Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05352815
Sponsor trial ID:	NN1535-4591
Official title of study:	A 52-week study comparing the efficacy and safety of once weekly IcoSema and once weekly insulin icodec, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with daily basal insulin. COMBINE 1
Document date*:	23 March 2023

*Document date refers to the date on which the document was most recently updated.

Protocol

Protocol Title:
A 52-week study comparing the efficacy and safety of once weekly IcoSema and once weekly insulin icodec, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with daily basal insulin. COMBINE 1

Substance: IcoSema (insulin icodec and semaglutide)

Redacted protocol
Includes redaction of personal identifiable information only.

Universal Trial Number: U1111-1260-8259
EudraCT Number: 2020-005281-34
IND Number: 145811

.

Study phase: 3a

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

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	**Date**	**Applicable in country(-ies) and/or site(s)**
Protocol version 6.0	23-Mar-2023	All countries
Protocol version 5.0	08-Feb-2022	Turkey only
Protocol version 4.0	18-Jan-2022	Japan only
Protocol version 3.0	10-Aug-2021	All countries
Protocol version 2.0	24-Jun-2021	All countries
Original protocol version 1.0	21-Jun-2021	Not submitted

Protocol version 6.0 (23-Mar-2023)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union,[1] because it neither significantly impacts the safety nor physical/mental integrity of participants nor the scientific value of the study.

Overall rationale for preparing protocol, version 6.0:

The protocol has been updated to correct the below errors detected, in addition to further changes shown below:

Section # and name	Description of change	Brief rationale
Section 1.3 – Flowchart – Phone contacts	Addition of a Flowchart for phone contacts	To clarify the procedures to be performed during phone contacts
Section 2 Introduction	Sentence added to describe that insulin icodec is a recombinant protein produced using yeast. Detailed information about the insulin icodec molecule has been deleted.	PMDA requirement For alignment with phase 3b protocol. The information is not relevant for trial conduct
Section 2.3 Benefit-rsik assessment	Text ~~crossed out~~ was deleted as follows: The risks of IcoSema presented in this section are a combination of important and non-important risks for IcoSema and for the mono-components insulin icodec and semaglutide. ~~All risks for mono-components that have not been identified for IcoSema directly, are classified as potential risks for IcoSema, although these may be classified as identified risks for the mono-components.~~	New risks from the mono-components are now evaluated using clinical data for IcoSema
Section 2.3.1 Risk assessment	The IcoSema IB is added as reference for benefits and risks of insulin icodec and semaglutide instead of the IBs of the mono-components.	Alignment with updated IBs

Section # and name	Description of change	Brief rationale
Section 4.1. Continuous Glucose Monitoring	Text ~~crossed out~~ was deleted as follows: To evaluate ~~the initial glycaemic control of participants switching from pre-trial insulin dose of 20-80 units to randomized treatment, and to evaluate~~ the overall glycaemic control as specified by	The deleted text had been included by mistake. This study only has CGM period (at the end of study)
Section 4.3 Justification for dose	Text in *italics* was added, and text ~~crossed out~~ was deleted as follows: The maximum dose and the ratio of IcoSema is based on the clinical findings *[reference to IcoSema IB]* ~~from the mono-components insulin icodec[4] and semaglutide s.c.[6]~~	Alignment with updated IBs
Section 5.3.1 – Meals and dietary restrictions	Text in *italic*s was added as follows: Randomised treatment *and other glucose lowering agents* should be withheld on the day of the fasting visit until blood sampling has been performed.	To clarify that participants should not take glucose lowering agents on the day of fasting visits until blood sampling has been performed
Sections 5.4, 6.2, 6.3, 7.1.1, 7.2, 8, Appendix 12 Abbreviations	Replacement of IWRS by RTSM	To reflect the change in systems used in the study
Section 8.2.2 – Physical Examinations	Text in *italics* was added, and text ~~crossed out~~ was deleted as follows: From the body weight and height *measured at V1*, the body mass index (BMI) should be calculated ~~at V2~~ *to evaluate inclusion criteria no. 7*	To clarify that the BMI should be calculated using the weight measured at visit 1
Section 8.3 Adverse events and other safety reporting	Addition of the clarifying note: "All cerebrovascular events are to be reported and sent for adjudication, however the EAC will only confirm strokes".	To clarify that the EAC will only confirm strokes
Section 8.2.1. Dose, Appendix 8: Titration guideline	In the description of collection of injection site "and insulin icodec" is added and "should" has been changed to "must".	eCRF correctly collects injection site area collected in both arms, while protocol erroneously only described it for IcoSema. Injection site area in both arms is required for originally planned population PK analysis to assess a potential differential effect of injection region between IcoSema and the mono-component
Section 8.2.4. Eye examination	Text in *italics* was added, and text ~~crossed out~~ was deleted as follows: For participants who discontinue randomised treatment, eye examination can be performed up to 2 weeks after ~~the visit at week 52~~ *visit 54A*.	Clarification of visit number to 54A
Appendix 2: Clinical laboratory tests	Text and footnotes in *italics* were added to table 10.2: *Hypersensitivity data will not be shared with investigators until after CSR finalisation.*	To clarify which hypersensitivity tests will be performed by which laboratories

Section # and name	Description of change	Brief rationale
	[c] *Samples collected from Chinese participants will be analysed by a central lab in China. Samples collected from participants in the rest of the world will be analysed by Novo Nordisk Måløv, Denmark* [d] *Samples will be analysed by Novo Nordisk Måløv, Denmark for all countries except China, where these tests will not be done (see Appendix 11, Section 10.11).* [e] *Samples collected from Chinese participants will be analysed in a special lab in China. Samples collected from participants in the rest of the world will be analysed by a special lab designated by Novo Nordisk.*	
Appendix 8. Titration guidance	Added text *in italics*: All participants should receive a loading dose at randomisation (V2), which consists of total daily basal insulin dose before randomisation x 7 + 50% of their total daily basal insulin dose *x 7*	Error in text, but calculations correct in table 10.5
Appendix 11: Country/Region specific requirements - China	Added text *in italics*: *The following hypersensitivity analytes are not possible to be tested in China, see Appendix 2 (Section 10.2), and will not be included in the hypersensitivity case assessment:* • *Anti-human insulin IgE* • *Anti-insulin icodec IgE* • *Anti-semaglutide IgE* *The following hypersensitivity analytes will be tested by the Central lab in China:* • *Tryptase* • *Total IgE antibodies* *The following hypersensitivity analytes will be tested by special lab in China:* • *Anti-insulin icodec binding antibodies* • *Anti-semaglutide binding antibodies*	To clearly reflect which hypersensitivity tests will be conducted in China due to local unavailability of some test and the impossibility of exporting samples outside China
Appendix 11: Country/Region specific requirements - Japan	Text added to describe which contraceptive methods included in the protocol (Table 10-3) have not been approved in Japan.	PMDA requirement
Appendix 11: Country/Region specific requirements - Turkey	Change of Exclusion Criteria 10 as follows: “Presence or history of pancreatitis (acute or chronic) ~~within 180 days before screening~~".	The use of GLP-1 RA is avoided in patients who have suffered pancreatitis due to treatment practice in Turkey
Section 11 References	Renumbering of references, version numbers of the IBs are updated.	Renumbering as previous ref #29 is now #1, newer versions of IBs have become available.

Section # and name	Description of change	Brief rationale
	The Ozempic® IB is deleted as reference.	The relevant information from the Ozempic® is included in the updated IcoSema IB,

Table of Contents

Page

1 Protocol summary

1.1 Synopsis

This is an interventional, multi-national, multi-centre, randomised, 52-week, open label, parallel group, treat-to-target, confirmatory study with two treatment arms.

Rationale

This study is designed to investigate the efficacy and safety of once weekly IcoSema, which is a combination product of insulin icodec and semaglutide. IcoSema will be compared to once weekly insulin icodec, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with daily basal insulin. The purpose is to show that there is an added benefit of the combination product compared to the once weekly insulin icodec mono-component according to regulatory guidelines on clinical development of fixed combination products.

Overall, the results of the present study will be important for evaluating the efficacy and safety of IcoSema in daily basal insulin experienced participants with type 2 diabetes when intensification is needed. Furthermore, once weekly IcoSema is developed to provide a simple treatment regimen.

Objectives, endpoints and estimand

Primary objective

To confirm superiority of once weekly IcoSema compared with once weekly insulin icodec both treatment arms with or without oral anti-diabetic drugs in terms of glycaemic control measured by change in HbA_{1c} from baseline after 52 weeks in participants with type 2 diabetes inadequately controlled with daily basal insulin.

Secondary objectives

To confirm superiority of once weekly IcoSema compared to once weekly insulin icodec, both treatment arms with or without OADs, in participants with T2D inadequately controlled with daily basal insulin in terms of:

- Change in body weight from baseline after 52 weeks
- Number of clinically significant hypoglycaemic (level 2) or severe hypoglycaemic (level 3) episodes during 52 weeks and the 5 week follow-up period

Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline week 0 (V2) to week 52 (V54)	%-point

Secondary endpoints

Endpoint title	Time frame	Unit
Change in body weight	From baseline week 0 (V2) to week 52 (V54)	Kg
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V56)	Number of episodes

Estimand

The primary estimand is described by the following 5 attributes:

- Treatment condition: The effect of randomised treatment (titration of once weekly IcoSema versus titration of once weekly insulin icodec) with or without oral anti-diabetic drugs, regardless of initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks and adherence to randomised treatment
- Population: type 2 diabetes inadequately controlled with daily basal insulin
- Endpoint: Change in HbA_{1c} from baseline to week 52
- Remaining ICEs: None. The two intercurrent events are captured under treatment condition and handled as follows:
  - Initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks by the treatment policy strategy
  - Discontinuation of randomised treatment for any reason by the treatment policy strategy
- Population-level summary: Difference in mean changes from baseline

Overall design

The study duration is approximately 59 weeks and consists of:

- an up to 2 weeks screening period
- a 52-week treatment period
- a 5-week follow-up period

Treatment arms and duration

1290 participants will be randomised (1:1) to receive once weekly IcoSema or once weekly insulin icodec, both treatment arms with or without oral anti-diabetic drugs.

When discontinuing randomised treatment, the participant will be transferred to a suitable marketed product at the discretion of the investigator.

Investigational medicinal products

- IcoSema 700 units/mL + 2 mg/mL, subcutaneous, solution for injection, 1.5 mL pre-filled PDS290 pen injector.
- Insulin icodec 700 units/mL, subcutaneous, solution for injection, 3 mL pre-filled PDS290 pen-injector

Participant characteristics

The participants will be male or female diagnosed with type 2 diabetes, inadequately controlled with daily basal insulin, and aged above 18 years at inclusion. They will meet the following key inclusion criteria and none of the following key exclusion criteria:

Key inclusion criteria

1. Male or female and age above or equal to 18 years at the time of signing informed consent.
2. Diagnosed with type 2 diabetes mellitus ≥ 180 days before screening.
3. HbA_{1c} of 7.0-10.0% (53.0-85.8 mmol/mol) (both inclusive) as assessed by central laboratory on the day of screening.
4. Treated with once daily or twice-daily basal insulin (neutral protamine hagedorn insulin, insulin degludec, insulin detemir, insulin glargine 100 units/mL, or insulin glargine 300 units/mL) 20-80 units/day ≥ 90 days before screening. Short term bolus insulin treatment for a maximum of 14 days before screening is allowed, as is prior insulin treatment for gestational diabetes. The treatment can be with or without any of the following anti-diabetic drugs with stable doses ≥ 90 days before screening:
   - Metformin
   - Sulfonylureas[a]
   - Meglitinides (glinides)[a]
   - DPP-4 inhibitors[a]
   - Sodium-glucose co-transporter 2 inhibitors
   - Alpha-glucosidase-inhibitors
   - Thiazolidinediones
   - Marketed oral combination products only including the products listed above.
5. Body mass index (BMI) ≤ 40.0 kg/m^2.

[a] Sulfonylureas, meglitinides (glinides) and DPP-4 inhibitors must be discontinued at randomisation.

Key exclusion criteria

1. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using a highly effective contraceptive method.
2. Anticipated initiation or change in concomitant medication (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or systemic corticosteroids).
3. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days before screening.
4. Any episodes[a] of diabetic ketoacidosis within 90 days before screening.
5. Presence or history of pancreatitis (acute or chronic) within 180 days before screening.
6. Any of the following: Myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within 180 days before screening.
7. Chronic heart failure classified as being in New York Heart Association Class IV at screening.
8. Recurrent severe hypoglycaemic episodes within the last year (12 months) as judged by the investigator.
9. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days before screening or in the period between

screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.

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

Data monitoring committee: No

1.2 Flowchart

	Protocol Sections	Screening	Randomisation	Treatment period																					Follow up		Discontinuation
Visit		V1	V2	V3	V4	V5	V6	V8	V12	V16	V20	V24[a]	V28	V30[a]	V34[a]	V38	V42[a]	V46	V49	V50[b]	V51	V52	V53	V54[b]	V55	V56	V54A
Weekly Phone Contact number (P)							P7	P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23	P25 P26 P27	P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48									
Timing of Visit (Weeks)		≤-2	0	1	2	3	4	6	10	14	18	22	26	28	32	36	40	44	47	48	49	50	51	52	54	57	
Visit Window (Days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-3/+2	±3	±3	±3	-2/+3	+3	+3	
Informed Consent and Demography	10.1.3 (App 1)	X																									
Eligibility Criteria	5.1, 5.2	X	X																								
Concomitant Medication	6.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History/Concomitant Illness	8.2	X	X																								
Tobacco Use	5.3.2	X																									
Childbearing Potential	10.4 (App 4)	X																									
Pregnancy Test	8.3.5, 10.4 (App 4)	X	X																					X		X	X
Body Measurements	8.2.2	X	X						X		X		X			X		X						X			X
Body Weight	8.2.2	X	X						X		X		X			X		X						X			X
Vital Signs	8.2.3	X	X						X		X		X			X		X						X			X
Physical Examination	8.2.2	X																						X			X

	Protocol Sections	**Screening**	**Randomisation**	**Treatment period**																					**Follow up**		**Discontinuation**
Visit		V1	V2	V3	V4	V5	V6	V8	V12	V16	V20	V24[a]	V28	V30[a]	V34[a]	V38	V42[a]	V46	V49	V50[b]	V51	V52	V53	V54[b]	V55	V56	V54A
Weekly Phone Contact number (P)							P7	P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23	P25 P26 P27	P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48									
Timing of Visit (Weeks)		≤-2	0	1	2	3	4	6	10	14	18	22	26	28	32	36	40	44	47	48	49	50	51	52	54	57	
Visit Window (Days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-3/+2	±3	±3	±3	-2/+3	+3	+3	
ECG	8.2.5	X																						X			X
Eye Examination	8.2.4	X																						X			X
CGM	8.1.2																		X	X	X	X	X	X			
Self Measured Plasma Glucose	8.1.1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event[c]	8.3, 10.3 (App 3) 10.7 (App 7)			X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments	10.2 (App 2)	X	X						X		X		X			X		X						X			X
HbA_{1c}		X	X						X		X		X			X		X						X			X
Antibodies	8.7		X		X			X	X		X		X			X								X		X	X
Pop-PK	8.4				X			X	X		X		X			X								X		X	X
Hypoglycaemia Unawareness	8.2	X																									
Diabetes Treatment Preference Questionnaire (IcoSema arm only) [d]	8.1.3																							X[d]			X

	Protocol Sections	Screening	Randomisation	Treatment period																						Follow up		Discontinuation
Visit		V1	V2	V3	V4	V5	V6	V8	V12	V16	V20	V24[a]	V28	V30[a]	V34[a]	V38	V42[a]	V46	V49	V50[b]	V51	V52	V53	V54[b]	V55	V56	V54A
Weekly Phone Contact number (P)							P7	P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23	P25 P26 P27	P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48									
Timing of Visit (Weeks)		≤-2	0	1	2	3	4	6	10	14	18	22	26	28	32	36	40	44	47	48	49	50	51	52	54	57	
Visit Window (Days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-3/+2	±3	±3	±3	-2/+3	+3	+3	
Drug Dispensing	6		X						X		X		X			X		X									
Training in Trial Product, Pen-handling	6.1		X	X				X	X		X		X			X		X									
Hand Out and Instruct in Devices	6		X																X								
Attend Visit Fasting	5.3.1		X						X		X		X			X		X						X			X

Notes:

a Visits V24, V30, V34 and V42 can be performed as either site visits, or phone/video contacts, at the discretion of the Investigator

b Special visit windows to optimize CGM data collection in relation to endpoints

c All AEs and SAEs must be collected from first administration of randomised treatment

d Questionnaire should be prompted to participants at V53

1.3 Flowchart – phone contacts

	Protocol Sections	P7-P48
Visit Window (Days)		±3
Concomitant Medication	6.8	X
Self Measured Plasma Glucose	8.1.1	X
Adverse Event[a]	8.3, 10.3 (App 3) 10.7 (App 7	X

[a] All AEs and SAEs must be collected from first administration of randomised treatment

2 Introduction

Diabetes mellitus is a metabolic disorder characterised by the presence of hyperglycaemia due to defective insulin secretion, insulin action or both. Chronic hyperglycaemia of diabetes mellitus is associated with significant long-term complications, particularly tissues damage and dysfunction or organ failure - especially the kidney, eye, and nerves.[2] Diabetes is generally classified according to aetiological factors, where type 1 diabetes and type 2 diabetes (T2D) constitutes the vast majority of cases. In the International Diabetes Federation's Diabetes Atlas (2019), the estimated worldwide diabetes prevalence was 463 million, with a prediction that by 2045, the number of people with diabetes will have increased to 700 million.[3]

T2D is a progressive disease, and the need for treatment intensification over time can be covered in a simple setting by a titratable fixed ratio combination product as IcoSema. IcoSema is a combination product of insulin icodec and the glucagon-like peptide 1 (GLP-1) receptor agonist semaglutide, which is developed to provide an effective and convenient, once weekly treatment regimen for people with T2D.

Insulin icodec is a novel long-acting insulin analogue which is under development (global phase 3a programme initiated during the fourth quarter of 2020) to safely cover the basal insulin requirements for a full week with a single subcutaneous (s.c.) injection. Insulin icodec has a terminal half-life of approximately 196 hours. Insulin icodec is a recombinant protein produced using yeast.

Semaglutide is a GLP-1 receptor agonist with a half-life of 149 to 164 hours, suitable for once weekly s.c. administration.[4] 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 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 safety of semaglutide has been confirmed. The mechanism of action of semaglutide was characterized in extensive non-clinical and clinical studies.[5, 6] Semaglutide (Ozempic®) is currently approved in more than 60 countries for the treatment of T2D. In addition, semaglutide is approved for use in combination with insulin.[5]

IcoSema is expected to provide an effect on HbA_{1c} reduction through actions on both fasting and prandial glycaemic control. IcoSema is also expected to reduce the risk of hypoglycaemic episodes and to provide weight loss compared to basal insulin and basal-bolus insulin treatment, and to show a comparable or better gastrointestinal adverse event (AE) profile as compared to semaglutide.

2.1 Study rationale

The present study is a 52-week, parallel study, with two treatment arms designed to investigate the efficacy and safety of once weekly IcoSema in comparison to once weekly insulin icodec, both treatment arms with or without oral anti-diabetic drugs (OADs), in participants with T2D inadequately controlled with daily basal insulin. The purpose is to show that there is an added benefit of the combination product compared to the once weekly insulin icodec mono-component according to regulatory guidelines on clinical development of fixed combination products.[7]

Overall, the results of the present study will be important for evaluating the efficacy and safety of IcoSema in daily basal insulin experienced participants with T2D when intensification is needed. Furthermore, once weekly IcoSema is developed to provide a simple treatment regimen.

