Cover Page for Protocol

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NCT number	NCT05144984
Sponsor trial ID:	NN9389-4606
Official title of study:	Investigation of the safety and efficacy of semaglutide s.c. in combination with NNC0480-0389 in participants with type 2 diabetes – a dose finding study
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*Document date refers to the date on which the document was most recently updated.

Note: The date in the header of page 2 is the date of compilation of the documents and not of an update to content.

9.1.1 Protocol and protocol amendments

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Protocol

Protocol Title: Investigation of the safety and efficacy of semaglutide s.c. in combination with NNC0480-0389 in participants with type 2 diabetes – a dose finding study

Substance number / name: Semaglutide s.c. and NNC0480-0389

Universal Trial Number: U1111-1259-2741

EudraCT Number: 2020-004863-14

Redacted protocol
Includes redaction of personal identifiable information only.

Study phase: 2

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	**Date**	**Applicable in country(-ies) and/or site(s)**
Protocol version 4.0	03 September 2021	Global
Protocol version 3.0	01 July 2021	Global
Protocol version 2.0	15 June 2021	Internal version only
Original protocol version 1.0	04 June 2021	Internal version only

Protocol version 4.0

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 subjects nor the scientific value of the trial.

Overall rationale for preparing protocol, version 4.0

This version of the protocol is prepared to include additional safety monitoring in the immediate period after dosing during the dose escalation period and after the first dose in the two maintenance periods based on the recommendation from FDA.

An overview of the updates is presented in the table below:

Section # and name	Description of change	Brief rationale
1.2 Flowchart	Phone contacts to assess adverse events after home dosing during dose escalation at weeks 1, 3, 5, 7 and 9. Additional ECGs at week 16 and week 28 during the maintenance periods. Addition of on-site dosing (weeks 0, 2, 4, 6, 8, 10 and 22).	Based on recommendation from FDA.
2.3.1 Risk assessment	Updated mitigation actions for hypoglycaemia, increased heart rate and decreased blood pressure.	Based on recommendation from FDA.
6.1 Study intervention(s) administered	Addition of on-site dosing (weeks 0, 2, 4, 6, 8, 10 and 22).	Based on recommendation from FDA.
6.1 Study intervention(s) administered	The description '(Blue pen)' for the PDS290 pen injector added to Table 6-3 for the dose ratio 1:9 or volume-matched placebo, NNC0480-0389 monotherapy or semaglutide monotherapy.	Alignment to wording in rest of Table 6-3.
6.1 Study intervention(s) administered	Minor edits to the PDS290 risk assessment text.	Alignment to wording in device risk assessment.
7.1 Discontinuation of study intervention	Added a discontinuation criterion for overall safety concern and a discontinuation criterion for unacceptable risk of hypoglycaemic events.	Based on recommendation from FDA.
8 Study assessments and procedures	Added a description of the diary dispensing.	To ensure that a detailed description of diary dispensing is included.
8 Study assessments and procedures	Up to 6 hours of on-site observation after dosing with measurements of blood pressure, pulse rate and ECG at weeks 0, 2, 4, 6, 8, 10 and 22.	Based on recommendation from FDA.
8.4. Adverse events and other safety reporting	Acute kidney injury and hepatic event included as AEs requiring additional data collection.	Based on recommendation from FDA.
9.3.3 Dose-response modelling	The comparator updated to be semaglutide monotherapy rather than placebo in two places.	Correction to clarify that the comparator should be semaglutide monotherapy and not placebo.
10.3.3 Description of AEs requiring additional data collection and other events requiring collection of additional information	Description of acute kidney injury and hepatic event added.	Based on recommendation from FDA.
10.6 Appendix 6 Retention of human biosamples for future research	Correction of wrong terminology from *end of study* to *end of treatment* to describe visit 24.	Correction of wrong terminology.

10.9 Appendix 9: Mitigations to ensure participant safety and data integrity during an emergency situation	Updated the visit numbers in-text and in Table 10-8.	To align with updates based on recommendation from FDA.

