description of change	Brief rationale
Section 1.2 flow chart	'x' for plasma glucose in self-assessments is deleted	For correctness
Table 3-2	Changed V54 to V36 and week 52 to week 34	For correctness
Table 2-1	Text related to 'neoplasms (malignant and non-malignant)' has been removed	Update of Ozempic IB
6 Study intervention(s) and concomitant therapy	Quotes have been deleted	To correct a typo (this change was added in version 2.0 of the protocol)
6.1 Study intervention(s) administered	The sentence about auxiliary supplies has been re-phrased	To correct an incomplete sentence (this change was added in version 2.0 of the protocol)
8.2.3 Vital signs	Changed 'end of intervention' to 'end of treatment'	For consistency
8.2.4 Eye examination	Added fundoscopy text according to the latest template	To add detail information on fundoscopy
8.3 Adverse events and other safety reporting	A sentence on the AE and SAE collection has been included	To give details on the time frame for AE and SAE collection (this change was added in version 2.0 of the protocol)
8.3.4 Regulatory reporting requirement for SAEs	A sentence on reporting of SUSARs to Eudravigilance database has been moved to section 10.10 Appendix 10 Country-specific requirements	To update local version 2.0 to a global version 3.0.
10.1.1 Regulatory and ethical considerations	A sponsor statement describing that the clinical study will be conducted in compliance with EU regulation (Regulation [EU] No 536/2014 Annex I) has been moved to section 10.10 Appendix 10 Country-Specific requirements	To update local version 2.0 to a global version 3.0
10.1.5 Data protection	A reference to EU regulation (Regulation [EU] No 536/2014 Annex I) has been moved to section 10.10 Appendix 10 Country-Specific requirements	To update local version 2.0 to a global version 3.0
10.1.14.1 Communication of results	The publication policy that was added in the sentence about public disclosure of the study data has been moved to section 10.10 Appendix 10 Country-Specific requirements	To update local version 2.0 to a global version 3.0
10.4.2: Contraceptive guidance	A sentence on the use of contraceptives after the last dose of semaglutide has been moved to section 10.10. Appendix 10 Country-Specific requirements and wording has been updated	This change was added in version 2.0 of the protocol based on EU feedback. Further update needed
10.10 Appendix 10: Country-specific requirements	Additional country-specific information for Poland and Czech Republic have been added as described above	To create a global version of the protocol