2.2 Background

Diabetes mellitus

T2D is characterised by insulin resistance, impaired insulin secretion, increased hepatic glucose output due to glucagon dysregulation resulting in chronic hyperglycaemia.[8] The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver.[9]

Treatment of type 2 diabetes mellitus

The current treatment cascade recommended by the American Diabetes Association and the European Association for the Study of Diabetes follows a stepwise approach comprising lifestyle changes in combination with pharmacological intervention.[10] Metformin is recommended as initial therapy, followed by combination therapy with other OADs, GLP-1 receptor agonists and insulin as the disease progresses.[10]

Despite the development of new treatments, a substantial proportion of people with T2D fail to achieve the recommended glycaemic targets. This clinical inertia prolongs the duration of peoples' hyperglycaemia, which consequently puts them at an increased risk of diabetes-associated complications and reduced life expectancy. Specifically, there is an unmet medical need for products with the potential to improve clinical outcomes through reduced treatment burden, i.e. fewer injections, and increased treatment adherence and persistence[11] compared to other treatment regimens requiring daily or several weekly injections.

For people with advanced T2D in need of improved fasting and prandial glycaemic control, combined treatment with a GLP-1 receptor agonist and a basal insulin can provide improved glycaemic outcomes.[12] Experiences with fixed ratio combination products e.g. insulin degludec/liraglutide (Xultophy®) has shown improved treatment effect whilst reducing the side effects compared to the mono-components.[13] However, market research has shown that people with diabetes would prefer fewer injections[14] and increased flexibility[15] than currently provided by once daily treatment.

IcoSema

IcoSema is a once weekly injectable fixed ratio combination product comprising the novel insulin icodec and the GLP-1 receptor agonist semaglutide and is developed for late stage treatment intensification for people with advanced T2D. The development of IcoSema is based on learnings from other fixed ratio combination products e.g. insulin degludec/liraglutide (Xultophy®), showing that combination products benefit from the complementary actions of both mono-components on glycaemic control. Hence, IcoSema benefits from both insulin icodec and the potent GLP-1 receptor agonist semaglutide. IcoSema has been investigated in a clinical pharmacology study (NN1535-4359) in participants with T2D. Data from NN1535-4359 has contributed to development of the IcoSema titration guidelines included in the phase 3a development programme. A

comprehensive review of the results from the clinical pharmacology study can be found in the current investigator's brochure[16] or any updates hereof.

Insulin icodec

Insulin icodec is a novel long-acting insulin analogue under development which is designed for s.c. administration with the aim of developing a safe once weekly injectable basal insulin treatment, with a terminal elimination half-life of approximately 196 hours. Data from three completed phase 2 clinical studies (NN1436-4383, -4465 and -4466) showed that once weekly insulin icodec provided similar glucose lowering effects compared to once daily insulin glargine 100 units/mL. In addition, time in range was comparable or improved with once weekly insulin icodec compared to once daily insulin glargine 100 units/mL. Overall, once weekly insulin icodec was well tolerated and no new safety issues related to insulin treatment were identified in the phase 2 studies. A comprehensive review of results from the non-clinical and clinical studies of insulin icodec can be found in the current investigator's brochure[17] or any updates hereof.

Study population

The study population will consist of participants with T2D inadequately controlled with daily basal insulin. The study population is further described in Section 4.2.

2.3 Benefit-risk assessment

The main benefits and risks related to participation in the study are described in the below sections.

The risks of IcoSema presented in this section are a combination of important and non-important risks for IcoSema and for the mono-components insulin icodec and semaglutide.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of IcoSema may be found in the current investigator's brochure[16] or any updates hereof.

2.3.1 Risk assessment

Table 2-1 Risk assessment

Risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
IcoSema		
Identified risk Gastrointestinal AEs (Nausea, vomiting and diarrhoea)	Gastrointestinal AEs is a class risk for all GLP-1 receptor agonist products. The precise mechanism remains unclear but involves a GLP-1 receptor-mediated activation and it is therefore considered a class risk for all GLP-1 receptor agonist products. In general, these reactions are mild or moderate in severity, of short duration, and dose dependent. In the phase 1 single dose study NN1535-4359, more participants experienced gastrointestinal AEs, predominantly nausea and vomiting, following administration of IcoSema compared to the mono-components. This was likely due to the relatively higher maximum concentration of semaglutide following IcoSema administration of 175 units / 0.5 mg compared to separate dose administration of 0.5 mg semaglutide. Gastrointestinal AEs have also been observed in non-clinical studies as well as the clinical studies with semaglutide. The most frequently reported AEs across the semaglutide clinical programmes were gastrointestinal AEs (e.g., nausea, vomiting and diarrhoea).	To mitigate the risk of gastrointestinal AEs, once weekly IcoSema will be initiated at a low starting dose of 40 dose steps (equivalent to 40 units of insulin icodec and 0.114 mg of semaglutide, i.e. half the semaglutide starting dose of 0.25 mg) and titrated with ±10 dose steps (equivalent to 10 units of insulin icodec and 0.029 mg of semaglutide) to a maximum dose of 350 dose steps (equivalent to 350 units of insulin icodec and 1 mg of semaglutide). Participants who experience vomiting and/or diarrhoea will be instructed to maintain adequate fluid intake to compensate for the volume depletion.
Identified risk Hypoglycaemia	Hypoglycaemia is an anticipated undesirable effect related to the pharmacological mechanism of insulin. In the phase 1 single dose study NN1535-4359 hypoglycaemic episodes were reported in ~33% participants in the IcoSema arm and 32% of the participants in the insulin icodec arm. No severe hypoglycaemic episodes were reported. Most hypoglycaemic episodes were asymptomatic. Hypoglycaemia has been observed in clinical studies with insulin icodec. There is a low risk of hypoglycaemic episodes when semaglutide is used as mono-therapy.	Participants with known hypoglycaemic unawareness will be excluded from the study. Frequent blood glucose measurements are encouraged throughout drug exposure by means of a blood glucose (BG) meter. The participant will receive written information describing hypoglycaemic symptoms and how to manage low blood glucose levels. Prevention or worsening of hypoglycaemia will be sought by early detection and administration of carbohydrates and medical treatment, if needed. When adjusting IcoSema dose, recommended titration schemes should be followed.
Potential risk: Hypersensitivity	As with all protein-based drugs, treatment with IcoSema may evoke allergic reactions, including severe	As a precaution, participants with suspected hypersensitivity to

Risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	systemic hypersensitivity reactions and angioedema. One non-serious type-1 drug-induced hypersensitivity reaction was reported in the IcoSema phase 1 single dose study NN1535-4359. No systemic hypersensitivity reactions have been observed in clinical studies with insulin icodec. Hypersensitivity is an adverse reaction identified in phase 3a studies for semaglutide in participants with T2D.	randomised treatment will not be enrolled in this study. Participants and investigators will be instructed about the signs and symptoms of allergic reactions and instructed to contact the site immediately in case of signs of hypersensitivity.
Potential risk: Serious allergic reactions	As with all protein-based drugs, treatment with IcoSema may evoke allergic reactions, including severe systemic hypersensitivity reactions and angioedema. No serious allergic reactions have been observed with IcoSema in the phase 1 single dose study NN1535-4359. No systemic hypersensitivity reactions have been observed in studies with insulin icodec. Events of allergic reactions (generally mild and non-serious) have been reported in participants with T2D treated with semaglutide. Few events of anaphylactic reaction were reported; however, none of these events were related to the treatment with semaglutide. Events of angioedema were also reported from post marketing sources.	As a precaution, participants with suspected hypersensitivity to randomised treatment will not be enrolled in this study. Participants and investigators will be instructed about the signs and symptoms of allergic reactions and instructed to contact the site immediately in case of signs of hypersensitivity.
Potential risk: Medication error due to potential mix-up	Despite the open-label study design, medication error is still an applicable risk for participants treated with multiple insulins. Medication errors can have clinical consequences such as hypoglycaemia or hyperglycaemia. No information is available from completed clinical studies with IcoSema. Very few medication errors have been observed in the completed clinical studies with insulin icodec, none associated with AEs.	Participants will be instructed to visually verify the dialled units on the dose counter of the pen. In studies involving different pens, participants must be instructed to always check the pen label before each injection to avoid potential mix-ups.
Potential risk: Injection site reactions	Injection site reactions may occur with all injectable peptide-based treatments. In the phase 1 single dose study NN1535-4359 with IcoSema, one event of injection site haematoma was reported after administration of the mono-component semaglutide.	Participants will be instructed to monitor for signs and symptoms of injection site reactions. Participants should be instructed to contact the site immediately in case of signs of worsening of injection site reactions for further action.

Risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	Injection site reactions were observed in participants with T2D treated with insulin icodec. In the studies with semaglutide s.c. for T2D, injection site reactions were reported by a low (approximately 1%) proportion of participants with semaglutide and were not recurrent in those individuals.	Participants will be instructed on the most appropriate injection techniques. Recommendations on rotation of the site of injection are included in Table 6-1.
Potential risk Diabetic retinopathy complications	The risk of diabetic retinopathy complications has been observed in T2D treated with semaglutide in clinical studies. In a 2-year clinical study with. semaglutide s.c (NN9535-3744) involving 3,297 participants with T2D, high cardio vascular risk, long duration of diabetes and poorly controlled blood glucose, EAC-confirmed events of diabetic retinopathy complications occurred in more participants treated with semaglutide s.c (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 was similar for semaglutide s.c and placebo. In the other clinical studies up to 1 year involving 4,807 participants with T2D, AEs related to diabetic retinopathy were reported in similar proportions of participants treated with semaglutide s.c (1.7%) and comparators (2.0%).	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. Participants will have an eye examination performed at baseline and at week 52. Diagnostic artificial intelligence algorithms may possibly be used as screening tool. If diagnostic artificial intelligence algorithms are used and in case of changes indicated by the algorithm, an additional eye examination must be performed, see section 8.2.4. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy is an exclusion criterion in this study.
Potential risk: Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. In the completed phase 3 studies 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 study periods and the overall rates were similar to the rates reported in background populations.	Participants should be informed of the characteristic symptoms of acute pancreatitis and if pancreatitis is suspected, IcoSema should be discontinued. If confirmed, IcoSema should not be restarted.

Risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Potential risk: Neoplasms (malignant and non-malignant)	Participants with T2D, as well as participants with overweight or obesity, have an increased risk of certain types of cancer. There is no evidence from clinical studies that GLP-1-based therapies increase the risk of neoplasms. However, in the semaglutide s.c. as well as oral semaglutide phase 3a studies, the proportion of participants with neoplasms (malignant and non-malignant) were slightly higher with semaglutide than with comparator. The number of participants exposed to semaglutide s.c. or oral semaglutide for a longer period is considered insufficient for a thorough assessment of the risk of neoplasms.	Participants with presence or history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this study. Basal and squamous cell skin cancer and any carcinoma in-situ is allowed.
Potential risk: Pancreatic cancer	Participants 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 based therapies increase the risk of pancreatic cancer. However, pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 receptor agonists by regulatory agencies. 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 studies.	Participants with history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this study.
Potential risk: Medullary thyroid cancer	Thyroid C-cell tumours were seen in 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.	Exclusion criteria related to personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.

Risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study procedures		
Risk of COVID-19 infection in relation to participation in study	Participants may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country.	The risk of COVID-19 transmission in relation to site visits is overall considered to be low, however this may vary between geographical areas. To minimize the risk as much as possible, the following measures have been taken: • 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. • Study procedures including the number and frequency of study procedures and assessments have been critically evaluated to limit the number of on-site visits to the extent possible. Remote visits can be performed either by phone or by video call depending on the preference of the participant and the investigator. • Guidance is provided to site staff to request that on-site visits are planned to be as short as possible. Physical contact between participants and site staff will be limited to the extent possible, and protective measures will be implemented (describe e.g. use of masks, sanitizers, no aerosol-generating procedures etc.). • Please refer to Appendix 10 (Section 10.10) which lists the additional actions to be taken in case a site or country are locked down and it is not possible for participants to visit the site.
Other		
Device medication error	If the pen-injector is damaged or used differently than described in the directions for use a risk of overdose or underdose of randomised treatment exists. This may cause hypoglycaemia due to overdose or hyperglycaemia due to underdose.	Training in injections and use of devices and guidance materials for investigator, site staff and participants will be provided.

Risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
For more information about the known and expected benefits and risks of insulin icodec, please refer to the IcoSema investigator's brochure.[16] For more information about the known and expected benefits and risks of semaglutide, please refer to the IcoSema investigator's brochure,[16] the current EMA summary of product characteristics for semaglutide,[5] the US prescribing information for semaglutide,[6] or any locally approved label.		
Pregnancy and fertility.	Studies with insulin icodec in rats have shown no effects on fertility, embryo-foetal survival or on major and minor foetal abnormalities. In an embryo-foetal development study in rabbits, no effect on major and minor foetal visceral and skeletal abnormalities at any dose levels was observed. Consequently, insulin icodec is categorised as 'unlikely risk of human teratogenicity/fetotoxicity. Studies in animals have shown reproductive toxicity in studies with semaglutide. There are limited data from the use of semaglutide in pregnant women.	The randomised treatment should not be used during pregnancy. Women of childbearing potential are required to use highly effective contraceptive methods when participating in the study, see Appendix 4 (Section 10.4, Table 10-3). If a participant wishes to become pregnant, or pregnancy occurs, the randomised treatment should be discontinued, please refer to Section 8.3.5 for further guidance). The effect of IcoSema on fertility in humans is unknown.

Risk assessment has been conducted for the PDS290 pen-injector for IcoSema in accordance with ISO 14971:2019 when using the PDS290 pen-injector in people with T2D. All identified risks (i.e. injection site reactions, see Table 2-1) associated with using the PDS290 pen-injector for IcoSema according to the clinical procedures specified in this protocol have been reduced as far as possible and are acceptable, taking into account the current state of the art. The use of the PDS290 pen-injector for IcoSema, in this study is therefore considered to be of non-significant risk.

2.3.2 Benefit assessment

Based on experience from the mono-components and on the learnings from insulin degludec/liraglutide as described in the introduction, we expect at positive benefit of the combination product IcoSema. This benefit assessment section is based on clinical data available for the mono-components insulin icodec and semaglutide in the T2D population.

Insulin icodec is currently in development and has been shown to have a long and stable pharmacokinetic and pharmacodynamic profile supporting a once weekly treatment. Market research has shown that people with diabetes mellitus would prefer fewer injections and greater flexibility than those provided by the current once daily treatment regiment.[14] Therefore, the compliance and quality of life are expected to increase by introducing a once weekly basal insulin treatment.

Clinical data on once weekly 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, once weekly dosing offers flexibility and fewer injections as opposed to current therapy.

Based on these data, the combination of semaglutide and insulin icodec in a once weekly fixed ratio combination product is expected to provide superior efficacy on HbA_{1c} lowering compared to the mono-components.

IcoSema is also expected to provide weight loss and to reduce the risk of hypoglycaemic episodes compared to basal insulin.

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

No new significant safety information that changes the current benefit-risk profile of IcoSema emerged from the completed phase 1 single dose IcoSema study NN1535-4359 or safety profile generated from clinical and non-clinical development programme for the mono-components.

Necessary precautions have been implemented in the design and planned conduct of the study in order to minimise the risks and inconveniences of participation in the study.

IcoSema is expected to provide an effect on HbA_{1c} reduction through actions on both fasting and prandial glycaemic control. IcoSema is also expected to reduce the risk of hypoglycaemic episodes and to provide weight loss compared to basal insulin and basal-bolus insulin treatment, and to show a comparable or better gastrointestinal AE profile as compared to semaglutide.

Considering the measures taken to minimise risk to participants, the potential risks identified in association with IcoSema are justified by the anticipated benefits that may be afforded to people with T2D.

More detailed information about the known and expected benefits and risks of IcoSema can be found in the current investigator's brochure[16] or any updates hereof.

3 Objectives, endpoints and estimands

3.1 Objectives

3.1.1 Primary objective

To confirm superiority of once weekly IcoSema compared with once weekly insulin icodec, both treatment arms with or without OADs, in terms of glycaemic control measured by change in HbA_{1c} from baseline after 52 weeks in participants with T2D inadequately controlled with daily basal insulin.

3.1.2 Secondary objectives

To confirm superiority of once weekly IcoSema compared to once weekly insulin icodec, both treatment arms with or without OADs, in participants with T2D inadequately controlled with daily basal insulin in terms of:

- Change in body weight from baseline after 52 weeks
- Number of clinically significant hypoglycaemic (level 2) or severe hypoglycaemic (level 3) episodes during 52 weeks and the 5 week follow-up period

To compare parameters of glycaemic control and safety of once weekly IcoSema with once weekly insulin icodec, both treatment arms with or without OADs, in participants with T2D inadequately controlled with daily basal insulin.

3.2 Endpoints

3.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Change in HbA_{1c}	From baseline week 0 (V2) to week 52 (V54)	%-point

3.2.2 Secondary endpoints

3.2.2.1 Confirmatory secondary endpoints

Endpoint title	Time frame	Unit
Change in body weight	From baseline week 0 (V2) to week 52 (V54)	Kg
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V56)	Number of episodes

3.2.2.2 Supportive secondary endpoints

Secondary efficacy endpoints

Endpoint title	Time frame	Unit
Time in range 3.9-10.0 mmol/L (70-180 mg/dL)*	From week 48 (V50) to week 52 (V54)	% of readings
Time spent < 3.0 mmol/L (54 mg/dL)*	From week 48 (V50) to week 52 (V54)	% of readings
Time spent > 10.0 mmol/L (180 mg/dL)*	From week 48 (V50) to week 52 (V54)	% of readings
Change in fasting plasma glucose (FPG)	From baseline week 0 (V2) to week 52 (V54)	mmol/L
Weekly basal insulin dose	From week 50 (V52) to week 52 (V54)	Units

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

Secondary safety endpoints

Endpoint title	Time frame	Unit
Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)	From baseline week 0 (V2) to week 57 (V56)	Number of episodes
Number of severe hypoglycaemic episodes (level 3)	From baseline week 0 (V2) to week 57 (V56)	Number of episodes

3.2.3 Exploratory endpoints

Not applicable for this study.

3.3 Primary estimand

The primary clinical question of interest

What is the treatment effect between once weekly IcoSema and once weekly insulin icodec in change in HbA_{1c} from baseline to week 52 in participants with T2D inadequately controlled with daily basal insulin regardless of discontinuation of randomised treatment for any reason and regardless of initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks?

The primary estimand is described by the following 5 attributes:

- Treatment condition: The effect of randomised treatment (titration of once weekly IcoSema versus titration of once weekly insulin icodec) with or without OAD(s), regardless of initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks and adherence to randomised treatment
- Population: T2D inadequately controlled with daily basal insulin
- Endpoint: Change in HbA_{1c} from baseline to week 52
- Remaining ICEs: None. The two intercurrent events are captured under treatment condition and handled as follows:
  - Initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks by the treatment policy strategy

- Discontinuation of randomised treatment for any reason by the treatment policy strategy
- Population-level summary: Difference in mean changes from baseline

The rationale for the primary estimand is that this estimand captures both the efficacy and safety of the randomised treatment with and without additional anti-diabetic/glucose-lowering medication and thus aims at reflecting clinical practice.

3.3.1 Secondary estimands

The secondary clinical question of interest related to secondary objective regarding body weight

What is the treatment effect between once weekly IcoSema and once weekly insulin icodec in change in body weight from baseline to week 52 in participants with T2D inadequately controlled with daily basal insulin regardless of discontinuation of randomised treatment for any reason and regardless of initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks?

The estimand addressing this secondary clinical question of interest and the rationale is the same as for the primary estimand with the endpoint attribute specified as: change in body weight from baseline to week 52.

The secondary clinical question of interest related to secondary objective regarding number of clinically significant hypoglycaemic episodes (level 2) or severe hypoglycaemic episodes (level 3)

What is the treatment effect between once weekly IcoSema and once weekly insulin icodec on number of clinically significant hypoglycaemic (level 2) or severe hypoglycaemic (level 3) episodes during the time that participants are considered exposed to randomised treatment in participants with T2D inadequately controlled with daily basal insulin regardless of initiation of non-randomised insulin treatment or additional anti-diabetic treatments, had all participants adhered to randomised treatment until week 52?