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1 Protocol summary

1.1 Synopsis

This is an interventional, 34-week, randomised, parallel-group, volume-matched placebo-controlled, ten-armed, multi-centre, multi-national dose finding phase 2 study. It will be double-blinded between each dose ratio arm and volume-matched placebo arm or volume-matched active comparator arm.

Rationale:

The study will investigate safety, tolerability, efficacy, and pharmacokinetics (PK) of the glucagon-like peptide-1 (GLP-1) receptor agonist (RA) semaglutide s.c. (referred to as semaglutide hereafter, unless otherwise specified) in combination with the glucose-dependent insulinotropic peptide (GIP) RA NNC0480-0389 administered s.c. by separate injections in participants with type 2 diabetes (T2D) inadequately controlled on diet and exercise with or without metformin. The study is designed to determine the dose ratio to be used in the development of a fixed dose combination (FDC) of semaglutide and NNC0480-0389. Different dose ratios (using a fixed dose of semaglutide and varying doses of NNC0480-0389) will be compared against placebo, NNC0480-0389 monotherapy and semaglutide monotherapy, respectively.

Objectives, endpoints and estimand(s):

Objectives	**Endpoints**		
Primary	Title	Time frame	Unit
To demonstrate superiority of subcutaneously co-administered semaglutide and NNC0480-0389 (in different dose ratios) versus placebo on change in HbA_{1c} (%-point) from baseline to week 34 in participants with T2D inadequately controlled on diet and exercise with or without metformin.	*Primary*		
	Change in HbA_{1c}	From baseline (week 0) to visit 24 (week 34)	%-point
Secondary			
Secondary objective 1: To demonstrate superiority of subcutaneously co-administered semaglutide and NNC0480-0389 (in different dose ratios) versus NNC0480-0389 and versus semaglutide on change in HbA_{1c} (%-point) from baseline to week 34 in participants with T2D inadequately controlled on diet and exercise with or without metformin.			
Secondary objective 2: To compare the effect of subcutaneously administered NNC0480-0389 monotherapy versus placebo on change in HbA_{1c} (%-point) from baseline to week 34 in participants with T2D inadequately controlled on diet and exercise with or without metformin.			

Objectives	Endpoints		
Secondary	Title	Time frame	Unit
Secondary objective 3: To compare the effect of subcutaneously co-administered semaglutide and NNC0480-0389 (in different dose ratios) versus placebo, versus NNC0480-0389 and versus semaglutide on change in fasting plasma glucose as well as body weight-related and cardio-metabolic parameters from baseline to week 34 in participants with T2D inadequately controlled on diet and exercise with or without metformin.	*Supportive secondary:*		
	Change in fasting plasma glucose (FPG)	From baseline (week 0) to visit 24 (week 34)	mmol/L
	Change in body weight (kg)	From baseline (week 0) to visit 24 (week 34)	kg
	Change in body weight (%)	From baseline (week 0) to visit 24 (week 34)	%
	Change in waist circumference	From baseline (week 0) to visit 24 (week 34)	cm
	Change in systolic blood pressure (SBP)	From baseline (week 0) to visit 24 (week 34)	mmHg
	Relative change in total cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in high-density lipoprotein (HDL)-cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in low-density lipoprotein (LDL)-cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in very-low-density lipoprotein (VLDL)-cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in triglycerides	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in free fatty acids	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in Apolipoprotein B (ApoB)	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in high-sensitivity C-Reactive Protein (hsCRP)	From baseline (week 0) to visit 24 (week 34)	Ratio
Secondary objective 4: To compare the safety and tolerability of subcutaneously co-administered semaglutide and NNC0480-0389 (in different dose ratios) versus placebo, versus NNC0480-0389 and versus semaglutide in participants with T2D inadequately controlled on diet and exercise with or without metformin.	*Supportive secondary:*		
	Number of treatment-emergent adverse events (TEAEs)	From baseline (week 0) to visit 25 (week 39)	Count of events

For the primary objective, a primary estimand and an additional estimand are defined. Two intercurrent events are identified: premature discontinuation of randomised treatment and initiation of any rescue medication (anti-diabetic medication). The primary and additional estimands will be used to address both the primary and secondary objectives for the primary endpoint.