11 References

1. American Diabetes Association. 2. Classification and Diagnosis of Diabetes:. Diabetes Care. 2019;42(Suppl 1):S13-S28.
2. Federation ID. IDF Diabetes Atlas, 10th Edition. Brussels, Belgium2021.
3. Moreira RO, Cobas R, Lopes Assis Coelho RC. Combination of basal insulin and GLP-1 receptor agonist: is this the end of basal insulin alone in the treatment of type 2 diabetes? Diabetol Metab Syndr. 2018;10:26.
4. Kellerer M, Kaltoft MS, Lawson J, Nielsen LL, Strojek K, Tabak Ö, et al. Effect of once-weekly semaglutide versus thrice-daily insulin aspart, both as add-on to metformin and optimized insulin glargine treatment in participants with type 2 diabetes (SUSTAIN 11): A randomized, open-label, multinational, phase 3b trial. Diabetes Obes Metab. 2022.
5. Rodbard HW, Lingvay I, Reed J, de la Rosa R, Rose L, Sugimoto D, et al. Semaglutide Added to Basal Insulin in Type 2 Diabetes (SUSTAIN 5): A Randomized, Controlled Trial. J Clin Endocrinol Metab. 2018;103(6):2291-301.
6. Novo Nordisk A/S. Clinical Trial Report (NN1436-4478). A 26-week trial comparing the effect and safety of once weekly insulin icodec and once daily insulin degludec, both with or without non-insulin anti-diabetic drugs, in subjects with type 2 diabetes treated with basal insulin. 15 Jun 2022.
7. ClinicalTrials.gov. A Research Study to Compare Two Types of Insulin, a New Weekly Insulin, Insulin Icodec and an Available Daily Insulin, Insulin Glargine, Both in Combination With Mealtime Insulin, in People With Type 2 Diabetes Who Use Daily Insulin and Mealtime Insulin (ONWARDS 4) 2022 [cited 2022 12 Jul].
8. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes. Diabetes Care. 2022;45(Supplement 1): S125–S143.
9. Kapitza C, Nosek L, Jensen L, Hartvig H, Jensen CB, Flint A. Semaglutide, a once-weekly human GLP-1 analog, does not reduce the bioavailability of the combined oral contraceptive, ethinylestradiol/levonorgestrel. J Clin Pharmacol. 2015;55(5):497-504.
10. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834-44.
11. Novo Nordisk A/S. Abbreviated Investigator's Brochure, semaglutide s.c. (Ozempic®), NN9535, (edition 17). 1 Oct 2020.
12. Novo Nordisk A/S. Ozempic® (semaglutide), EU Summary of product characteristics (SmPC). 27 Mar 2020.
13. Novo Nordisk A/S. Ozempic® (semaglutide), US prescribing Information (PI). Jan 2020.
14. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet. 2014;384(9961):2228-34.
15. Diamant M, Nauck MA, Shaginian R, Malone JK, Cleall S, Reaney M, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care. 2014;37(10):2763-73.
16. Balena R, Hensley IE, Miller S, Barnett AH. Combination therapy with GLP-1 receptor agonists and basal insulin: a systematic review of the literature. Diabetes Obes Metab. 2013;15(6):485-502.
17. Novo Nordisk AS. Investigator's Brochure, Insulin Icodec, project NN1436 , (edition 9). 16 Mar 2023.
18. Polonsky WH, Fisher L, Hessler D, Bruhn D, Best JH. Patient perspectives on once-weekly medications for diabetes. Diabetes Obesity & Metabolism. 2011;13(2):144-9.
19. Novo Nordisk A/S NNAS. Clinical Trial Report (NN1436-4466). A

trial comparing NNC0148-0287 C (insulin 287) versus insulin glargine U100, both in combination with metformin, with or without DPP4 inhibitors and with or without SGLT2 inhibitors, in basal insulin treated subjects with type 2 diabetes mellitus. 01 Jun 2020.

20. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. http://www.kidney-international.org. 2013 2013.
21. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care. 1995;18(4):517-22.
22. The European Parliament and the Council of the European Council of the European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Annex VI - Labelling of Investigational medicinal products and auxiliary medicinal products. 27 May 2014.
23. Novo Nordisk A/S. Investigator Brochure, semaglutide (s.c.), Ozempic NN9535 (Edition 19). 27 Jul 2022.
24. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.
25. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R2), Current step 4 version. 09 Nov 2016.
26. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351(12):1250-1.
27. U.S. Department of Health and Human Services, Food and Drug Administration. Food and Drug Administration Amendments Act of 2007 as amended by the Final Rule "Clinical Trials Registration and Results Information Submission". 21 September 2016.
28. The European Parliament and the Council of the European Council of the European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. 27 May 2014.
29. The European Parliament and the Council of the European Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. 30 April 2004.
30. The European Parliament and the Council of the European Council. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, article 41. Official Journal of the European Communities. 27 Dec 2006.
31. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals; current version available at www.icmje.org.
32. Clinical Trial Facilitation Group (CTFG), Heads of Medicines Agency. Recommendations related to contraception and pregnancy testing in clinical trials. 21 Sep 2020.
33. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of

the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2017;40(1):155-7.

34. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S55-S64.
35. Abraham MB, Jones TW, Naranjo D, Karges B, Oduwole A, Tauschmann M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes. 2018;19 Suppl 27:178-92.
36. Agiostratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, et al. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care. 2017;40(12):1622-30.
37. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017;40(12):1631-40.
38. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95.
39. The European Parliament and the Council of the European Union. Regulation (EU) No 536/2014 on Clinical trials on medicinal products for human use. Annex 1. 19 May 2023.