The secondary estimand addressing this clinical question of interest is described by the following 5 attributes:

- Treatment condition: The effect of randomised treatment (titration of once weekly IcoSema versus titration of once weekly insulin icodec) with or without OAD(s), regardless of initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks and had all participants adhered to randomised treatment
- Population: T2D inadequately controlled with daily basal insulin
- Endpoint: Number of clinically significant hypoglycaemic (level 2) or severe hypoglycaemic (level 3) episodes during 52 weeks and the 5 week follow-up period
- Remaining ICEs: None. The two intercurrent events are captured under treatment condition and handled as follows:
  - Initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks by the treatment policy strategy
  - Discontinuation of randomised treatment for any reason by the hypothetical strategy

- Population-level summary: Rate ratio

Rationale for the secondary estimand: The estimand reflects the interpretation of the effect of randomised treatment with and without additional anti-diabetic/glucose-lowering medication without the confounding effect of discontinuation of randomised treatment. This interpretation is considered to be the most relevant interpretation for clinical practice and in alignment with the evaluation of other safety parameters included in the study. In addition, collection of hypoglycaemic episode data after discontinuation of randomised treatment (beyond the standard 5 week follow-up period) will require operational measures that will increase the study burden on participants. This could lead to increased withdrawal rates and missing assessments on the primary endpoint jeopardising the primary objective of this study.

4 Study design

4.1 Overall design

This is an interventional, multi-national, multi-centre, randomised, 52-week, open label, parallel group, treat-to-target confirmatory study with two treatment arms. The study investigates the efficacy and safety of treatment with once weekly IcoSema compared to once weekly insulin icodec, both treatment arms with or without OADs, in participants with T2D inadequately controlled with daily basal insulin.

The study duration is approximately 59 weeks and consists of:

- an up to 2 weeks screening period
- a 52-week treatment period
- a 5-week follow-up period

The study includes a screening visit (V1) to assess participant's eligibility. After screening, all eligible participants will be randomised (1:1) at visit 2 (V2). The overall study design and visit schedule are outlined in Figure 4-1 and the study flowchart (Section 1.2), respectively.

Figure 4-1 Study design

1290 participants will be randomised (1:1) to receive once weekly IcoSema or once weekly insulin icodec. With the exception of sulfonylureas, glinides and DPP-4 inhibitors that must be discontinued at randomisation (V2), the dose and dosing frequency of any pre-study OADs should not be changed during the study, unless due to safety concerns.

During the study, participants will measure daily self-measured plasma glucose (SMPG). The SMPG measurements will be evaluated by the investigator at the weekly contact either as site visits, by phone or video call. At the weekly contacts, the dosing will be adjusted in accordance with the participant's needs and safety, see also titration guidelines Appendix 8 (Section 10.8). However, it is always up to the discretion of the investigator to assess participant's individual needs and safety in accordance with local standard of care.

After the 52 weeks of treatment, participants will come in for visit V54, where data for the primary endpoint will be collected. The visit at week 52 (V54) will be one week after the last dose of once weekly IcoSema or once weekly insulin icodec. After the 52 weeks of treatment participants will be transferred to a suitable marketed product at the discretion of the investigator. See also titration guideline, Appendix 8 (Section 10.8).

The treatment period is followed by a 5-week follow-up period to ensure safety data collection. During the follow-up period, two follow-up visits (V55 and V56) will be performed, 2 and 5 weeks after the visit at week 52 (V54), respectively. Hence, the last follow-up visit (V56) will take place 6 weeks after the last dose of once weekly IcoSema or once weekly insulin icodec. The last follow-up visit (V56) is scheduled to allow for appropriate wash-out of randomised treatment, following at least 5 half-lives of once weekly IcoSema or once weekly insulin icodec.

To evaluate the overall glycaemic control as specified by the endpoints (see Section 3.2.2.2), participants will have continuous glucose monitoring (CGM) profiles collected, as specified by the flowchart (Section 1.2). The CGM will be blinded for both participants and investigators.

In case of persistent and unacceptable hyperglycaemia as judged by the investigator based on the daily SMPGs, and in accordance with local standard of care, treatment with non-randomised insulin (basal or bolus) limited to up to 14 consecutive days can be considered to be added to the randomised treatment at the discretion of the investigator to safeguard the participants. Initiation of new anti-diabetic medication and any changes hereto must be recorded on the concomitant medication form in the eCRF.

Event adjudication will be performed for acute coronary syndrome events (acute myocardial infarction and unstable angina pectoris requiring hospitalisation), cerebrovascular events (stroke and transient ischemic attack), heart failure (requiring hospitalisation and urgent heart failure visit) and all-cause death. All AEs will be collected from visit 2 and recorded from visit 3.

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

4.2 Scientific rationale for study design

The study is designed in alignment with the estimands (Section 3) to investigate the efficacy and safety of once weekly IcoSema compared to once weekly insulin icodec during 52 weeks.

In order to confirm the superiority of the fixed ratio combination of IcoSema to its insulin mono-component, once weekly insulin icodec is the comparator. The treatment arms will be open label in order to avoid the risk of pen-mix-up in a double-blind, double dummy study, as the initiation and titration doses of IcoSema and insulin icodec differ – specifically in terms of no loading dose/loading dose, respectively, see Appendix 8 (Section 10.8). Blinding of the study would increase the treatment complexity and hence increase the burden on the participants. Further, the maximum allowed weekly dose of IcoSema will be 350 dose steps (equivalent to 350 units insulin icodec and 1 mg semaglutide) while there is no maximum allowed weekly dose of insulin icodec.

The treatment duration of 52 weeks is evaluated to be adequate for assessing efficacy on glycaemic control as well as safety. This duration will also ensure sufficient time to reach the maintenance dose of IcoSema for the broad study population and allow adequate time in maintenance phase. The treat-to-target approach has been chosen to ensure optimal titration of both treatment arms based on SMPG values with the aim of improving HbA_{1c} in the treatment period.

The evaluation of time in range will be based on continuous glucose monitoring (CGM) profiles. To avoid influence on titration and the glycaemic control the CGM data will be blinded for both participants and investigator.

Participants entering the study will be inadequately controlled with daily basal insulin with or without OADs ensuring a study population representative of a broad and advanced T2D population.

Risk of hypoglycaemia increases when insulin secretagogues like sulfonylureas and glinides are used in association with insulin and combination injectable anti-diabetic therapy.[10, 18] Hence, to minimise the risk, sulfonylureas and glinides are discontinued at randomisation (V2). DPP-4 inhibitors must likewise be discontinued since the combined use of a GLP-1 receptor agonist (semaglutide component of IcoSema) and a DPP-4 inhibitor is not currently recommended.[19]

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

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

4.3 Justification for dose

The IcoSema pen is developed with one ratio and one titration algorithm for the phase 3a programme in order to simplify the treatment regiments for patients and physicians.

Once weekly IcoSema will be switched from the pre-study daily basal insulin. IcoSema will be initiated at 40 dose steps (equivalent to 40 units of insulin icodec and 0.114 mg of semaglutide), and titrated to target according to the principles outlined in the titration guideline in Appendix 8 (Section 10.8).

The starting dose of 40 dose steps (equivalent to 40 units of insulin icodec and 0.114 mg of semaglutide) is selected based on pharmacokinetics (PK) findings from the development programme of IcoSema. The combination of the starting dose and the titration algorithm of ±10 dose step increments (equivalent to 10 units of insulin icodec and 0.029 mg of semaglutide) is considered to be safe, due to the combined action of the two mono-components on both fasting and prandial glycaemic control. Furthermore, the selected starting dose and titration algorithm are expected to ensure a comparable or better gastrointestinal adverse event (AE) profile as compared to semaglutide s.c.

The maximum dose of 350 dose steps is equivalent to 350 units insulin icodec and 1 mg semaglutide, which is the currently approved maximum dose for semaglutide s.c. in treatment of T2D (as of 21 June 2021).[5,6] The maximum dose and the ratio of IcoSema is based on the clinical findings[16] and learnings from the once daily fixed ratio combination product, insulin degludec/liraglutide (Xultophy®).[13] The ratio is selected with the focus on balancing the benefits from semaglutide and the expected durability of treatment with the insulin component. Providing 350 units of insulin icodec to 1 mg of semaglutide, is expected to meet the clinical needs for the majority of the target population, while their safety is also ensured.

Once weekly insulin icodec will be switched from the pre-study daily basal insulin, and initiated according to the principles outlined in the titration guideline in Appendix 8 (Section 10.8). A 50% loading dose will be applied to avoid glycaemic deterioration during the first few weeks of treatment. No safety concerns have been identified in subjects with T2D, including vulnerable subjects, using a loading dose when initiating insulin icodec (trial NN1436-4466).

After randomisation, participants should start once weekly injections of IcoSema or insulin icodec on the same day as randomisation. Due to the long half-life of the IcoSema and insulin icodec, the last once weekly injections must be taken 51 weeks after randomisation.

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

Guidance on missed doses can be found in the titration guideline in Appendix 8 (Section 10.8).

4.4 End of study definition

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

A participant is considered to have completed the study if he/she has completed all periods of the study including the visit at week 52 (V54) and the last follow-up visit (V56).

The primary endpoint is evaluated at the visit at week 52 (V54). The primary completion date is defined as the date of visit at week 52 (V54) on which the last participant in the clinical study has an assessment for the primary endpoint. If the last participant is withdrawn early from the study, the primary completion date is considered the date when the second-to-last participant completes the visit at week 52 (visit 54).

5 Study population

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

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

For country-specific requirements to the inclusion and exclusion criteria, please refer to Appendix 11 (Section 10.11) for further information.

5.1 Inclusion criteria

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

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Male or female.
3. Age above or equal to 18 years at the time of signing informed consent.
4. Diagnosed with type 2 diabetes mellitus ≥ 180 days before screening.
5. HbA_{1c} of 7.0-10.0% (53.0-85.8 mmol/mol) (both inclusive) as assessed by central laboratory on the day of screening.
6. Treated with once daily or twice-daily basal insulin (neutral protamine hagedorn insulin, insulin degludec, insulin detemir, insulin glargine 100 units/mL, or insulin glargine 300 units/mL) 20-80 units/day ≥ 90 days before screening. Short term bolus insulin treatment for a maximum of 14 days before screening is allowed, as is prior insulin treatment for gestational diabetes. The treatment can be with or without any of the following anti-diabetic drugs with stable doses ≥ 90 days before screening:
   - Metformin
   - Sulfonylureas[a]
   - Meglitinides (glinides)[a]
   - DPP-4 inhibitors[a]
   - Sodium-glucose co-transporter 2 inhibitors
   - Alpha-glucosidase-inhibitors
   - Thiazolidinediones
   - Marketed oral combination products only including the products listed above.
7. Body mass index (BMI) ≤ 40.0 kg/m^2.
8. Not currently using real time continuous or flash glucose monitoring.

[a] Sulfonylureas, meglitinides (glinides) and DPP-4 inhibitors must be discontinued at randomisation.

5.2 Exclusion criteria

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

1. Known or suspected hypersensitivity to randomised treatment 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 a highly effective contraceptive method, as defined in Appendix 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 and if simultaneous participation is allowed by local authorities.
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. Anticipated initiation or change in concomitant medication (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or systemic corticosteroids).
7. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days before screening.
8. Any episodes[a] of diabetic ketoacidosis within 90 days before screening.
9. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.
10. Presence or history of pancreatitis (acute or chronic) within 180 days before screening.
11. Any of the following: Myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within 180 days before screening.
12. Chronic heart failure classified as being in New York Heart Association Class IV at screening.
13. Planned coronary, carotid or peripheral artery revascularisation.
14. Renal impairment measured as estimated glomerular filtration rate value of < 30 ml/min/1.73 m^2 at screening as defined by KDIGO 2012.[20]
15. Impaired liver function, defined as alanine aminotransferase ≥ 2.5 times or bilirubin > 1.5 times upper normal limit at screening.
16. Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8.[21].
17. Recurrent severe hypoglycaemic episodes within the last year (12 months) as judged by the investigator.
18. Inadequately treated blood pressure defined as systolic ≥ 180 mmHg or diastolic ≥ 110 mmHg at screening.
19. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days before screening or in the period between screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination, see 8.2.4.
20. Presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in situ prostate cancer) within 5 years before screening.

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

A participant, who does not fulfil the eligibility (inclusion/exclusion) criteria, must not be randomised. Randomisation in violation of any of the eligibility criteria is good clinical practice (GCP) non-compliance and must be reported to the sponsor without delay. This will be handled as

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

5.3 Lifestyle considerations

5.3.1 Meals and dietary restrictions

The participants should be fasting when attending some of the visits, see flowchart (Section 1.2). Fasting is defined as at least eight hours without food and drink intake, except for water and other prescribed medication. Randomised treatment and other glucose lowering agents should be withheld on the day of the fasting visit until blood sampling has been performed. Any other prescribed medication should be taken as usual. If the participant attends a fasting visit in a non-fasting state, the blood sampling procedures and weight measurements should be re-scheduled.

5.3.2 Caffeine, alcohol and tobacco

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

5.4 Screen failures

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.

A screen failure session must be made in the Randomisation and Trial Supply Management system (RTSM).

Individuals who do not meet the criteria for participation in this study may not be rescreened. If the participant has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters, re-sampling is not allowed. However, in case of technical issues (e.g., haemolysed or lost sample), re-sampling is allowed for the affected parameter(s).

5.5 Run-in criteria, randomisation criteria and dosing day criteria

Not applicable for this study.

6 Study interventions and concomitant therapy

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

Study interventions comprise IcoSema, insulin icodec, and OADs. BG meter and CGM are not considered study interventions.

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

Trial products consist of IcoSema and insulin icodec. OADs are NIMPs but not considered trial products in this protocol.

Randomised treatment consists of IcoSema and insulin icodec. Hence randomised treatment and IMPs are covering the same.

Trial products and randomised treatment consist of IcoSema and insulin icodec. Randomised treatment will be used throughout the protocol while trial products is used when addressing product accountability.

6.1 Study interventions administered

Training in the pen-injectors is the responsibility of the investigator or a delegate and must be repeated during the study at regular intervals, as specified in the flowchart (see Section 1.2.) in order to ensure correct use of the pen-injector. The following documents must be provided to the participants:

IcoSema: directions for use
Insulin icodec: directions for use

Investigational medicinal products (IMP)

All IMPs are listed in Table 6-1.

Table 6-1 Investigational medicinal products

Intervention	IcoSema treatment arm	Comparator treatment arm
Intervention name	IcoSema	Insulin icodec
Intervention type	IMP, test product	IMP, reference therapy
Pharmaceutical form	Solution for injection	Solution for injection
Route of administration	s.c. (into the thigh, upper arm or abdomen)	s.c. (into the thigh, upper arm or abdomen)
IMP strength	700 units/mL + 2 mg/mL	700 units/mL
Dose and dose frequency	Administer IcoSema once weekly, on the same day each week, at any time of the day. For more information, please refer to Appendix 8 (Section 10.8)	Administer insulin icodec once weekly, on the same day each week, at any time of the day. For more information, please refer to Appendix 8 (Section 10.8)
Dosing instructions and administration	The day of weekly administration can be changed if necessary, by up to 3 days. A minimum of 4 days between injections should always be ensured. Rotation of injection site within the same area is recommended. For more information, please refer to Appendix 8 (Section 10.8)	The day of weekly administration can be changed if necessary, by up to 3 days. A minimum of 4 days between injections should always be ensured. Rotation of injection site within the same area is recommended. For more information, please refer to Appendix 8 (Section 10.8)
Transfer from other therapy	Please refer to Appendix 8 (Section 10.8)	Please refer to Appendix 8 (Section 10.8)
Sourcing	Manufactured and supplied by Novo Nordisk A/S	Manufactured and supplied by Novo Nordisk A/S
Packaging and labelling	1.5 mL pre-filled PDS290 pen-injector.	3 mL pre-filled PDS290 pen-injector.

- At randomisation visit (V2) participants should administer IcoSema or insulin icodec at site.
- Instructions on missed doses can be found in the titration guideline in Appendix 8 (Section 10.8).
- It is not allowed to split a dose between two pens.
- Information about the PDS290 pre-filled pen-injector and can be found in the directions for use provided in the eDiary.

Non-investigational medicinal products (NIMP)

After randomisation participants should continue their pre-study OADs (see list of allowed OADs in Section 5.1) throughout the entire study except for treatment with sulfonylureas, glinides and DPP-4 inhibitors that must be discontinued at randomisation. The OADs should be maintained at the stable, pre-study dose and at the same frequency during the entire treatment period unless due to safety concerns, which will be assessed at the discretion of the investigator. Combination products containing either sulfonylureas, glinides or DPP-4 inhibitors must also be discontinued, while the residual anti-diabetic mono-component of the combination product should in general be maintained at the pre-study dose throughout the study similar to other OADs. If the pre-study dose of the residual anti-diabetic medication is not available, the participant should increase the dose to the next available dose.

In addition, the OADs:

- are considered to be NIMP
- will not be supplied or reimbursed by Novo Nordisk unless required by local law and should be purchased or otherwise delivered to participants in accordance with local health plans
- should be used in accordance with standard of care or local label in the individual country.

Auxiliary supplies including medical device(s) not under investigation

Auxiliary supplies comprise supplies other than trial products. Auxiliary supplies will be provided in accordance with the Trial Materials manual, please also see Table 6-2.

Table 6-2 Auxiliary supplies

Auxiliary	Model	Details	Manufacturer
Needles	NovoFine® needles or similar according to local requirements	Only needles with a max length of 6 mm provided and approved by Novo Nordisk must be used for administration of randomised treatment. Needle must be discarded after each injection and the pen-injector should be stored without a needle attached.	Novo Nordisk
Continuous Glucose Monitoring (CGM) system	Dexcom G6®	At week 47 (V49) participants must be instructed in handling of the CGM. Please refer to the provided Participant CGM Guide. For countries where the CGM system is not approved, please refer to Appendix 11 (Section 10.11)	Dexcom Inc.
Blood glucose (BG) meter (including auxiliaries)	Roche Accu-Chek® Guide / Instant	At randomisation (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 Trial tablet, & Cloud Service. Please refer to the eDiary site guide.	Novo Nordisk

6.2 Preparation, handling, storage and accountability

Only participants enrolled in the study may use randomised treatment and only delegated site staff may supply randomised treatment. Each site will be supplied with sufficient randomised treatment for the study on an ongoing basis according to recruitment and randomisation.
The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.

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

The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any participant before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the Trial Materials Manual.

The investigator or designee is responsible for trial product accountability and record maintenance (i.e., receipt, accountability and final disposition records). Drug accountability should be performed in the RTSM.

The investigator or designee must instruct the participant to return all IMPs (both used and not used) at the next dispensing visit.

The investigator or designee must instruct the participant on how to manage and record the in-use time of the dispensed products. The in-use time can be found in the Trial Materials Manual.

Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.

All returned (used or un-used), expired or damaged trial products (for technical complaint samples, see Appendix 5 [Section 10.5]) must be stored separately from non-allocated trial products. No temperature monitoring is required.

Non-allocated trial products, including expired or damaged products, must be accounted as unused, at the latest at closure of the site.

Acceptable temperature ranges and conditions for storage and handling of each trial product when not in use and when in use are described in the Trial Materials Manual and trial product label.

Each single pen should be accounted for.

6.3 Measures to minimise bias: Randomisation and blinding

All participants will be screened and centrally randomised using an RTSM and assigned to the next available treatment according to the randomisation schedule. Trial product will be allocated by the RTSM and dispensed by the investigator at the study visits summarised in the flowchart (Section 1.2).

This is an open-label study; however, the specific trial products for a participant will be assigned using an RTSM. The site will access the RTSM before the start of trial product administration for each participant. Potential bias will be reduced by central randomisation and adjudication.