The primary estimand addresses the main question of interest: What is the effect of subcutaneously co-administered semaglutide and NNC0480-0389 versus placebo on change in HbA_{1c} (%-point)

from baseline to week 34 in participants with T2D, with or without metformin, had all participants remained on randomised treatment without use of rescue medication (anti-diabetic medications)?

The additional estimand addresses an additional question of interest: What is the effect of subcutaneously co-administered semaglutide and NNC0480-0389 versus placebo on change in HbA_{1c} (%-point) from baseline to week 34 in participants with T2D, with or without metformin, regardless of premature discontinuation of randomised treatment and initiation of rescue medication (anti-diabetic medications)?

Overall design:

The study consists of an up to 2-week screening period followed by a 34-week intervention period and a 5-week follow-up period. The 34-week intervention period includes a 10-week dose escalation followed by two 12-week maintenance periods until end-of-treatment (week 34/V24).

Study intervention groups and duration:

There are 10 arms in this study. For each participant, the maximum intervention duration is 34 weeks and the maximum study duration is 41 weeks.

All study arms will contain once-weekly s.c. co-administered separate injections of semaglutide (or semaglutide matched placebo) and NNC0480-0389 (or NNC0480-0389 matched placebo).

The 10 study arms consist of 6 active treatment arms and 4 placebo arms, as follows:

- Dose ratio 1:1; 2.4 mg semaglutide and 2.4 mg NNC0480-0389 (75 participants)
- Dose ratio 1:3; 2.4 mg semaglutide and 7.2 mg NNC0480-0389 (75 participants)
- Dose ratio 1:5; 2.4 mg semaglutide and 12.0 mg NNC0480-0389 (75 participants)
- Dose ratio 1:9; 2.4 mg semaglutide and 21.6 mg NNC0480-0389 (75 participants)
- NNC0480-0389 21.6 mg and semaglutide matched placebo (volume-matched to the dose ratio 1:9 arm) (60 participants)
- Semaglutide 2.4 mg and NNC0480-0389 matched placebo (volume-matched to the dose ratio 1:9 arm) (75 participants)
- 4 placebo arms matching the dose ratio arms: each with semaglutide matched placebo and NNC0480-0389 matched placebo (15 participants in each arm, 60 participants on placebo in total)

Following a screening period of up to 2 weeks, the participants will be randomised 75:75:75:75:60:75:60 to the four dose ratios, NNC0480-0389 monotherapy, semaglutide monotherapy, and the pooled placebo group, respectively, at the randomisation visit (V2). Randomisation will be stratified according to treatment with metformin at screening (yes/no), country (Japan/Other), and HbA_{1c} at screening (<8.5%/≥8.5%).

The 4 placebo arms have different injection volumes to match the different dose levels of the corresponding dose ratio arms. The active treatment arm and the corresponding volume-matched placebo arm will be blinded towards each other. The four dose ratios will not be blinded towards each other as different injection volumes are used. The active comparator arms (NNC0480-0389 monotherapy and semaglutide monotherapy) as well as the dose ratio 1:9 and corresponding placebo arm will use the same injection volumes and will be blinded.

Two different strengths of semaglutide and NNC0480-0389, respectively, will be used to administer the planned doses in this study. Accordingly, two different semaglutide placebo products will be used to match 1.34 mg/mL and 3.0 mg/mL semaglutide, respectively. Placebo A will be used for NNC0480-0389 and is visually identical to both the 10 mg/mL and 30 mg/mL strength; however, the packaging of placebo A will be blinded towards 10 mg/mL and 30 mg/mL NNC0480-0389, respectively.