6.4 Drug treatment compliance

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

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

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

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 randomised treatment after end of study

Randomised treatment will not be accessible after end of study. When discontinuing randomised treatment, the participant should be transferred to a suitable marketed product at the discretion of the investigator, please see the titration guideline in Appendix 8 (Section 10.8). The medication should be recorded in the concomitant medication form, as described in Section 6.8.

6.7 Treatment of overdose

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.3 and Appendix 3 (Section 10.3) for further details.

In the event of an overdose, the investigator should closely monitor the participant for overdose-related AEs/serious adverse events (SAEs).

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

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

Severe hypoglycaemia where the participant is not able to treat him/herself, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, by other drugs for the indication of treatment hypoglycaemia in accordance with local guidelines or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the participant does not respond to glucagon within 10-15 minutes. If the participant has been unconscious, administration of oral carbohydrates is recommended for the participant upon regaining consciousness, in order to prevent a relapse.

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the participant and in accordance with local standard of care.

For more information on overdose, also consult the current version of the IcoSema[16] and insulin icodec[17] investigator's brochures.

6.8 Concomitant therapy

Any medication that the participant is receiving at screening visit (V1) or receives until the visit at week 52 (V54) must be recorded. From week 52 (V54) and until the last follow-up visit (V56) only anti-diabetic medication and medication related to SAEs must be recorded. The medication must be recorded along with:

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

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

For information regarding restrictions to anti-diabetic medication other than the randomised treatment, please see Section 6.1.

For information regarding concomitant medication collection for participants who discontinue randomised treatment, see Section 7.1.1.

6.8.1 Rescue medicine

Not applicable for this study. In case of lack of efficacy, please refer to section 7.1.1.

7 Discontinuation of study intervention and participant withdrawal

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

7.1 Discontinuation of study intervention

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

7.1.1 Discontinuation of randomised treatment

Discontinuation of randomised treatment corresponds to discontinuation of IcoSema or insulin icodec.

If a participant discontinues randomised treatment, the participant should as soon as possible attend the discontinuation visit (V54A).

The investigator should change participant status in the healthcare professional (HCP) web portal to 'follow-up' at the discontinuation visit (V54A) to ensure that the participant should no longer report randomised treatment dose.

The participant should also complete the two follow-up visits (V55 and V56).

Hypoglycaemic episodes will not be collected after the last follow-up visit (V56).

Efforts must be made to have the participants who discontinue randomised treatment attend the visit at week 52 (V54) to collect:

- Data for primary endpoint (HbA_{1c}).
- Data for confirmatory secondary endpoint for body weight.

AEs, medication related to SAEs, and anti-diabetic medication should be collected and recorded in the eCRF until the visit at week 52 (V54). No other concomitant medication than medication related to SAEs and anti-diabetic medication will be collected and reported in the eCRF for participants who discontinue randomised treatment.

Please, refer to Section 6.6 for treatment after discontinuation of randomised treatment.

The site should stay in contact with the participants who discontinue randomised treatment by phone, video call and/or site visits to motivate the participants to attend the follow-up visits (V55 and V56) and the visit at week 52 (V54). Site contacts should be documented in the medical record.

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

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 randomised treatment.

The randomised treatment must be discontinued, if any of the following applies for the participant:

1. Safety concern related to randomised treatment or unacceptable intolerability
2. Pregnancy
3. Intention of becoming pregnant
4. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study
   Note: Simultaneous participation in a study with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or post-infectious conditions is allowed at the investigator's discretion without discontinuation of randomised treatment if simultaneous participation is allowed by local authorities.
5. Lack of efficacy, defined as fulfilment of ALL criteria (a, b and c) below after week 8 and onwards:
   a. Mean of pre-breakfast SMPG values (on the two days before and on the day of visit) of 3 consecutive weeks after week 8 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 fasting plasma glucose (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.

To allow time for up-titration of the randomised treatment and to observe the expected effect of randomised treatment on glycaemic parameters, lack of efficacy criteria will be applied on week 8 and onwards.

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

7.1.2 Temporary discontinuation of randomised treatment

The participant should adhere to the randomised treatment to the extent possible, with the exception of any AEs such as hospitalisation or safety concerns, at the discretion of the investigator. If a participant due to an AE or safety concern temporarily has discontinued randomised treatment, she/he is allowed to restart randomised treatment, unless any of the discontinuation criteria specified in Section 7.1 applies.

7.1.3 Rescue criteria

Not applicable for this study.

7.2 Participant withdrawal from the study

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

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

If a participant withdraws consent after randomisation, the investigator must ask the participant if he/she is willing, as soon as possible, to have assessments performed according to discontinuation visit V54A. The investigator should also ask the participant if he/she is willing to attend the two follow-up visits V55 and V56 (see Section 7.1 regarding the scheduling of the follow-up visits). See the flowchart for data to be collected.

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

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

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

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

7.2.1 Replacement of participants

If a participant discontinues randomised treatment, withdraws consent or is withdrawn from the study 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'.

8 Study assessments and procedures

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

Informed consent must be obtained before any study-related activity, see Appendix 1 (Section 10.1.3).

All screening evaluations must be completed and reviewed to confirm that potential participants meet all inclusion criteria and none of the exclusion criteria.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reason for screen failure, as applicable.

At screening, participants will be provided with a card stating that they are participating in a study and giving contact details of relevant site staff that can be contacted in case of emergency.

Adherence to the study design requirements, including those specified in the flowchart (Section 1.2), is essential and required for study conduct.

Assessments should be carried out according to the clinic's standard of practice unless specified in the current section. Efforts should be made to limit the bias between the assessments. The suggested order of the assessments at randomisation visit (V2) is as follows:

- Blood sample collection
- Other assessments to confirm eligibility
- Randomisation in RTSM
- The investigator should create a participant profile and record administrative information (e.g. subject ID, year of birth and gender) and treatment arm in the HCP web portal
- Participants should be provided with an eDiary and instructed in how to use it
- The BG meter should be connected with the eDiary
- A fasting SMPG should be measured using the BG meter
- Dispensing and dosing of randomised treatment.

For information regarding the eDiary and HCP web portal please refer to the site guide.
Please refer to Section 6.4 for drug treatment compliance.
All data entered in the eDiary is considered source data. The investigator should review all the data for the participants through the HCP web portal, before or during each visit/phone contact.

Review of eDiaries, ECG, laboratory reports, eye- and physical examinations must be documented in the source documents or the participant's medical record. If clarification of entries or discrepancies in the eDiary is needed, the participant must be questioned, and a conclusion made in the participant's source documents. Care must be taken not to bias the participant.

Source data of clinical assessments performed and recorded in the eCRF must be available and will usually be in the participant's medical records.

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) and in appendix 2 10.2.

8.1.1 Self-measured glucose

Participants will be provided with a blood glucose meter (BG meter) including auxiliaries. The BG meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display.

The BG meter provided by Novo Nordisk should be used for the measurements required in the protocol.

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

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

Pre-breakfast daily self-measured plasma 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).

8.1.2 Continuous glucose monitoring

Participants will be equipped with a CGM device during the treatment period from week 47 (V49) to week 52 (V54). The CGM system used in this study will be the Dexcom G6®. The CGM readings will be blinded to both the participant and investigator and will not be used for any insulin dose titration or hypoglycaemic episode reporting.

If a participant withdraws consent during the study at a timepoint where she/he wears CGM, a site visit should be scheduled in order to remove the CGM sensor and to ensure data upload

CGM fitting and training

The site staff will closely supervise and assist on fitting of the sensor and transmitter on the participant during the site visits. Training in the CGM is the responsibility of the investigator or site staff at the relevant visits. For information on fitting, and changing of the CGM parts, please refer to the Investigator's CGM manual and participant CGM guide provided.

If a participant is to have an x-ray, Magnetic Resonance Imaging, Computed Tomography scan or high-frequency electrical heat (diathermy), the Dexcom G6 sensor, transmitter, and receiver should be removed.

CGM sensor check

The CGM sensor has an in-use period of 10 days. The sensor will automatically stop recording data exactly 10 days after sensor insertion and start. This should be taken into account when scheduling the clinic visits.

The site staff should ensure that the participant has fitted the sensor correctly and that the CGM receiver is working. This will be done during the clinic visit, as specified in the flowchart (Section 1.2).

CGM data upload

CGM data must be uploaded at the site by the site staff to the CGM software following the instruction provided to the sites. The upload will be documented by the system directly. Special visit windows are included to optimize CGM data collection, please see Section 1.2.

The serial number of the CGM receiver must be recorded in the eCRF at the start of each CGM period. In case the CGM receiver is being replaced, the serial number should be updated.

8.1.3 Clinical outcome assessments

This section is only relevant for participants randomised to IcoSema. No clinical outcome assessments will be measured for the participants randomised to insulin icodec. The patient reported outcome questionnaire is to be completed by the participant without assistance of the site personnel. It takes approximately 5 minutes to complete the questionnaire.

The following patient reported outcome questionnaire will be supplied in the eDiary in a linguistically validated version in all languages relevant for this study:

- Diabetes Treatment Preference Questionnaire (DTPQ). The DTPQ will be used to measure the preference of treatment and reasons for preference of participants randomised to IcoSema, considering pre-study basal insulin as comparator. Data will be collected between week 51 and week 52 (V54).

8.1.4 Clinical efficacy

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

8.2 Safety assessments

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

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 IcoSema and insulin icodec 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 trial product in the eCRF.

During the study, starting at randomisation (V2), participants must be instructed to report date, actual dose applied and time of once weekly IcoSema or once weekly insulin icodec in the eDiary. The injection site area of IcoSema and insulin icodec must be reported in the eCRF.

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

8.2.2 Physical examinations

A physical examination will include assessments of:

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

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

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

Body measurements will be measured and recorded in the eCRF. Height will be measured and recorded at screening visit V1. Body weight will be measured and recorded accordingly to the flowchart (Section 1.2). Waist circumference will be measured and recorded at visits V2, V28, V54 and V54A (if applicable).

- Fasting body weight should be measured in kilogram (kg) or pounds (lb) without coat and shoes wearing only light clothing. Body weight will be recorded to one decimal.
- Body weight should be assessed with the same equipment throughout the study, if possible.
- Height should be measured in centimetres (cm) or inches (in) without shoes. Height will be recorded to the nearest whole number.
- The waist 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 waist circumference should be performed and recorded in the eCRF to the nearest ½ cm or ¼ in 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 subject is breathing out gently.

From the body weight and height measured at V1, the body mass index (BMI) should be calculated to evaluate inclusion criteria no.7 and recorded in the participant's medical records

8.2.3 Vital signs

Pulse rate as well as systolic and diastolic blood pressure will be assessed.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., no use of television, cell phones).

Blood pressure and pulse rate measurements will be assessed sitting with a completely automated device. Manual techniques must be used only if an automated device is not available.

Blood pressure and pulse rate are collected at screening (V1), randomisation (V2), V12, V20, V28, V38, V46, V54, and V54A.

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 CRF.

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 CRF.

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 randomisation to assess eligibility. The eye examination should be performed as a fundus photography (e.g., 2-field 60 degree or better, colour or red-free) or by slit-lamp biomicroscopy examination (e.g., using a pre-corneal or corneal contact lens examination). Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination. If diagnostic artificial intelligence algorithms are used an additional eye examination may be necessary if indicated so by the algorithm.

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

It is recommended that high risk T2D patients (individuals with T2D duration of ≥10 years, a baseline HbA1c >8% and confirmed diabetic retinopathy at baseline) will have an additional eye examination in accordance with local standard of care, i.e. every 6-month 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.

Eye examinations required at the visit at week 52 (V54) can be performed within 2 weeks before the visit, if results are available for evaluation at the visit. For participants who discontinue randomised treatment, eye examination can be performed up to 2 weeks after visit 54A. The investigator should examine the outcome of each eye examination. Relevant findings before randomisation must be recorded as concomitant illness/medical history. While relevant findings occurring after randomisation should be reported as an AE, please refer to Section 8.3 and Appendix 3 (Section 10.3).

8.2.5 Electrocardiograms

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 randomisation (V2) but at the latest at randomisation (V2). The results must be interpreted by the investigator before randomisation in order to determine the eligibility of the participant.

The ECG required at the visit at 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 randomisation 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 protocol flowchart (Section 1.2) and the laboratory manual.

8.2.7 Pregnancy testing

Woman 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 11 (Section 10.11).

8.3 Adverse events and other safety reporting

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

The definition of AEs and SAEs can be found in Appendix 3 (Section 10.3), along with a description of AEs requiring additional data collection. The definition and description of events for adjudication can be found in Appendix 9 (Section 10.9).

Some AEs require additional data collection on a specific event form. The relevant event(s) are listed below in Table 8-1, together with event(s) for adjudication and other events requiring collection of additional information.

Events for adjudication require completion of an adjudication form, please refer to Appendix 9 (Section 10.9).

Table 8-1 AEs requiring additional data collection, events for adjudication and other events requiring collection of additional information

Event type	AE requiring additional data collection	Event for adjudication	Other events requiring collection of additional information
Medication error	X		
Misuse and abuse	X		
Hypersensitivity	X		
Injection site reactions	X		
Acute gallbladder diseases	X		
Malignant neoplasms	X		
Hypoglycaemic episodes			X
Death		X	
Acute coronary syndrome (including acute myocardial infarction and unstable angina pectoris requiring hospitalisation)		X	
Cerebrovascular event (including stroke and transient ischemic attack)[a]		X	
Heart failure (including requiring hospitalisation and urgent heart failure visit)		X	

[a] All cerebrovascular events are to be reported and sent for adjudication, however the EAC will only confirm strokes

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 and Appendix 9 (Section 10.9) for events requiring adjudication.

8.3.1 Time period and frequency for collecting adverse event information

All AEs and SAEs must be collected from first administration of randomised treatment and until the last follow-up 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 identified during screening or during other study-related procedures performed before exposure to randomised treatment, 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 within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

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

8.3.2 Method of detecting adverse events

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

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

8.3.3 Follow-up of adverse events

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 serious adverse events

Prompt notification by the investigator to Novo Nordisk of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, 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 in female participants will be collected after first exposure to IMP and until the new-born infant is one month of age. For details regarding collection and reporting of pregnancy information, please refer to Appendix 4 (Section 10.4).

8.3.6 Technical complaints

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

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

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

8.4 Pharmacokinetics

Samples will be used to evaluate the PK of insulin icodec and semaglutide. For participants randomised to IcoSema, PK samples of insulin icodec and semaglutide will be collected, and for

participants randomised to insulin icodec, PK samples of insulin icodec will be collected. PK samples will be collected at the visits outlined in the flowchart (Section 1.2). The investigator must record the exact date and time for blood sampling in the laboratory requisition form.

Procedures for sampling, handling, storage, labelling and shipments of the specimens must be performed in accordance with the laboratory manual. A randomisation list will be provided to the special laboratory.

Bioanalysis of insulin icodec samples will be performed at a special laboratory using a validated luminescent oxygen channelling immunoassay. The exact method will be outlined in a bioanalytical report. Bioanalysis of semaglutide samples will be performed at a special laboratory using a validated Liquid Chromatography Mass Spectometry assay. The exact methods will be outlined in a bioanalytical report.

Genetic analyses will not be performed on these plasma/serum/whole blood samples. Participant confidentiality will be maintained.

For retention of metabolism samples (PK samples), please refer to Appendix 6 (Section 10.6).

Participants should be instructed to report dosing information in the eDiary as per Section 8.2.1.

The investigator will not be able to review the PK analysis report during the study, as the results will only be available after the last participant's last visit. Results from the PK analyses measured according to the flowchart (Section 1.2) will be available to Investigators after the completion of the study.

8.5 Genetics

Not applicable for this study.

8.6 Biomarkers

Not applicable for this study.

8.7 Immunogenicity assessments

8.7.1 Anti-drug antibodies

Anti-drug antibody samples will be collected according to the flowchart (Section 1.2). For participants randomised to IcoSema, anti-insulin icodec antibody samples and anti-semaglutide antibody samples will be collected. For participants randomised to insulin icodec, anti-insulin icodec antibody samples will be collected.

All samples must be drawn before administration of randomised treatment if randomised treatment administration is planned on the sampling day. Assessment of anti-drug antibodies in serum will be performed at a Novo Nordisk appointed laboratory. For details on blood sampling, serum preparation and storage, please refer to the laboratory manual.

Analysis for anti-drug antibodies will be done as listed in flowchart (Section 1.2) with a binding anti-drug antibody assay. Positive samples to insulin icodec will be further characterised for titre,

and cross-reactivity to human insulin. Positive samples to anti-semaglutide antibodies will be further characterised for titre, and cross-reactivity to human GLP-1.

Detailed description of the assay methods will be included in an analytical report. Antibody assays were validated according to international guidelines and recommendations.

At the end of the study, the following data will be transferred to the Novo Nordisk database:

- Anti-insulin icodec binding antibodies (positive/negative)
- Anti-semaglutide binding antibodies (positive/negative)
- Titre of anti-insulin icodec antibody positive samples
- Titre of anti-semaglutide antibody positive samples
- Anti-insulin icodec binding antibodies cross-reacting with human insulin status (positive/negative)
- Anti-semaglutide binding antibodies cross-reacting with human GLP-1 status (positive/negative).

The investigator will not be able to review the results of antibody measurements in relation to AEs as the results will only be available after the last participant's last visit. Results from the binding anti-drug antibody analyses measured according to the flowchart (Section 1.2) will be available to Investigators after the completion of the study.

For retention of antibody samples, please refer to Appendix 6 (Section 10.6).

8.7.2 Hypersensitivity

Participants randomised to IcoSema or insulin icodec and investigators will be instructed to detect signs and symptoms of systemic hypersensitivity.

In the event of a systemic hypersensitivity reaction (not locally at the injection site), the participant should be called in as soon as possible to have additional blood samples taken (Section 10.2).

The blood sampling should be repeated 2-4 weeks following onset of the systemic hypersensitivity reaction. If possible, the tests should also be performed on samples drawn before first administration of IcoSema or insulin icodec.

For details related to blood sampling, plasma preparation and storage, please refer to the laboratory manual.

Analysis will be performed by Novo Nordisk or a Novo Nordisk appointed special laboratory (please refer to Attachment I). The results will be reported in a separate report and attached to the clinical study report.

For retention of residual hypersensitivity samples, please refer to Appendix 6 (Section 10.6).

Digital pictures

For participants randomised to IcoSema and icodec the investigator or the participant must take digital pictures of the affected area at time of identification, using any device available (mobile

phone, camera etc.) and thereafter as often as judged necessary by the investigator. The pictures should include subject ID, date and time, time after dosing and a ruler for scaling. All pictures must be stored as part of source documentation at site.

9 Statistical considerations

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

9.1 Statistical hypotheses

The primary objective is to show that IcoSema is superior to insulin icodec in terms of change in HbA_{1c} from baseline week 0 (V2) to week 52 (V54).

Formally, let D be the mean treatment difference 'IcoSema' minus 'insulin icodec' of the change in HbA_{1c} (%) from baseline week 0 (V2) to week 52 (V54). The null-hypothesis of IcoSema not being superior will be tested against the alternative hypothesis of superiority as given by

$$H_0: D \geq 0\% \text{ against } H_A: D < 0\%$$

Superiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval for D is strictly below 0 %.

The following sections detail the confirmatory secondary hypotheses. The confirmatory secondary objectives are to show that:

- IcoSema is superior to insulin icodec in terms of change in body weight from baseline week 0 (V2) to week 52 (V54)
- IcoSema is superior to insulin icodec in terms of number of hypoglycaemic episodes (level 2 and 3 combined) from baseline week 0 (V2) to week 57 (V56)

Formally, let D_W be the mean treatment difference 'IcoSema' minus 'insulin icodec' in change in body weight (kg) from baseline week 0 (V2) to week 52 (V54). The null-hypothesis of IcoSema not being superior will be tested against the alternative hypothesis of superiority as given by:

$$H_0: D_W \geq 0 \text{ kg against } H_A: D_W < 0 \text{ kg.}$$

Superiority will be considered confirmed if the test procedure was not stopped, see section 9.1.1 for details on the testing procedure, and if the upper bound of the two-sided 95% confidence interval for D_W is strictly below 0 kg.