The following trial products (including strength and container/device) are used in the study:
- Semaglutide B 1.34 mg/mL in 1.5 mL PDS290 pre-filled pen-injector
- Semaglutide B 3.0 mg/mL in 3.0 mL PDS290 pre-filled pen-injector
- NNC0480-0389 A 10 mg/mL in 3 mL cartridge, to be administered with NovoPen® 4
- NNC0480-0389 A 30 mg/mL in 3 mL cartridge, to be administered with NovoPen® 4
- Semaglutide placebo (1.34 mg/mL) in 1.5 mL PDS290 pre-filled pen-injector
- Semaglutide placebo (3.0 mg/mL) in 3.0 mL PDS290 pre-filled pen-injector
- Placebo A (for NNC0480-0389) in 3 mL cartridge, to be administered with NovoPen® 4

Number of participants:

Approximately 660 participants will be screened to achieve 495 participants randomly assigned to study intervention.

Participant characteristics:

The participants will be male or female of non-childbearing potential aged 18-75 years (both inclusive) *(For Japan only: Age 20-75 years (both inclusive))* at the time of signing informed consent who meet the following key inclusion criteria and none of the following key exclusion criteria:

Key inclusion criteria:
- Diagnosed with type 2 diabetes mellitus ≥ 180 days before screening
- Participants treated with diet and exercise as monotherapy or in combination with stable daily dose(s) ≥ 90 days before screening of any metformin formulations ≥ 1500 mg or maximum tolerated or effective dose
- HbA_{1c} 7.0-10.0% (53-86 mmol/mol) (both inclusive)
- BMI ≥25 and <40 kg/m^2

Key exclusion criteria:
- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days before screening. However, short term insulin treatment for a maximum of 14 days and prior insulin treatment for gestational diabetes are allowed
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within 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
- Presence or history of any clinically relevant respiratory, metabolic, renal, hepatic cardiovascular, gastrointestinal, or endocrinological conditions (except conditions associated with T2D)

Efficacy and safety data will be collected at 2-week intervals throughout the study

Data monitoring committee: No

1.2 Flowchart

Procedure	Protocol section	Screening	Randomisation	Intervention period																				End of treatment	End of study
				Dose escalation										Maintenance period 1						Maintenance period 2						
Visit		V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25
Timing of visit (Weeks)		-2	0	1	2	3	4	5	6	7	8	9	10	12	14	16	18	20	22	24	26	28	30	32	34	39
Visit window (Days)[a]		-14/0	±0	0/1	±3	0/1	±7	0/1	±7	0/1	±7	0/1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	0/7
Informed consent and demography	10.1	X																								
Tobacco use	8.1	X																								
Childbearing potential	10.4	X																								
Eligibility criteria	5.1 5.2	X	X																							
Randomisation criteria and randomisation	5.5		X																							
Discontinuation criteria	7.1		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	8.3	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
Body measurements	8.3.1	X	X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	8.3.1	X																	X						X	
Vital signs	8.3.2	X	X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Eye examination	8.3.3	X																							X	

Procedure	Protocol section	Screening	Randomisation	Intervention period																					End of treatment	End of study
				Dose escalation										Maintenance period 1						Maintenance period 2						
Visit		V1	V2	P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25
Timing of visit (Weeks)		-2	0	1	2	3	4	5	6	7	8	9	10	12	14	16	18	20	22	24	26	28	30	32	34	39
Visit window (Days)[a]		-14/0	±0	0/1	±3	0/1	±7	0/1	±7	0/1	±7	0/1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	0/7
ECG	8.3.4	X	X		X		X		X		X		X			X			X			X			X	
Adverse event	8.4 10.3			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	10.7			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Technical complaint	10.5	X	X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments	10.2	X	X		X				X				X	X	X		X		X		X		X		X	X
PK sampling [b]	8.5.1		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Antibodies	8.8		X				X				X				X				X						X	X
Attend visit fasting	5.3.1		X		X				X				X	X	X		X		X		X		X		X	
Samples for exploratory biomarker analysis	8.7 10.2		X																X						X	
Biosamples for future research	8.9 10.6		X																X						X	
Drug dispensing	6.2		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X		
Training in devices	6.1		X		X								X						X							
On-site dosing			X		X		X		X		X		X						X							

Abbreviations: ECG, electrocardiogram; P, phone contact; PK, pharmacokinetic; V, site visit.