Let RR be the rate ratio 'IcoSema' compared to 'insulin icodec' of the rate of hypoglycaemic episodes (level 2 and level 3 combined). The null-hypothesis of IcoSema not being superior will be tested against the alternative hypothesis of superiority as given by:

$$H_0: RR \geq 1 \text{ against } H_A: RR < 1.$$

Superiority will be considered confirmed if the test procedure was not stopped, see section 9.1.1 for details on the testing procedure, and if the upper bound of the two-sided 95% confidence interval for RR is strictly below 1.

9.1.1 Multiplicity adjustment

The type I error will be controlled in the strong sense using a hierarchical (fixed sequence) testing procedure. This is based on priority ordering of the null hypotheses and testing them in this order using the 2-sided 95% confidence interval approach until an insignificant result appears. Consequently, the null hypothesis will only be tested if the previous null hypotheses have been rejected in favour of IcoSema.

The steps in the hierarchical testing procedure are as follows:

- Step 1: Change in HbA_{1c} from baseline week 0 (V2) to week 52 (V54) superiority of IcoSema versus insulin icodec
- Step 2: Change in body weight from baseline week 0 (V2) to week 52 (V54) superiority of IcoSema versus insulin icodec
- Step 3: Number of hypoglycaemic episodes (level 2 and 3 combined) from baseline week 0 (V2) to week 57 (V56) superiority of IcoSema versus insulin icodec.

9.2 Analysis sets

The following populations are defined:

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

The following data points sets are defined:

Data points sets	Description
In-study	All data from randomisation until the last date of any of the following: • The last direct participant-site contact • Withdrawal for participants who withdraw their informed consent • The last participant-investigator contact as defined by the investigator for participants who are lost to follow-up (i.e. possibly an unscheduled phone visit) • Death for participants who die before any of the above
On-treatment	All data from the date of first dose of randomised treatment as recorded on the eCRF until the first date of any of the following: • The last follow-up visit (V56) • The last date on randomised treatment +6 weeks (corresponding to 5 weeks after the end of the dosing interval for both treatment arms) • The end-date for the in-study data points sets

The on-treatment data points set represent data collected in the period in which a participant is considered exposed to randomised treatment.

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

The full analysis set and the in-study data points set will be used to estimate the primary estimand and the confirmatory secondary estimand related to body weight. For the confirmatory secondary estimands related to hypoglycaemic episodes the full analysis set and the on-treatment data points set will be used.

9.3 Statistical analyses

9.3.1 General considerations

Baseline is defined as information collected at week 0 (V2). In case a measurement is not available at week 0 (V2) the most recent measurement prior to week 0 (V2) will be used as baseline.

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

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

- Randomised treatment: Once weekly IcoSema, Once weekly insulin icodec
- Region: Asia, Europe, North America, Other

The regions will be defined as follows:

- Asia: Japan, China, Taiwan, South Korea
- Europe: Italy, Poland, Serbia, Romania, Bulgaria, Croatia, Belgium, Finland, Norway, Portugal
- North America: United States
- Other: India, South Africa, Turkey, Russia, Mexico, Australia

9.3.2 Primary estimand analysis

The primary endpoint is change in HbA_{1c} from baseline week 0 (V2) to week 52 (V54).

The estimand (see Section 3), will be estimated based on the full analysis set using the in-study data points set which includes all HbA_{1c} measurements obtained at week 52 (V54) especially measurements from participants experiencing intercurrent events. The imputation approach for the primary estimand is a multiple imputation similar to the one described by McEvoy.[22]

- Missing HbA_{1c} measurements at week 52 (V54) for participants experiencing intercurrent events will be imputed from participants experiencing intercurrent events and have a measurement at week 52 (V54) in each treatment arm.
- Missing HbA_{1c} measurements at week 52 (V54) for participants not experiencing intercurrent events are imputed from available measurements at week 52 (V54) from participants not experiencing intercurrent events in each treatment arm.

The multiple imputation approach will be done the following way:

- Imputation: An ANCOVA model for change in HbA_{1c} from baseline week 0 (V2) to week 52 (V54) for participants experiencing intercurrent events and have a measurement at week 52 (V54) with randomised treatment as fixed factor, last available planned on-treatment HbA_{1c}

observation without initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks, the time point (study day) of last available planned on-treatment HbA_{1c} observation without initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks and baseline HbA_{1c} as covariate. If participants not experiencing intercurrent events are missing measurements at week 52 (V54) an ANCOVA model will be defined in a similar way using available data from participants not experiencing intercurrent events. The estimated parameters, and their variances, from the imputation models will be used to impute missing HbA_{1c} measurements at week 52 (V54). This will be done 1000 times and results in 1000 complete datasets.

- For each of the complete data sets, the primary endpoint will be analysed using an ANCOVA model with region and randomised treatment as fixed factors, and baseline HbA_{1c} as covariate. The estimates and standard deviations for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.[23]
- From the pooled estimate and standard deviation the 95% confidence interval for the treatment difference will be calculated. The corresponding two-sided p-value will also be calculated.

This analysis has the underlying assumption that participants with missing data behave similarly as comparable participants within the same treatment arm i.e. that participants experiencing intercurrent events with missing data at week 52 (V54) behave like participants experiencing intercurrent events with data at week 52 (V54) within the same treatment arm and similar for participants not experiencing intercurrent events.

9.3.2.1 Sensitivity analysis

The following sensitivity analysis will evaluate the robustness of the results towards the missing data assumption.

For the primary endpoint, a two-dimensional tipping point analysis will be performed where participants having imputed HbA_{1c} measurement at week 52 (V54) are assumed to have a worse outcome in the IcoSema arm and a better outcome in the insulin icodec arm compared to what was imputed in the primary analysis. This is done by adding or subtracting values Δ_i to the imputed HbA_{1c} values before analysing the data. The value of Δ_i will be varied independently in the two treatment arms. The plausibility of the values of Δ_i where the conclusion of the primary analysis change will be evaluated to assess the robustness of the primary analysis results.

9.3.3 Secondary estimand analyses

9.3.3.1 Confirmatory secondary estimands

9.3.3.1.1 Estimand related to change in body weight from baseline week 0 (V2) to week 52 (V54)

The secondary estimand regarding change in body weight from baseline week 0 (V2) to week 52 (V54) will be estimated using a model similar to the primary analysis above substituting body weight for HbA_{1c}.

The robustness of the results towards the missing data assumption will be evaluated using an method following similar principles as for the primary estimand.

9.3.3.1.2 Estimand related to number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L [54 mg/dL], confirmed by BG meter) or severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 57 (V56)

The secondary estimand regarding number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L [54 mg/dL], confirmed by BG meter) or severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 57 (V56) will be analysed as described below. The endpoint is defined as described in Appendix 7 (Section 10.7).

For participants who discontinued randomised treatment, the number of episodes in the period where hypoglycaemic episodes are not collected (the period from time of follow-up 2 visit (V56) to planned end of the on-treatment data point set) will be imputed using a multiple imputation technique, assuming that the episode rate pre-follow-up 2 (V56) follows the respective treatment arms rate whilst post-follow-up 2 (V56) episode rate is the rate of the comparator arm. The imputation will be done as follows:

- First, a Bayes negative binomial model with log-link function is fitted to the number of episodes data for participants in the comparator arm to obtain the posterior distribution of model parameters. The model will include region as fixed factor and the logarithm of the time period in which a participant is considered exposed to randomised treatment as offset.

- Second, based on the estimated parameters for the comparator arm in this model, the number of episodes in the missing period will be imputed for participants having discontinued randomised treatment. One thousand (1000) complete dataset are generated by sampling from the estimated distribution.

- For each of the complete datasets, the number of episodes will be analysed using a negative binomial model with log-link function, treatment and region fixed factors and offset as described in step 1. The estimates and standard errors for the 1000 data sets will be pooled to one estimate and associated standard deviation using Rubin's rule.[23]

- From the pooled estimate and standard deviation the 95% confidence interval will be calculated and back-transformed to the original scale resulting in a treatment ratio and a 95% confidence interval for the treatment ratio. The corresponding two-sided p-value will also be calculated.

The analysis has the underlying assumption that participants discontinuing randomised treatment behave similarly to participants in the comparator arm after the follow-up period. The robustness of the results towards the missing data assumption will be evaluated using a method following similar principles as for the primary estimand.

9.3.3.2 Supportive secondary estimands

Details on analysis of secondary estimands related to supportive secondary endpoints will be included in a SAP.

9.3.4 Exploratory estimand analysis

Not applicable for this study.

9.3.5 Other safety analyses

The standard safety assessments (AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively; including any notable changes of clinical interest in laboratory parameters.

9.3.6 Other analyses

9.3.6.1 Pharmacokinetic modelling

Insulin icodec serum concentration data and semaglutide plasma concentration data will be used for population PK analysis. The objective of the population PK analysis is to evaluate the effects of relevant covariates on insulin icodec and semaglutide exposure.

The population PK analysis will be performed by Quantitative Clinical Pharmacology, Novo Nordisk. A more technical and detailed elaboration of the population PK analysis will be given in a modelling analysis plan, which will be prepared before database lock. In brief, previously developed PK models for insulin icodec and semaglutide will be applied. The absorption rate constants in the models will be fixed, and the apparent clearance and volume of distribution parameters will be re-estimated. The covariates of interest will be incorporated into the PK models using criteria which will be specified in the modelling analysis plan.

The population PK analysis will be reported in a separate modelling report, which will not be part of the clinical study report. The individual insulin icodec serum concentration data and the individual semaglutide plasma concentration data will be tabulated in the bioanalytical report.

9.4 Interim analysis

Not applicable for this study.

9.5 Sample size determination

The sample size is determined in order to have at least 90% power for meeting the primary hypothesis and reasonable marginal power (at least 90%) for also meeting the confirmatory secondary hypotheses.

It is assumed that the amount of participants experiencing an intercurrent event will be similar to what was observed in the subcutaneous semaglutide for T2D development program, and that the intercurrent events will have the same impact on effect size and are equally distributed between treatment arms. The amount of participants experiencing an intercurrent event ranged from 14.1% to 25.7% in open-label studies with various durations except for semaglutide 0.5 mg in the Japan studies, see Table 9-1. Based on this the percentage of participants experiencing an intercurrent event is expected to be 17%.

Table 9-1 Participants experiencing an intercurrent event – open-label subcutaneous semaglutide for diabetes studies (NN9535)

Study ID	Description	Study duration	Participants experiencing intercurrent events (%)	
			Semaglutide 0.5 mg	Semaglutide 1.0 mg
3624	SUSTAIN 3: Semaglutide 1.0 mg vs. Exenatide ER 2.0 mg	56 weeks		25.7
3625	SUSTAIN 4: Semaglutide 1.0/0.5 mg vs. Insulin glargine	30 weeks	17.4	17.8
4216	SUSTAIN 7: Semaglutide 1.0/0.5 mg vs. Dulaglutide 1.5/0.75 mg	40 weeks	16.6	16.6
4339	SUSTAIN 10: Semaglutide 1.0 mg vs. Liraglutide 1.2 mg	30 weeks		15.5
4092	SUSTAIN Japan: Semaglutide 1.0/0.5 mg vs. Sitagliptin	30 weeks	3.9	14.7
4091	SUSTAIN Japan: Semaglutide 1.0/0.5 mg vs. One additional OAD	56 weeks	6.3	14.1

Participants experiencing an intercurrent event is participants discontinuing randomised treatment or initiating rescue medication. The definition of rescue medication differ across the studies and is different from the current study.

For the primary hypothesis and confirmatory secondary hypothesis that IcoSema is superior to insulin icodec in terms of change from baseline to week 52 (V54) in HbA_{1c} and body weight respectively, the sample size considerations are based on the IDegLira (insulin degludec/liraglutide) studies where participants are previously treated with a basal insulins, see Table 9-2.

Table 9-2 HbA_{1c} and body weight results – IDegLira studies (NN9068)

Study ID	Description	Study duration	Change from baseline in HbA_{1c} (%-point)		Change from baseline in body weight (kg)	
			ETD [95% CI]	SD	ETD [95% CI]	SD
3912	DUAL II: IDegLira vs. IDeg	26 weeks	-1.04 [-1.25;-0.84]	1.0	-2.51 [-3.21;-1.82]	3.5
3952	DUAL V: IDegLira vs. IGlar	26 weeks	-0.66 [-0.80;-0.52]	0.8	-3.20 [-3.77;-2.64]	3.4
4184	DUAL II Japan: IDegLira vs. IDeg	26 weeks	-1.23 [-1.45;-1.01]	0.8	-1.41 [-2.26;-0.56]	3.1
4166	DUAL II China: IDegLira vs. IDeg	26 weeks	-0.92 [-1.09;-0.75]	0.9	-1.13 [-1.72;-0.55]	3.0

CI: Confidence interval, ETD: Estimated treatment difference, IDeg: Insulin degludec, IGlar: Insulin glargine, IDegLira: insulin degludec/liraglutide, SD: Standard deviation. In the DUAL II studies the insulin degludec dose was capped at 50 units. Data from after participants discontinuing randomised treatment were not collected in the studies. Change from baseline in HbA_{1c} and change from baseline in body weight for DUAL II China were analysed using a mixed-effect model for repeated measurements. Change from baseline in body weight for DUAL II, DUAL II Japan and DUAL V were analysed using an analysis of variance model where missing data was imputed using last observation carried forward.

However, the current study and the IDegLira studies in Table 9-2 are different in key study design aspects such as: in the IDegLira studies the insulin degludec dose was capped at 50 units (except NN9068-3952), the titration target was lower (4.0-5.0 mmol/L [72-90 mg/dL]), the study duration was shorter, the population was different e.g. pre-study basal insulin dose was 20-50 units per day and for participants discontinuing randomised treatment data were not collected after discontinuation and hence not included. In addition the statistical methods to be used in the current study also differ. The differences across development programmes are expected to impact the expected treatment differences. Based on these considerations it is considered reasonable to be able to detect a treatment difference of at least a -0.33%-point in change in HbA_{1c} between the treatment arms for participants not experiencing intercurrent events and no treatment difference for

participants experiencing intercurrent events. Thus, with 17% of participants expected to experience any of the specified intercurrent events before week 52 (V54), this leads to a mean treatment difference of (1-0.17) · -0.33%-point = -0.274%-point for the specified primary estimand in the overall population. The standard deviation (SD) is assumed to be 1.1%-point based on the IDegLira studies.

To be able to detect a treatment difference of -0.274%-point with the above considerations it requires 680 participants to ensure 90% power.

Based on the same considerations as above for change in HbA_{1c} it is considered reasonable to be able to detect at least a -2.5 kg difference for change in body weight between treatment arms for participants not experiencing intercurrent events and no treatment difference for participants experiencing intercurrent events. Thus, with 17% of participants expected to experience any of the specified intercurrent events before week 52 (V54), this leads to a mean treatment difference of (1-0.17) · -2.5kg = -2.075kg for the specified secondary estimand in the overall population. The standard deviation (SD) is assumed to be 4.5 kg based on the IDegLira studies.

To be able to detect a treatment difference of -2.075kg with the above considerations it requires 200 participants to ensure 90% power.

For the confirmatory secondary hypothesis that IcoSema is superior to insulin icodec in terms of number of hypoglycaemic episodes (level 2 and 3 combined) the sample size considerations are based on results from IDegLira studies for severe or BG confirmed hypoglycaemic episodes, see Table 9-3. However considering that the hypoglycaemic episode definition is different and the titration target is higher in the current study, which result in fewer hypoglycaemic episodes,[24] it is therefore expected that participants treated with IcoSema will experience 0.8 hypoglycaemic episodes (level 2 and 3 combined) per year compared to 0.8 / 0.65 = 1.23 episodes per year for participants treated with insulin icodec (Expected Rate ratio (RR) of 0.65). It is assumed that there is no treatment difference in rates after experiencing intercurrent events, corresponding to a treatment ratio of 1 in this period. Discontinuation of randomised treatment is assumed to be distributed equally over the study duration. Thus, with 17% of participants expected to experience any of the specified intercurrent events before week 52 (V54), this leads to an expected RR of 1 · 0.17 / 2 + 0.65 · (1 - 0.17 / 2) = 0.68 for the specified secondary estimand in the overall population. The dispersion parameter is assumed to be 3.6 based on the IDegLira studies.

Table 9-3 Severe or BG confirmed hypoglycaemic episodes results – IDegLira studies (NN9068)

Study ID	Description	Episode rate per year		Estimated rate ratio [95% CI]	Dispersion parameter
		IDegLira	Comparator		
3912	DUAL II: IDegLira vs. IDeg	1.2	1.8	0.66 [0.39; 1.13]	5.7
3952	DUAL V: IDegLira vs. IGlar	1.3	2.9	0.43 [0.30; 0.61]	3.3
4184	DUAL II Japan: IDegLira vs. IDeg	2.2	1.9	1.16 [0.57; 2.34]	5.2
4166	DUAL II China: IDegLira vs. IDeg	0.3	0.5	0.53 [0.30; 0.94]	3.2

CI: Confidence interval, IDeg: Insulin degludec, IGlar: Insulin glargine, IDegLira: insulin degludec/liraglutide. In the DUAL II studies the insulin degludec dose was capped at 50 units. The number of hypoglycaemic episodes was analysed using a negative binomial regression model.

From the above assumptions 1290 participants will be required to ensure sufficient marginal power (90%) for the confirmatory secondary hypothesis that IcoSema is superior to insulin icodec in terms of number of hypoglycaemic episodes (level 2 and 3 combined) and this is the hypothesis determining the sample size.

In table Table 9-4 the assumptions the sample size calculation is based on is summarised along with the marginal and joint power with 1290 participants.

Table 9-4 Sample size assumptions and power with 1290 randomised participants

Hypothesis	Assumptions	Randomised participants	Marginal power	Joint power
Change in HbA_{1c}, superiority	Treatment difference: -0.33%-point Standard deviation: 1.1% Intercurrent events: 17% Treatment difference adjusted: -0.274%-point	1290	99.4%	99.4%
Change in body weight, superiority	Treatment difference: -2.5 kg Standard deviation: 4.5 kg Intercurrent events: 17% Treatment difference adjusted: -2.075kg	1290	>99.9%	99.4%
Number of hypoglycaemic episodes (level 2 and 3 combined), superiority	Rate ratio: 0.65 IcoSema episode rate per year: 0.8 icodec episode rate per year: 1.23 Intercurrent events: 17% Rate ratio adjusted: 0.68 Dispersion parameter: 3.6	1290	90%	89.5%

The joint power is calculated under the assumption of independence of the hypotheses by multiplying the respective marginal powers.

The sample size calculation above is sensitive to the assumptions made for the confirmatory secondary hypothesis of superiority in terms of number of hypoglycaemic episodes (level 2 and level 3 combined), and in Table 9-5 the power is presented for different rate assumptions.

Table 9-5 Power with different rates for level 2 and 3 (combined) hypoglycaemic episodes

Randomised participants	IcoSema episode rate per year	icodec episode rate per year	Rate ratio	Adjusted rate ratio	Marginal power	Joint power
1290	1.0	1.54	0.65	0.68	91.2%	90.7%
1290	0.8	1.23	0.65	0.68	90.0%	89.5%
1290	0.6	0.92	0.65	0.68	88.0%	87.5%
1290	1.0	1.42	0.70	0.73	77.0%	76.5%
1290	0.8	1.14	0.70	0.73	75.1%	74.7%
1290	0.6	0.86	0.70	0.73	72.2%	71.8%
1290	1.0	1.33	0.75	0.77	60.9%	60.5%
1290	0.8	1.07	0.75	0.77	58.9%	58.6%
1290	0.6	0.80	0.75	0.77	56.0%	55.6%

Adjusted rate ratio is adjusted for 17% of participants experiencing intercurrent events. Dispersion parameter is set to 3.6.

From the above assumptions and requirements for the primary and confirmatory secondary analyses, 1290 participants will be randomly assigned to treatment. This will ensure sufficient marginal power of 90% for confirming superiority for the primary and the confirmatory hypotheses, and a joint power of 89.5%.

9.6 Partial database lock

A partial database lock may be performed at the end of the treatment period for all participants, i.e. after the date of the last participant last treatment visit. The database will be updated after the partial database lock to include remaining safety information. The full database lock will be performed after the date of the last participant last visit.

The analysis of the primary endpoint and all other efficacy endpoints will be performed based on the data from the partial database lock. Analysis of safety data will be performed after the full database lock. This approach is implemented to allow earlier availability of IcoSema to a T2D patient population in need of treatment intensification expected to benefit from an insulin and GLP-1 combination product. A detailed plan for data handling and operational aspects of the partial database lock and the database update will be finalised before the partial database lock.

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[25] and applicable ICH Good Clinical Practice (GCP) Guideline[26]
- Applicable laws and regulations

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

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

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

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

The investigator will be responsible for:

- providing written summaries of the status of the study annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- ensuring submission of the CSR synopsis to the IRB/IEC
- reporting any potential serious breaches to the sponsor immediately after discovery

10.1.2 Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and one year after completion of the study.
Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

10.1.3 Informed consent process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. This includes the use of an impartial witness where required according to local requirements.

The investigator must ensure the participant ample time to come to a decision whether or not to participate in the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH GCP[26] guidelines, Declaration of Helsinki,[25] privacy and data protection requirements, where applicable, and the IRB/IEC or site.

The medical record must include a statement that written informed consent was obtained before any study-related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any study-related activity.

The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.

Participants must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

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

10.1.4 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.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

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

10.1.6.2 Event adjudication committee

An independent external EAC is established to perform ongoing blinded adjudication of selected AEs and deaths (see Table 8-1 and Appendix 9 (Section 10.9)).

The EAC will evaluate events sent for adjudication using pre-defined definitions and guidelines in accordance with the EAC charter. The evaluation is based on review of pre-defined clinical data collected by the sites. The EAC is composed of permanent members covering all required medical specialities. EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk. The EAC will have no authority to impact study conduct, study protocol or amendments. The assessments made by both the event adjudication committee and the investigator will be evaluated and included in the CSR.

10.1.7 Dissemination of clinical study data

Study information will be disclosed at clinicaltrials.gov and novonordisk-trials.com and, if applicable, also on other national or regional study registries. It will be disclosed according to applicable requirements, relevant recommendations or regulations, such as the Declaration of Helsinki,[25] the International Committee of Medical Journal Editors (ICMJE),[27] the Food and Drug Administration Amendment Act (FDAAA),[28] European Commission Requirements[1, 29, 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, and review the HCP web portal.

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

The following will be provided as paper CRFs:

- Pregnancy forms

The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints on study intervention not yet allocated to a participant)

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

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

10.1.8.2 Monitoring

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the study. If the electronic source data does not have a visible audit trail, the investigator must provide the monitor with signed and dated

printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone).

Study monitors will perform ongoing source data verification of critical data points to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents. Study monitors will perform ongoing source data review to ensure that the study is being conducted in accordance with the current approved protocol and any other study agreements, ICH GCP[26], 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.

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

10.1.8.3 Protocol compliance

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

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

10.1.9 Source documents

All data entered in the eCRF or paper CRF must be verifiable in source documentation.
Data in the service providers' database is considered source data e.g. laboratory data and CGM. For eDiary (including patient reported outcomes), data in eDiary database is considered source data, unless stated otherwise in source documentation agreements.

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 or paper CRF from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

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

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 must 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 must be able to access his/her study documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other participant data will be provided in an electronic readable format to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. Site-specific CRFs and other participant data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.

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

10.1.11 Study and site closure

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

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

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

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

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

10.1.12 Responsibilities

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

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

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

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. This also includes ensuring that no indirect sharing of user credentials for IT systems used in this study takes place (e.g., by not sharing IT equipment with others in a way where user credentials have the possibility of being shared). The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

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

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

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

10.1.13 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with local laws/acts/guidelines, see Section 10.11 for more information.

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 or two investigators will be appointed by Novo Nordisk to review and sign the CSR (signatory investigators) 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 2content 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 randomisation code after results are available.

10.2 Appendix 2: Clinical laboratory tests

The tests detailed in Table 10-1 and Table 10-2 will be performed by the central laboratory and by the special laboratories.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g., to follow-up on AEs, this must be done at a local laboratory.

The central 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 Standard Operating Procedures. 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, with the exception of the pharmacokinetics and antibodies (sections 8.4 and 8.7.1), as these results will not be available to the investigator until after finalisation of the clinical study report.

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

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

Human bio samples will be stored as described in Appendix 6 (Section 10.6).

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism V2, V12, V20, V28, V38, V46, V54/V54A	• Fasting plasma glucose (FPG)[a] • HbA_{1c} (also at V1)
NOTES: [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, V28, V38, V54/V54A	• Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Thrombocytes • Basophils • Eosinophils • Lymphocytes

Laboratory assessments	Parameters
	• Monocytes • Neutrophils
Biochemistry[a] V1, V12, V28, V38, V54/V54A	• Alanine Aminotransferase (ALT) • Albumin • Alkaline phosphatase (ALP) • Aspartate Aminotransferase (AST) • Creatinine • Potassium • Sodium • Total bilirubin • Gamma-glutamyltransferase (GGT) (only at V1, V28 and 54/V54A)
Lipids V2, V12, V20, V28, V38, V46, V54/V54A	• Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Very low density lipoprotein (VLDL) cholesterol • Triglycerides • Free fatty acids
Pregnancy testing[b] V1, V2, V54/V54A, V56	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test
Anti-drug antibodies V2, V4, V8, V12, V20, V28, V38, V54/V54A, V56	• Anti-insulin icodec binding antibodies (IcoSema and icodec arms) • Anti-semaglutide binding antibodies (IcoSema arm)
Pharmacokinetics (V4, V8, V12, V20, V28, V38, V54/V54A, V56)	• Insulin-icodec serum concentration (IcoSema and icodec arms) • Semaglutide plasma concentration (IcoSema arm)

Other tests
 	
Hypersensitivity samples should be collected as soon as possible after the systemic hypersensitivity reaction, and again 2-4 weeks following onset of the systemic hypersensitivity reaction
	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation (V1).
	
	• In case of systemic hypersensitivity reaction in participants in the IcoSema arm (Section 8.7.2):
	  • Tryptase (optimal 0.5-2 hours post the hypersensitivity reaction)[c]
	  • Total immunoglobulin E (IgE) antibodies[c]
	  • Anti-human insulin IgE antibodies[d]
	  • Anti-insulin icodec IgE antibodies[d]
	  • Anti-insulin icodec binding antibodies[e]
	  • Anti-semaglutide IgE antibodies[d]
	  • Anti-semaglutide binding antibodies.[e]
	
	• In case of systemic hypersensitivity reaction in participants in the icodec arm (Section 8.7.2):
	  • Tryptase (optimal 0.5-2 hours post the hypersensitivity reaction)[c]
	  • Total immunoglobulin E (IgE) antibodies[c]
	  • Anti-human insulin IgE antibodies[d]
	  • Anti-insulin icodec IgE antibodies[d]
	  • Anti-insulin icodec binding antibodies[e]
	
	Hypersensitivity data will not be shared with investigators until after CSR finalisation.

Notes: [a]Details of required actions for increased liver parameters are given in Appendix 3 (Section 10.3).	

Laboratory assessments	Parameters
[b]For women of childbearing potential, as needed, local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC, see Appendix 4 (Section 10.4). [c] Samples collected from Chinese participants will be analysed by a central lab in China. Samples collected from participants in the rest of the world will be analysed by Novo Nordisk Måløv, Denmark [d] Samples will be analysed by Novo Nordisk Måløv, Denmark for all countries except China, where these tests will not be done (see Appendix 11, Section 10.11). [e] Samples collected from Chinese participants will be analysed in a special lab in China. Samples collected from participants in the rest of the world will be analysed by a special lab designated by Novo Nordisk.	

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 adverse event

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 adverse events:

- 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 a serious adverse event

An SAE is any untoward medical occurrence that fulfils at least one of the following criteria:

- **Results in death**

- **Is life-threatening**
  - The term 'life-threatening' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

- **Requires inpatient hospitalisation or prolongation of existing hospitalisation**

  - Hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.
  - Hospitalisation for elective treatment (e.g., elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE.

  Note: Hospitalisations for administrative, study-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for medical or surgical procedures, planned before study inclusion, are not considered AEs or SAEs

- **Results in persistent or significant disability/incapacity**

  - The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

- **Important medical event:**

  - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
  - The following must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:
    - Suspicion of transmission of infectious agents via IMP
    - Risk of liver injury defined as alanine aminotransferase or aspartate aminotransferase >3x UNL and total bilirubin >2x UNL where no alternative aetiology exists (Hy's law)

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

Hypersensitivity:

Systemic hypersensitivity can be manifested as isolated symptoms such as urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain), or as anaphylaxis or anaphylactic shock.

Anaphylaxis is an acute, potentially lethal, multisystem syndrome resulting from the sudden release of mast cell- and basophil-derived mediators into the circulation.[32] It most often results from immunologic reactions to foods, medications, and insect stings, although it can also be induced through nonimmunologic mechanisms by any agent capable of producing a sudden, systemic degranulation of mast cells or basophils[33]. Characteristic symptoms and signs, occurring minutes to a few hours after exposure to potential triggering agents or events may include: flushing, urticaria, angioedema, hoarseness, throat tightness, stridor, wheezing, coughing, shortness of breath, abdominal pain, vomiting, and/or hypotension, dizziness or collapse.

Local hypersensitivity reactions, including rash, redness, pruritus and oedema, may occur at the site of investigational drug injection.

Drug hypersensitivity reactions are the adverse effects of pharmaceutical formulations (including active drugs and excipients) that clinically resemble allergy.[34] They can be allergic and non-allergic.

If a hypersensitivity event is suspected, the participants must contact the site staff as soon as possible for further guidance. All events must be reported, and in case of systemic hypersensitivity, additional information must be provided on a separate form.

Injection site reactions:

If an event of injection site reaction is observed, additional information must be obtained if available on a separate form.

Acute gallbladder diseases:

Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis)

Malignant neoplasms:

Confirmed malignant neoplasm by histopathology or other substantial clinical evidence

Other events requiring collection of additional information

Hypoglycaemic episodes

All hypoglycaemic episodes must be recorded by the participant in the eDiary. Instructions on how to transfer SMPG values to the eDiary will be given to the participants. If the hypoglycaemic episode fulfils the criteria for an SAE the investigator/site must report it as such. One AE form and safety information form can cover several hypoglycaemic episodes, if the participant has not recovered between the episodes. For more information on hypoglycaemic episodes, please refer to Appendix 7 (Section 10.7).

10.3.4 Recording and follow-up of adverse event and/or serious adverse event

10.3.4.1 Adverse event and serious adverse event recording

The investigator will record all relevant AE/SAE information in the CRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event.

There may be instances when copies of source documents (e.g., medical records) for certain cases are requested by Novo Nordisk. In such cases, all participant identifiers, with the exception of the

subject ID, must be redacted on the copies of the source documents before submission to Novo Nordisk.

For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the study at the latest. For sign-off of SAE-related forms, refer to "AE and SAE reporting via paper CRF" later in this section.

Novo Nordisk products used as concomitant medication or NIMP: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as NIMP or concomitant medication in the study, it is important that the suspected relationship is reported to Novo Nordisk, e.g., in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this AE to relevant regulatory authorities.

10.3.4.2 Assessment of severity

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

- **Mild**: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: An AE that is assessed as severe should not be confused with an SAE. Both AEs and SAEs can be assessed as severe.

10.3.4.3 Assessment of causality

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

Relationship between an AE/SAE and the relevant IMP should be assessed as:

- **Probable** - Good reason and sufficient documentation to assume a causal relationship.
- **Possible** - A causal relationship is conceivable and cannot be dismissed.
- **Unlikely** - The event is most likely related to aetiology other than the IMP.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, should be considered and investigated.

The investigator should use the investigator's brochure and/or product information, for marketed products, for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data**.

The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.

The causality assessment is one of the criteria used when determining regulatory reporting requirements

10.3.4.4 Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved**: The participant has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented
- **Recovering/resolving**: The condition is improving, and the participant is expected to recover from the event. This term may also be applicable for AEs ongoing at the time of death (where death was due to another AE).
  Note: For SAEs, this term is only applicable if the participant has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae**: The participant has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved**: The condition of the participant has not improved, and the symptoms are unchanged, or the outcome is not known. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal**: This term is only applicable if the participant died from a condition related to the reported AE. Outcomes of other reported AEs in a participant before he/she died should be assessed as 'recovered/resolved', 'recovering/resolving', 'recovered/resolved with sequelae' or 'not recovered/not resolved'. An AE with a fatal outcome must be reported as an SAE.
- **Unknown**: This term is only applicable if the participant is lost to follow-up

10.3.4.5 Follow-up of adverse event and serious adverse event

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.

If a participant dies during participation in the study or during a recognised follow-up period, the investigator should, upon request, provide Novo Nordisk with a copy of the autopsy report including histopathology.

New or updated information should be recorded in the CRF.

10.3.5 Reporting of serious adverse events

Adverse event and serious adverse event reporting via CRF

Relevant forms must be completed in the CRF.

For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information forms within the designated reporting timelines (see Figure 10-1):

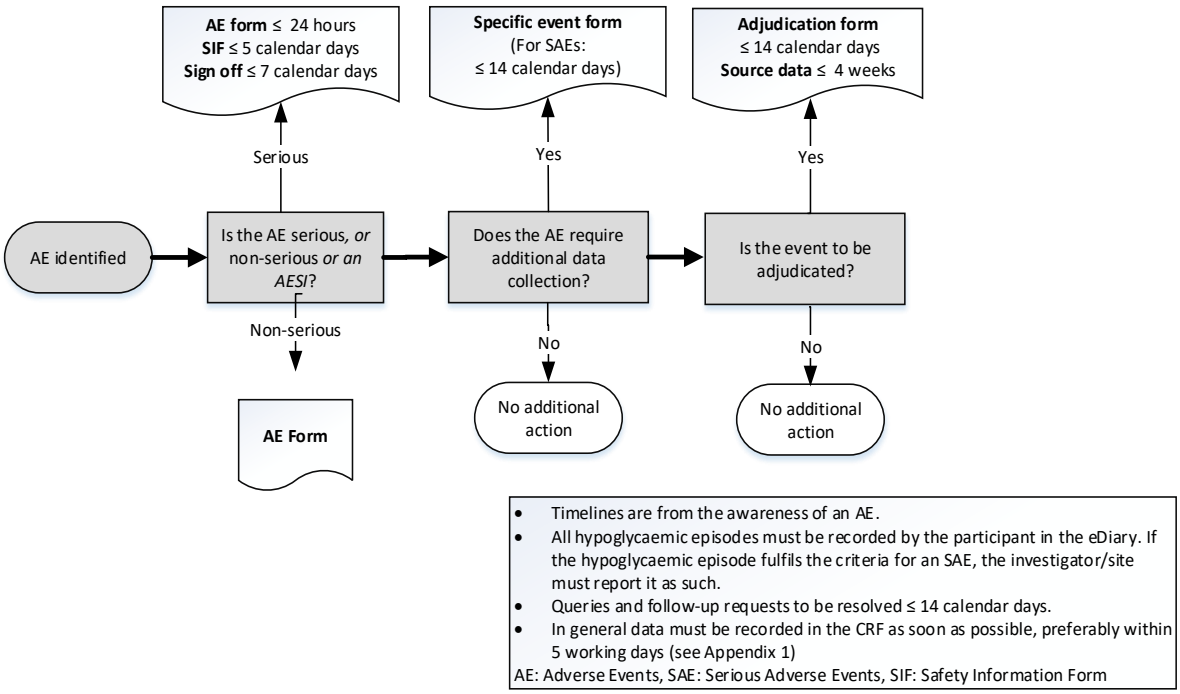
- AE form within 24 hours
- Safety information form within 5 calendar days
- AE form and safety information form must be signed within 7 calendar days after first knowledge by the investigator.
- Specific event form within 14 calendar days.
- For timelines related to events for adjudication, refer also to Appendix 9 (Section 10.9) and Figure 10-1.

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

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

After the study is completed, the study database will be locked, and the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a participant or receives updated information on a previously reported SAE after CRF decommission, the site can report this information on a paper AE and safety information form (see below) or to Novo Nordisk by telephone.

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



For further information on events for adjudication, refer to Appendix 9 (Section 10.9).
If the event adjudication system (EAS) is not available for document upload, the investigator should ensure that the relevant source documents are collected and saved locally until the EAS is available again.

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

10.3.6 Reporting of adverse events for non-Novo Nordisk medical devices

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

All complaints should be reported directly to the manufacturer. Any AEs related to the complaint should be reported to both 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 total hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For females with permanent infertility due to an alternate medical cause other than the above (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining study enrolment.
3. Postmenopausal female:
   - A postmenopausal state is defined as amenorrhoea for at least 12 months without an alternative medical cause in a female > 45 years of age. Alternative medical causes for amenorrhoea include, but are not limited to, hormonal contraception or hormonal replacement therapy.
   - Females ≥ 60 years of age can be considered postmenopausal.

Females on hormone replacement therapy and whose menopausal status is in doubt are considered of childbearing potential and will be required to use one of the 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 required as the risk of teratogenicity/fetotoxicity caused by transfer of insulin icodec or semaglutide in seminal fluid is unlikely.[35]

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly. Table 10-3 lists the highly effective methods of contraception allowed. Local regulations may apply, see Appendix 11 (Section 10.11).

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

Highly effective contraception should be utilised for a least 35 days after last dose of IMP (corresponding to time during treatment and until the end of relevant systemic exposure).

Table 10-3 Highly effective contraceptive methods allowed[36]

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**
• **Vasectomized partner**
Vasectomized 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.

NOTES a. Contraceptive use by men or women should comply with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

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.

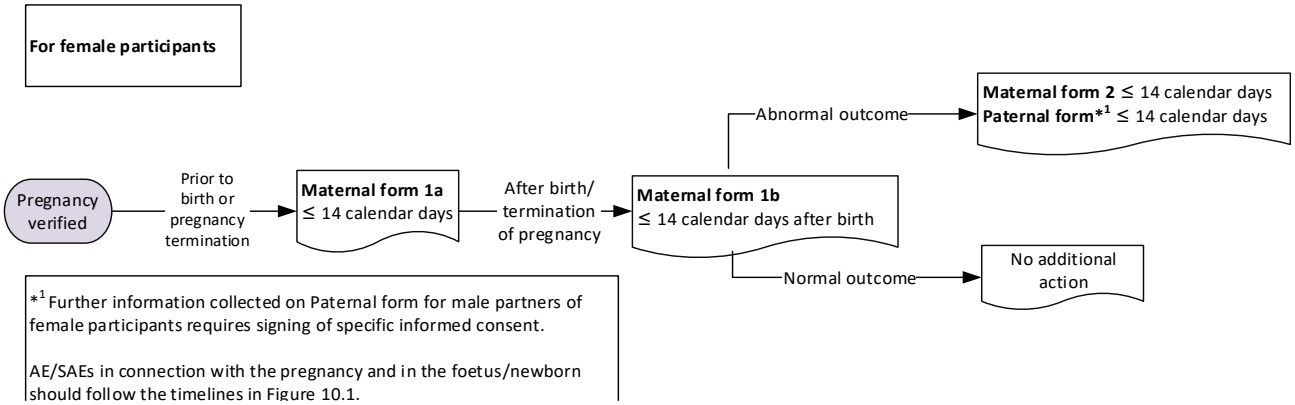
Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

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

Pregnancy outcome should be documented in the 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 randomised treatment.

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

10.5.1 Definition of technical complaint

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

Examples of technical complaints:

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

Time period for detecting technical complaints

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

10.5.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk

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

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

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

Timelines for reporting technical complaints to Novo Nordisk

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

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

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

Follow-up of technical complaints

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

Collection, storage and shipment of technical complaint samples

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

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

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

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

10.6 Appendix 6: Retention of human biosamples

Hypersensitivity reaction samples

In case of a systemic hypersensitivity reaction, the additional blood samples taken in relation to the reaction (Section 8.7 and 10.2) may be retained to follow-up on the hypersensitivity reaction. If deemed relevant by Novo Nordisk, relevant exploratory tests may be performed, e.g. histamine release (basophil activation). If measured, such data will be reported in a separate report.

The samples will be stored at a central laboratory, at a central storage facility, and/or at an analysing laboratory contracted by Novo Nordisk. The samples might be transferred to other countries, if not prohibited by local regulations. Only Novo Nordisk staff and bio-repository personnel will have access to the stored samples. The samples may be shipped to a contract research organisation for analysis.

The samples will be anonymised (identified only by a unique sample ID, visit number, study identification number and sampling date). Confidentiality and personal data protection will be ensured during storage after the end of the study and no direct identification of the participant will be stored together with the samples.

Potential further analyses of the samples will not have any consequences for the participant and their relatives. Participants can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

The samples will be stored at Novo Nordisk or a Novo Nordisk designated referral central bio-repository after the end of the study and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from the end of the study, after which they will be destroyed.

Antibody samples

Antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug, if required by health authorities or for safety reasons. A fraction of the individual participant samples may be pooled and used for further development of antibody assays, or for generating reagents for in study validation and control of future assay performance.

The antibody samples will be stored at Novo Nordisk or at a designated referral central bio-repository after the end of the study and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from the end of the study after which they will be destroyed.

Metabolism samples (PK samples)

Samples for metabolism analysis may be retained for later analysis of metabolites if needed. The samples will be stored at Novo Nordisk or at a designated referral central bio-repository after end of study and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of study after which they will be destroyed.

10.7 Appendix 7: Hypoglycaemic episodes

Table 10-4 Classification of hypoglycaemia

Classification of hypoglycaemia		
Level	Glycaemic criteria	Description
Hypoglycaemia alert value (level 1)	< 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (level 2)	< 3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (level 3)[1]	No specific glucose threshold	[1]Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery
Notes: The Novo Nordisk terms are adapted from The International Hypoglycaemia Study Group,[37] ADA,[38] ISPAD,[39] type 1 diabetes outcomes program,[40] Advanced Technologies & Treatments for Diabetes.[41] Severe hypoglycaemia as defined by Seaquist[42] and ISPAD.[39]		

Severe hypoglycaemia

[1]Severe hypoglycaemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[42]

Nocturnal hypoglycaemia

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

Reporting of hypoglycaemic episodes

Reporting of hypoglycaemic episodes by BG meters:

Plasma glucose (PG) should always be recorded in the (e)diary 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 e-diary. The investigator should ensure correct reporting of the hypoglycaemic episode. In case a participant is not able to fill in the e-diary (e.g., in case of hospitalisation), the investigator should still report the hypoglycaemic episode on the hypoglycaemic episodes form.

Upon onset of a hypoglycaemic episode the participant is recommended to measure PG every 15 minutes until the PG value is ≥3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines.[42]

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.[42]

Please refer to Section 10.3.3 for information regarding reporting of hypoglycaemia in the eDiary.

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 treatment with insulin and combination products containing insulin should be individualised, and the specific titration algorithms may not be applicable in certain clinical situations. Hence, it is important that other information, such as symptoms of hypo/hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the participant's level of glycaemic control, is taken into consideration when decisions on dosing are made. The investigator is responsible for the treatment of the participants and can therefore overrule the guidelines to avoid safety hazards.

Initiation of trial products

At randomisation, eligible participants will be randomised to receive IcoSema or insulin icodec.

IcoSema should be taken once weekly at the same day of the week. The starting dose at randomisation (V2) will be 40 dose steps, which is equivalent to 40 units of insulin icodec and 0.114 mg of semaglutide.

Insulin icodec should be taken once weekly at the same day of the week. All participants should receive a loading dose at randomisation (V2), which consists of total daily basal insulin dose before randomisation 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. In Table 10-5, the weekly V2 and V3 doses for participants receiving from 20 units to 80 units per day have been calculated. Please, note that the displayed values are rounded to the nearest dose that is dividable by 10.

Table 10-5 V2 and V3 doses for participants randomised to insulin icodec

Total daily dose before randomisation	V2 insulin icodec dose	V3 insulin icodec dose	Total daily dose before randomisation	V2 insulin icodec dose	V3 insulin icodec dose
20	210	140	51	540	360
21	220	150	52	550	360
22	230	150	53	560	370
23	240	160	54	570	380
24	250	170	55	580	390
25	260	180	56	590	390
26	270	180	57	600	400
27	280	190	58	610	410
28	290	200	59	620	410
29	300	200	60	630	420
30	320	210	61	640	430
31	330	220	62	650	430
32	340	220	63	660	440
33	350	230	64	670	450
34	360	240	65	680	460
35	370	250	66	690	460
36	380	250	67	700	470
37	390	260	68	710	480
38	400	270	69	720	480
39	410	270	70	740	490
40	420	280	71	750	500
41	430	290	72	760	500
42	440	290	73	770	510
43	450	300	74	780	520
44	460	310	75	790	530
45	470	320	76	800	530
46	480	320	77	810	540
47	490	330	78	820	550
48	500	340	79	830	550
49	510	340	80	840	560
50	530	350			

Dose adjustment of trial products during the study

After randomisation IcoSema and insulin icodec should be adjusted once weekly by the investigator in connection with the visits/phone contacts.

The dose adjustment will be based on the three pre-breakfast SMPG values measured on two days prior to the dose adjustment and on the day of the contact.

If one or more pre-breakfast SMPG values are missing, the dose adjustment should be performed on the remaining SMPG value(s).

Adjustment of IcoSema and insulin icodec will be done in accordance with Table 10-6.

Table 10-6 Adjustment of trial products

Pre-breakfast SMPG			**Icodec adjustment**	**IcoSema adjustment**
Value to use	mmol/L	mg/dL	Units	dose steps
Lowest of the SMPG values	<4.4	<80	-20	-10
Mean of the SMPG values	4.4-7.2	80-130	0	0
	>7.2	>130	+20	+10

Deviations from the algorithm

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

Missing IcoSema and insulin icodec dose guidance

If an IcoSema or insulin icodec dose is missed for ≤ 3 days after the planned dosing day, the participants should inject the planned dose. If the dose is missed for > 3 days, the participants should await the next planned day of injection. Please note that the visit window is +/- 3 days.

Dose recommendation from end of treatment and during follow-up

If it is decided that the participant should continue basal insulin treatment after end of study it is recommended that the participant is switched from IcoSema or insulin icodec to any available daily basal insulin at the discretion of the investigator. The following should be considered:

- Calculate the new *daily* basal insulin dose by dividing the latest IcoSema dose in dose step or insulin icodec dose in units by 7.
- Initiate the new daily basal insulin *two weeks* after the last injection of IcoSema or 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), consider initiating the daily basal insulin dose earlier than two weeks after the last dose of IcoSema or 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.

If it is decided that the participant is switched to a GLP-1 receptor agonist, the start should also await *two weeks* off IcoSema. Thereafter, the treatment can be initiated in accordance with local label for the individual product.

Data collection

The participant should be instructed to report the following:

- Date, dose and time of IcoSema or insulin icodec injections should be reported in the eDiary.
- Injection site area of IcoSema and insulin icodec. The investigator must then register the injection site area in the eCRF
- SMPG values with an indication of "pre-breakfast" or "other" should be reported in the eDiary.
- Hypoglycaemic episodes as described in Appendix 3 (Section 10.3) and Appendix 7 (Section 10.7) should be reported in the eDiary.

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

- IcoSema or insulin icodec doses prescribed at this contact.
- Reasons for deviation from the titration algorithm, if applicable.

Data surveillance

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

Titration data will consist of:

- Relevant SMPG values
- Recommended IcoSema or insulin icodec doses
- Prescribed IcoSema or insulin icodec doses
- Actual IcoSema or insulin icodec doses taken by the participant
- Reasons for deviation from the titration guidelines. Deviations are divided into
  - "hypoglycaemia"
  - "gastrointestinal adverse event"
  - "other, please specify"
- Hypoglycaemia information

It is important that titration data are entered into the eDiary and into the eCRF in a timely manner, as the aim is to reduce the time in which the participant may receive inadequate treatment.

The titration data should be reviewed by Novo Nordisk within 24 hours (on workdays). Novo Nordisk may contact the investigator by phone or via an online portal (CONNECT) after e-mail notification 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).

Novo Nordisk will also monitor changes in HbA_{1c}. Novo Nordisk's medical staff may (virtually) visit at regular intervals to discuss progress in glycaemic control and titration of individual participants.

10.9 Appendix 9: Events requiring adjudication

Event adjudication will be performed in randomised participants. An event for adjudication is a selected AE or death evaluated by an independent external Event adjudication committee (EAC) in a blinded manner, please refer to Table 10-7 for event types in scope.

For details on the EAC, refer to Appendix 1 (Section 10.1.6.2).

Table 10-7 Adverse events requiring event adjudication

Event type (AE category) (serious and non-serious AEs)	**Description**
Death	• All cause death
Acute coronary syndrome (acute myocardial infarction and unstable angina pectoris requiring hospitalisation)	• All types of acute myocardial infarction and unstable angina pectoris requiring hospitalisation
Cerebrovascular event (stroke and transient ischemic attack)	• Episode of focal or global neurological dysfunction that could be caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or ischemia, with or without infarction
Heart failure (requiring hospitalisation and urgent heart failure visits)	• New episode or worsening of existing heart failure leading to an urgent, unscheduled hospital admission or clinic/office/emergency department visit

There are four ways to identify events relevant for adjudication as described below:

1. Investigator-reported events for adjudication: investigator selects the appropriate AE category relevant for adjudication (see Table 10-7).
2. AEs reported with fatal outcome
3. AE search (standardised screening): All AEs not reported with an AE category relevant for adjudication will undergo screening to identify potential events for adjudication. Investigators will be notified of these events in the CRF.
4. EAC-identified events: Unreported events relevant for adjudication identified by the EAC during review of source documents provided for another event for adjudication. Investigators will be notified of these events in the CRF and has the option to report the EAC-identified event.

For each event relevant for adjudication, an event type specific adjudication form should be completed in the CRF within 14 days (Figure 10-1).

Copies of source documents should be uploaded to the EAS as soon as possible and preferably within 4 weeks (Figure 10-1). In cases where the EAS is not accessible for document upload, the investigator should ensure that the relevant source documents are collected and saved locally until the EAS is available. If no, or insufficient source documents are provided to the adjudication supplier, the investigator can be asked to complete a clinical narrative to be uploaded to the EAS.

If new information becomes available for an event sent for adjudication, it is the responsibility of the investigator to ensure the new information is uploaded to the EAS.

An Event Adjudication Site Manual will be provided to each site detailing which source documents are relevant and how these should be provided to the adjudication supplier. The anonymization and labelling requirements are also described in the event adjudication site manual.

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

10.10.1 Definition and scope of appendix

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

In case local restrictions due to a major emergency, e.g. due to a COVID-19 outbreak, 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 10-8 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.

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

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

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

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

10.10.2 Visits

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

Visits 4 and 8 should always be performed as on-site visits to ensure collection of, at least, antibodies and PK samples.

The visit at week 52 (V54) should always be performed as on-site visit. The visit window can be extended for up to 28 days. Participants should continue randomised treatment until the visit at week 52 (V54) takes place.

The last follow-up visit (V56) should always be performed as on-site visit to ensure, at least, collection of antibodies and PK samples.

On-site visits (visits V3, V5, V6, V12, V16, V20, V24, V28, V30, V34, V38, V42, V46, V49, V50, V51, V52, V53, V55) can be converted to remote visits (video, phone or similar) or home or off-site visits.

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

10.10.3 Assessments

Assessments used for safety or the confirmatory endpoints (i.e., HbA1c, and body weight) should be prioritised, as well as antibodies, PK and CGM. The preferred order for the method of assessment is shown in Table 10-8):

HbA_{1c} should be prioritised and be performed on-site at least at V1, V2 and V54.

Body weight should be prioritised and be performed on-site at least at V1, V2 and V54.

Antibodies and PK should be prioritised and be performed on-site at least at V2 (antibodies only), V4, V8, V54 and V56.

CGM fitting and training at V49 should be prioritised and preferably be on-site visit, but if not possible then home and off-site visit can be performed. If not on site remember to perform device initialisation at site before meeting the participant for CGM fitting.

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

The site should instruct the participants in manually stopping the sensor in the receiver menu when each sensor session is complete, and to keep the battery charged.

If not possible to perform V50, V52 and V53 as on-site visit, this can be performed as home, off-site visit or be conducted over the phone or as video call.

CGM fitting at V51 should be prioritised and preferably be on-site visit, but if not possible then home and off-site visit can be performed. CGM data must be uploaded by the site staff to the CGM software.

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

CGM data upload at V54 should be prioritised and be performed as on-site visit. CGM data must be uploaded at the site by the site staff to the CGM software.

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

Specifications regarding how to perform these assessments using remote visits (phone visits or video contact) or as home visits or off-site visits will be provided by Novo Nordisk or the vendor.

All laboratory samples should be analysed at the central and special laboratories. In case of lock down of the site, samples of V1, V2, V4, V8, V54 and V56 should be prioritised, and the Lack of Efficacy Criteria 5, Section 7.1.1 would be evaluated based on the SMPG only (instead of evaluating based on SMPG and FPG).

Home measurements of pregnancy tests and vital signs (other than the ones to be collected at V1, V2 and V54) 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 CRF. Pregnancy tests and equipment to perform vital signs can be delivered to the participants if on-site visits are not possible. The site is responsible for contracting a suitable courier and costs will be reimbursed by Novo Nordisk. Participants´ own home scales cannot be used for measuring body weight.

If the assessments indicated in Table 10-8 cannot be performed as on-site visits, home-visits or remote visits (video, phone or similar), they should be performed at the first possible timepoint following the originally scheduled visit in agreement with Novo Nordisk.

10.10.4 Study intervention

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

VV-CLIN-270392

0.1

Table 10-8 Minimum assessments following randomisation

Please refer to Section 1.2 for the full flowchart.

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

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

Procedures marked with a red X can subsequently be cancelled.

	Protocol Sections	**Screening**	**Randomisation**	**Treatment period**																				**Follow up**		**Discontinuation**
Visit (preferred visit format)		V1	V2	V3	V4	V5	V6	V8	V12	V16	V20	V24	V28	V30	V34	V38	V42	V46	V49	V50	V51	V52	V53	V54	V55	V56	V54A
Alternative visit format				H/O/R/P		H/O/R/P	H/O/R/P		H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P		H/O/R/P		
Weekly Phone Contact number (P)							P7	P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23	P25 P26 P27	P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48									
Timing of Visit (Weeks)		**<-2**	**0**	1	2	3	4	6	10	14	18	22	26	28	32	36	40	44	47	48	49	50	51	**52**	54	57	
Visit Window (Days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-3/+2	±3	±3	±3	**-2/+28**	+3	+3	
Informed Consent and Demography	10.1.3 (App 1)	**X**																									

	Protocol Sections	**Screening**	**Randomisation**	**Treatment period**																					**Follow up**		**Discontinuation**
Visit (preferred visit format)		V1	V2	V3	V4	V5	V6	V8	V12	V16	V20	V24	V28	V30	V34	V38	V42	V46	V49	V50	V51	V52	V53	V54	V55	V56	V54A
Alternative visit format				H/O/R/P		H/O/R/P	H/O/R/P		H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P		H/O/R/P		
Weekly Phone Contact number (P)							P7	P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23	P25 P26 P27	P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48									
Timing of Visit (Weeks)		**<u>+</u>2**	**0**	1	2	3	4	6	10	14	18	22	26	28	32	36	40	44	47	48	49	50	51	**52**	54	57	
Visit Window (Days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-3/+2	±3	±3	±3	**-2/+28**	+3	+3	
Eligibility Criteria	5.1, 5.2	**<u>X</u>**	**<u>X</u>**																								
Concomitant Medication	6.8	**<u>X</u>**	**<u>X</u>**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**<u>X</u>**	X	X	**<u>X</u>**
Medical History/Concomitant Illness	8.2	**<u>X</u>**	**<u>X</u>**																								
Tobacco Use	5.3.2	**<u>X</u>**																									
Childbearing Potential	10.4 (App 4)	**<u>X</u>**																									

	Protocol Sections	**Screening**	**Randomisation**	**Treatment period**																					**Follow up**		**Discontinuation**
Visit (preferred visit format)		V1	V2	V3	V4	V5	V6	V8	V12	V16	V20	V24	V28	V30	V34	V38	V42	V46	V49	V50	V51	V52	V53	V54	V55	V56	V54A
Alternative visit format				H/O/ R/P		H/O/ R/P	H/O/ R/P		H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P		H/O/ R/P		
Weekly Phone Contact number (P)							P7	P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23	P25 P26 P27	P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48									
Timing of Visit (Weeks)		**≤1-2**	**0**	1	2	3	4	6	10	14	18	22	26	28	32	36	40	44	47	48	49	50	51	**52**	54	57	
Visit Window (Days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-3/+2	±3	±3	±3	**-2/+28**	+3	+3	
Pregnancy Test	8.3.5, 10.4 (App 4)	**X**	**X**																					**X**		X	**X**
Body Measurements	8.2.2	**X**	**X**						X		X		X			X		X						**X**			**X**
Body Weight	8.2.2	**X**	**X**						X		X		X			X		X						**X**			**X**
Vital Signs	8.2.3	**X**	**X**						X		X		X			X		X						**X**			**X**
Physical Examination	8.2.2	**X**																						**X**			**X**

	Protocol Sections	**Screening**	**Randomisation**	**Treatment period**																					**Follow up**		**Discontinuation**
Visit (preferred visit format)		V1	V2	V3	V4	V5	V6	V8	V12	V16	V20	V24	V28	V30	V34	V38	V42	V46	V49	V50	V51	V52	V53	V54	V55	V56	V54A
Alternative visit format				H/O/R/P		H/O/R/P	H/O/R/P		H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P		H/O/R/P		
Weekly Phone Contact number (P)							P7	P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23	P25 P26 P27	P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48									
Timing of Visit (Weeks)		**≤-2**	**0**	1	2	3	4	6	10	14	18	22	26	28	32	36	40	44	47	48	49	50	51	**52**	54	57	
Visit Window (Days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-3/+2	±3	±3	±3	**-2/+28**	+3	+3	
ECG	8.2.5	**X**																						**X**			**X**
Eye Examination	8.2.4	**X**																						**X**			**X**
CGM	8.1.2																		[c]	X	[c]	X	X	**X**			
Self Measured Plasma Glucose	8.1.1		**X**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	X	X	

	Protocol Sections	**Screening**	**Randomisation**	**Treatment period**																					**Follow up**		**Discontinuation**
Visit (preferred visit format)		V1	V2	V3	V4	V5	V6	V8	V12	V16	V20	V24	V28	V30	V34	V38	V42	V46	V49	V50	V51	V52	V53	V54	V55	V56	V54A
Alternative visit format				H/O/R/P		H/O/R/P	H/O/R/P		H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P		H/O/R/P		
Weekly Phone Contact number (P)							P7	P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23	P25 P26 P27	P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48									
Timing of Visit (Weeks)		**≤1 2**	**0**	1	2	3	4	6	10	14	18	22	26	28	32	36	40	44	47	48	49	50	51	**52**	54	57	
Visit Window (Days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-3/+2	±3	±3	±3	**-2/+28**	+3	+3	
Adverse Event[a]	8.3, 10.3 (App 3)			X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	X	X	**X**
Laboratory Assessments[b]	10.2 (App 2)	**X**	**X**						X		X		X			X		X						**X**			**X**
HbA1c[b]		**X**	**X**						X		X		X			X		X						**X**			**X**
Antibodies[b]	8.7		**X**		**X**			**X**	X		X		X			X								**X**		**X**	**X**
Pop-PK[b]	8.4				**X**			**X**	X		X		X			X								**X**		**X**	**X**

	Protocol Sections	**Screening**	**Randomisation**	**Treatment period**																				**Follow up**		**Discontinuation**
Visit (preferred visit format)		V1	V2	V3	V4	V5	V6	V8	V12	V16	V20	V24	V28	V30	V34	V38	V42	V46	V49	V50	V51	V52	V53	V54	V55	V56	V54A
Alternative visit format				H/O/R/P		H/O/R/P	H/O/R/P		H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P	H/O/R/P		H/O/R/P		
Weekly Phone Contact number (P)							P7	P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23	P25 P26 P27	P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48									
Timing of Visit (Weeks)		**+/- 2**	**0**	1	2	3	4	6	10	14	18	22	26	28	32	36	40	44	47	48	49	50	51	**52**	54	57	
Visit Window (Days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-3/+2	±3	±3	±3	**-2/+28**	+3	+3	
Hypoglycaemia Unawareness	8.2	**X**																									
Diabetes Treatment Preference Questionnaire (IcoSema arm only)[d]	8.1.3																							**X**			**X**
Drug Dispensing	6		**X**						X		X		X			X		X									
Training in Trial Product, Pen-handling	6.1		**X**	X				X	X		X		X			X		X									

	Protocol Sections	**Screening**	**Randomisation**	**Treatment period**																					**Follow up**		**Discontinuation**
Visit (preferred visit format)		V1	V2	V3	V4	V5	V6	V8	V12	V16	V20	V24	V28	V30	V34	V38	V42	V46	V49	V50	V51	V52	V53	V54	V55	V56	V54A
Alternative visit format				H/O/ R/P		H/O/ R/P	H/O/ R/P		H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P	H/O/ R/P		H/O/ R/P		
Weekly Phone Contact number (P)							P7	P9 P10 P11	P13 P14 P15	P17 P18 P19	P21 P22 P23	P25 P26 P27	P29	P31 P32 P33	P35 P36 P37	P39 P40 P41	P43 P44 P45	P47 P48									
Timing of Visit (Weeks)		**+/- 2**	**0**	1	2	3	4	6	10	14	18	22	26	28	32	36	40	44	47	48	49	50	51	**52**	54	57	
Visit Window (Days)				±3	± 3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-3/+2	±3	±3	±3	**-2/+28**	+3	+3	
Hand Out and Instruct in Devices	6		**X**																X								
Attend Visit Fasting	5.3.1		**X**						X		X		X			X		X						**X**			**X**

Notes:

a All AEs and SAEs must be collected from first administration of randomised treatment

b Laboratory assessments, including HbA_{1c}, PK and antibodies, should be collected at the site and sent to the central laboratory. All efforts should be made to collect the samples on-site at the original frequency, but if on-site visits are not possible due to lock-down, then the sample collection can be cancelled.

c CGM fitting and/or training at V49 and V51 should be prioritised and preferably be on-site visit, but if not possible then home and off-site visit can be performed.

d Questionnaire should be prompted to participants at V53

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

10.11 Appendix 11: Country/Region-specific requirements

Australia

Indemnity Statement: Comply with Medicines Australia Guidelines for Compensation for Injury Resulting from Participation in a Company Sponsored Clinical Trial, version 160104 16 January 2004.

Belgium

- **Indemnity statement:** "Law concerning experiments on the human person of 07 May 2004 - Article 29: §1. Even if without fault, the sponsor is liable for the damage which the subject and/or his rightful claimants sustain and which shows either a direct or an indirect connection with the trial.

Bulgaria

According to Regulation 31 (for defining the rules of Good Clinical Practice, 12 Aug 2007), art. 4, par. (2) - The protocol is prepared according to the requirements of GCP and contains as a minimum the following: 1) assessment of the expected benefits and risks; 2) definition of inclusion and exclusion criteria; 3) rationale for study population, especially when it is expected to include participants that cannot consent personally and other vulnerable groups; 4) description of the procedures for recruiting participants and getting informed consent when it is expected to include patients who are temporarily or constantly unable to consent personally and when it is expected to receive consent from an independent witness; 5) description of the plan and the procedures for assuring complementary medical care for the participants after the study is ended; 6) monitoring procedures; 7) publication policy.

Contraceptive guidance: Hormonal contraception (oral, intravaginal, injectable, implantable), vasectomised partner or sexual abstinence.

Home and off-site visits in case of lock-downs: Home and off-site visits are **not applicable for Bulgaria.**

China

- **Continuous Glucose Monitor:** CGM will not be used in China.
- **Study Population:** pre-screening activities are not applicable in China.
- **Regulatory and ethical considerations:**
    - Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CSR according to national requirements.
    - For China, an international cooperative relevant report of related China's Human Genetic Resources will be submitted based on local regulation.
- **Clinical laboratory tests**: All laboratory assessments will be analysed in a central laboratory or special laboratory located in China. There will be no exploratory tests/exploratory

endpoints/investigations for Chinese participants. In case of systemic hypersensitivity reaction, the samples required in Section 8.7.2 and 10.2 should be taken and stored at the central laboratory before further analysis in the special laboratory.

The following hypersensitivity analytes are not possible to be tested in China, see Appendix 2 (Section 10.2), and will not be included in the hypersensitivity case assessment:

- Anti-human insulin IgE
- Anti-insulin icodec IgE
- Anti-semaglutide IgE

The following hypersensitivity analytes will be tested by the Central lab in China:

- Tryptase
- Total IgE antibodies

The following hypersensitivity analytes will be tested by special lab in China:

- Anti-insulin icodec binding antibodies
- Anti-semaglutide binding antibodies

- Retention of human biosamples:

  - Laboratory samples for Chinese participants including samples for antibody analysis will be destroyed according to local regulatory requirement. No sample will be stored after the latest date of local regulatory approval.

  - For China, remaining samples after test at site local laboratory, will be immediately destroyed according to local bio-waste procedure.

  - Remaining samples after test at the central laboratory will be destroyed according to bio-waste procedure after the protocol required test.

  - If required by health authorities, Antibody samples, Biomarker samples, Gene test samples and other special test samples will be retained for further analysis and/or characterisation of responses towards drug. These samples (include their backup) will be stored at a central bio-repository after end of trial and until marketing authorisation approval or until the research project terminates, after which they will be destroyed.

  - All samples' collection, shipment, analysis, temporary storage and destruction will be clearly recorded.

  - The participant’s identity will remain confidential and the samples will be identified only by subject ID, visit number and trial identification number. No direct identification of the participant will be stored together with the samples.

  - Only Novo Nordisk staff and laboratory personnel involved in the analyses will have access to the stored antibody samples.

- Participants can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

- **Dissemination of clinical study data:** Information of the study will be disclosed at clinicaltrials.gov, chinadrugtrials.org.cn and novonordisk-trials.com.

- **Inclusion and Exclusion criteria:** The inclusion/exclusion criteria will be assessed at the investigator's discretion unless otherwise stated.

- **Exclusion criteria 4:** the 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 and if simultaneous participation is allowed by local authorities" **is not applicable for China.**

- **Discontinuation criteria 4:** the 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 randomised treatment if simultaneous participation is allowed by local authorities**, is not applicable for China.**

- **Retention of clinical trial documentation:** About site specific data storage, sites have the equal right with sponsor. Long term preservation of Chinese Patients' Trial Data is Prohibited in any other entities.

Croatia

- **Exclusion criteria 4:** the 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 and if simultaneous participation is allowed by local authorities" **is not applicable for Croatia.**

- **Discontinuation criteria 4:** the 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 randomised treatment if simultaneous participation is allowed by local authorities**, is not applicable for Croatia.**

Italy

- **Additional exclusion criteria:** known severe diabetic autonomic neuropathy as judged by the investigator.

Japan

- **Inclusion criteria 3:** age ≥ 20 years at the time of signing informed consent

- **Preparation/Handling/Storage/Accountability:** The head of the study site or the study product storage manager assigned by the head of the study site (a pharmacist in principle) is responsible for control and accountability of the trial products.

- **Trial governance consideration:** A name and seal is accepted as signature.

- **Exclusion criteria 4:** the 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 and if simultaneous participation is allowed by local authorities" **is not applicable for Japan.**

- **Discontinuation criteria 4:** the 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 randomised treatment if simultaneous participation is allowed by local authorities**, is not applicable for Japan.**

- **Table 10-3:** Following contraceptive methods are not approved in Japan.
  - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - intravaginal
    - transdermal

  - Progestogen-only hormone contraception associated with inhibition of ovulation
    - injectable
    - implantable

Mexico

Withdrawal from the study: Should the participant, his/her family members, parents or legal representative decide to withdraw the consent for participation in the study, the participant will be entitled to receive appropriate, free of charge medical care and/or trial product during the follow-up period of the protocol when it will be established with certainty that no untoward medical consequences of the participant´s participation in the research occurred.

Study governance considerations: In the case of Mexico, the following responsibilities for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and sponsor within their scope of responsibility: a) Investigation follow-up; b) Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the Participant; c) Timely compliance of the terms in which the authorization of a research for health in human beings had been issued; d) To present in a timely manner the information required by the Health Authority.

Indemnity Statement: a) Novo Nordisk carries product liability for its products assumed under the special laws, acts/and/or guidelines for conducting studies in any country, including those

applicable provisions on the Mexican United States. If the participant feels that something goes wrong during the course of this study, the participant should contact the study staff in the first instance.

b) If during their participation in the study the participant experiences a disease or injury that, according to the study doctor and the sponsor, is directly caused by the study medication and/or a study procedure that otherwise would not have been part of his/her regular medical care, the participant will receive from the institution or medical care establishment and free of charge, the appropriate medical treatment as required. In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by the study sponsor in accordance with the terms provided by all applicable regulations; even if the participant discontinues his/her participation in the study by his own will or by a decision from the investigator.

c) By signing the informed consent, the participant will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the study; any additional expense resulting from the participant's participation in the study will be covered by the trial sponsor.

South Korea

- **Exclusion criteria 4:** the 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 and if simultaneous participation is allowed by local authorities" is **not applicable for South Korea**.

- **Discontinuation criteria 4:** the 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 randomised treatment if simultaneous participation is allowed by local authorities, is **not applicable for South Korea**.

- **Home and off-site visits in case of lock-downs:** Home and off-site visits are **not applicable for South Korea**

Taiwan

Inclusion criteria: Legal age in Taiwan is 20 years per local law. Thus, age limitation for adult studies shall be above or equal to 20 years in the entry criteria**.**

Turkey

Study assessments and procedures: blood samples will be shipped outside of Turkey and will be analysed by a central lab according to Attachment I of the protocol.

Exclusion criteria 10: stricter criteria applies in Turkey as follows: Presence or history of pancreatitis (acute or chronic).

For USA:

- **Haematology samples:** For haematology samples (differential count) where the test result is not normal, then a part of the sample may be kept for up to two years or according to local regulations.

- **FDA Form 1572:** All US investigators will sign FDA Form 1572

For USA sites: Intended for US sites**.** Conducted under the IND

All US investigators, as described above, will sign FDA Form 1572

For sites outside the USA: Intended for participating sites outside of the USA. Not conducted under the IND

All investigators outside of the USA will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

For Russia, Mexico, Serbia, Taiwan and India, where CGM Dexcom G6 is not approved at the time of the final protocol version 1.0:

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

The CGM has been selected in order to provide the best data accuracy and to be consistent in the global clinical programme. Technical complaints on the CGM must be reported to [redacted] on a special technical complaint paper form.

Timelines for reporting, from the trial site obtaining knowledge of the technical complaint:
- Technical complaint assessed as related to a SAE within 24 hours
- All other technical complaints within 5 calendar days

AEs and SAEs related to the technical complaint must be reported both on the special technical complaint paper form and in the eCRF. In addition they must be reported in accordance with the standard protocol requirements for AE and SAE reporting as described in Section 8.3.

At the end of the trial CGM must be collected by the investigator.

If the CGM is approved in any of the countries during the trial conduct, the procedures above are not applicable any more in the said country and technical complaints reporting should follow the standard vigilance procedures.

10.12 Appendix 12: Abbreviations

ADA	American Diabetes Association
AE	adverse event
BG	blood glucose
CGM	continuous glucose monitoring
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTFG	Clinical Trial Facilitation Group
DMSES	diabetes management self-efficacy
DPP-4	dipeptidyl peptidase-4
DRE	disease related event
DTPQ	Diabetes Treatment Preference Questionnaire
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DUN	dispensing unit number
EAC	Event Adjudication Committee
EASD	European Association for the Study of Diabetes
EAS	event adjudication system
ECG	electrocardiogram
EMA	European Medical Agency
eCRF	electronic case report form
ETD	estimated treatment difference
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide 1
GCP	Good Clinical Practice
$HbA1_c$	glycated haemoglobin
HCP	healthcare professional
ICE	intercurrent event
ICH	International Council for Harmonisation
IEC	independent ethics committee
IHSG	The International Hypoglycaemia Study Group
IMP	investigational medicinal product
IND	investigational new drug

IRB	institutional review board
ISO	International Organization for Harmonization
ISPAD	International Society for Pediatric and Adolescent Diabetes
NIMP	non-investigational medicinal product
OAD	oral anti-diabetic drug
PG	plasma glucose
PK	pharmacokinetics
RTSM	Randomisation and Trial Supply Management system
SAE	serious adverse event
SAP	Statistical Analysis Plan
s.c.	subcutaneous
SD	standard deviation
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
T2D	type 2 diabetes mellitus
SUSAR	suspected unexpected serious adverse reaction
V	visit
WOCBP	woman of childbearing potential

10.13 Appendix 13: Protocol amendment history

The Protocol amendment summary of changes table for the current protocol version is located directly before the table of contents.

Overall rationale for preparing protocol, version 5.0, 08-Feb-2022, Turkey only:

The protocol has been amended to implement the below changes to reflect the treatment practice in Turkey:

Section # and name	Description of change	Brief rationale
Appendix 11: Country/Region-specific requirements-Turkey	Change of Exclusion Criteria 10 as follows: "Presence or history of pancreatitis (acute or chronic) ~~within 180 days before screening~~".	The use of GLP-1 RA is avoided in patients who have suffered pancreatitis due to treatment practice in Turkey

Protocol version 4.0, including versions 1, 2 and 3: 18 January 2022, Japan only

Overall rationale for preparing protocol, version 4.0:

The protocol has been amended to implement the below changes per request of the PMDA:

Section # and name	Description of change	Brief rationale
Introduction	Sentence added to describe that Insulin icodec is a recombinant protein produced using yeast.	PMDA request
Appendix 11: Country/Region-specific requirements - Japan	Text added to describe which contraceptive methods in the protocol (Table 10-3) have not been approved in Japan.	PMDA request

Protocol version 3.0, including versions 1 and 2: 10-Aug-2021, global

The protocol has been updated to correct the below errors detected:

Section # and name	Description of change	Brief rationale
Protocol amendment summary of changes table	Date format changed from DD-MM-YYYY to DD-MMM-YYYY	DD-MMM-YYYY is the standard Novo Nordisk date format.
1.1 Synopsis, Key Exclusion Criteria, 5.2 Exclusion criteria	Anticipated initiation or change in concomitant medication (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid~~,~~ hormones, or systemic corticosteroids).	Typo. It should say “thyroid hormones”, not “thyroid, hormones”
Table 6-2, Auxiliary supplies	NovoFine® Plus 32G, 4 mm needles and NovoFine® Plus 32G, 6 mm needles were renamed to NovoFine® needles or similar according to local requirements	Typo in the name NovoFine® Plus 32G, 6mm (it should not contain “Plus”). NovoFine® needles is more general and it covers all sizes needed. “or similar according to local requirements” allows the use of similar needles if NovoFine® is not approved in a specific country.
10.2 Appendix 2 Clinical laboratory tests	Addition of tryptase to systemic hypersensitivity samples (IcoSema arm)	Tryptase should be collected in both arms in case of systemic hypersensitivty.

11 References

1. The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. 2001.
2. American Diabetes Association. 2. Classification and Diagnosis of Diabetes:. Diabetes Care. 2019;42(Suppl 1):S13-S28.
3. International Diabetes Federation. IDF Diabetes Atlas, 9th Edition. 2019.
4. 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.
5. Novo Nordisk A/S. Ozempic® (semaglutide), EU Summary of product characteristics (SmPC). 27 Mar 2020.
6. Novo Nordisk A/S. Ozempic® (semaglutide), US prescribing Information (PI). Jan 2020.
7. European Medicines Agency, CHMP. Guideline on clinical development of fixed combination medicinal products. 2017.
8. Leahy JL. Pathogenesis of type 2 diabetes mellitus. Arch Med Res. 2005;36(3):197-209.
9. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am. 2004;88(4):787-835, ix.
10. Davies M, D'Alessio D, Fradkin J, Kernan W, Mathieu C, Mingrone G, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41(12):2669-701.
11. Alatorre C, Fernández Landó L, Yu M, Brown K, Montejano L, Juneau P, et al. Treatment patterns in patients with type 2 diabetes mellitus treated with glucagon-like peptide-1 receptor agonists: Higher adherence and persistence with dulaglutide compared with once-weekly exenatide and liraglutide. Diabetes Obes Metab. 2017;19(7):953-61.
12. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015;58(3):429-42.
13. Novo Nordisk A/S. Xultophy® (Insulin Degludec/Liraglutide), EU Summary of Product Characteristics (SmPC). 2015.
14. Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. Eur J Health Econ. 2011;12(3):219-30.
15. Evans M, Jensen HH, Bøgelund M, Gundgaard J, Chubb B, Khunti K. Flexible insulin dosing improves health-related quality-of-life (HRQoL): a time trade-off survey. J Med Econ. 2013;16(11):1357-65.
16. Novo Nordisk A/S. Investigator's Brochure, IcoSema, NN1535, (edition 4). 17 March 2023.
17. Novo Nordisk A/S. Investigator's Brochure, insulin icodec, NN1436, (edition 9). 16 March 2023.
18. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment:. Diabetes Care. 2021;44(Suppl 1):S111-S24.
19. American Diabetes Association. American Diabetes Association standards of medical care in diabetes 2019. Diabetes Care2019. p. S1–S187.
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. McEvoy BW. Missing data in clinical trials for weight management. J Biopharm Stat. 2016;26(1):30-6.
23. Little R, Rubin D. Statistical analysis with missing data. Sons. JW, editor. New York.: John Wiley & Sons. 1987.
24. Blonde L, Merilainen M, Karwe V, Raskin P. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessmentof two different fasting plasma glucose targets - the TITRATE™ study. Diabetes Obes Metab. 2009;11:623-31.
25. 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.
26. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R2), Current step 4 version. 09 Nov 2016.
27. 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.
28. 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.
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. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second Symposium on the Definition and Management of Anaphylaxis: Summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. Annals of Emergency Medicine. 2006;47(4):373-80.
33. Kemp SF, Lockey RF. Anaphylaxis: a review of causes and mechanisms. J Allergy Clin Immunol. 2002;110(3):341-8.
34. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113(5):832-6.
35. Scialli AR, Bailey G, Beyer BK, Bøgh IB, Breslin WJ, Chen CL, et al. Potential seminal transport of pharmaceuticals to the conceptus. Reprod Toxicol. 2015;58:213-21.
36. Clinical Trial Facilitation Group (CTFG), Heads of Medicines Agency. Recommendations related to contraception and pregnancy testing in clinical trials. 21 Sep 2020.
37. 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.

38. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S55-S64.
39. 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.
40. 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.
41. 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.
42. 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.