[a] The visit window for the phone contacts (P3, P5, P7, P9, and P11) is in relation to the administration of the study medication, i.e. these phone contacts must be performed either on the day of administration (post-dose) or the next day at the latest. [b] For participants who have prematurely discontinued randomised treatment, PK samples should only be taken at the 3 next visits after discontinuation.

2 Introduction

2.1 Study rationale

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) both play an important role in regulating glucose homeostasis. Consequently, dosing a combination of analogues of both hormones may be beneficial in the treatment of type 2 diabetes (T2D). This phase 2 study will investigate safety, tolerability, efficacy, and pharmacokinetics (PK) of the GLP-1 receptor agonist (RA) semaglutide s.c. (referred to as semaglutide hereafter, unless otherwise specified) in combination with the GIP RA NNC0480-0389 administered s.c. by separate injections in participants with T2D inadequately controlled on diet and exercise with or without metformin.

The study is designed to determine the dose ratio to be used in the development of a fixed dose combination (FDC) of semaglutide and NNC0480-0389. Different dose ratios (using a fixed dose of semaglutide and varying doses of NNC0480-0389) will be compared against placebo, NNC0480-0389 monotherapy and semaglutide monotherapy, respectively. NNC0480-0389 and semaglutide are included as active comparators to enable comparisons of the combination therapy versus each component as monotherapy. Placebo is included as comparison to the combination therapy, and moreover, to allow comparison to NNC0480-0389 monotherapy as limited scientific knowledge on a long-acting GIP RA is available.

Knowledge obtained from the present study will be used in the future clinical development of the semaglutide and NNC0480-0389 combination.

2.2 Background

GLP-1 and GIP are both incretin hormones and thus share common actions on the pancreatic islet β-cells to regulate glucose homeostasis through activation of GLP-1 receptors and GIP receptors, respectively. In healthy people, postprandial incretin-receptor activation leads to glucose-dependent insulin secretion. In addition, GLP-1 inhibits glucagon secretion which contributes to the blood glucose lowering effect, whereas GIP has no effect on glucagon secretion during hyperglycaemia.[2] The acute insulinotropic response to native GIP is substantially diminished in people with T2D[3], and GIP RAs are thus expected to have limited effect on HbA_{1c}. However, the insulinotropic effect of GIP may be restored upon combined treatment with a GLP-1 RA that lowers blood glucose to near normal levels.[2]

The addition of a GIP RA to GLP-1 RA treatment is hypothesised to provide additional benefits beyond GLP-1 RA monotherapy. This includes effects on insulin secretion and weight loss and potentially also improvement of insulin sensitivity, lipids and inflammation.[4] Collectively, these effects may provide further reductions of HbA_{1c} and cardiovascular (CV) benefits compared to GLP-1 RA treatment. Additionally, native GIP is reported to have a role in regulating bone remodelling in both healthy people and in people with T2D[5]; however, whether long-term application of a GIP RA will modulate bone turnover in humans is still unknown.

Semaglutide and NNC0480-0389 are being developed as combination treatment for people with T2D. Semaglutide is a semi-recombinant acylated GLP-1 RA, and NNC0480-0389 is an acylated synthetic GIP RA. Both semaglutide and NNC0480-0389 are stabilised against enzymatic degradation by amino acid substitution in the native human peptides and acylated by di-fatty acids

which causes a specific binding to serum albumin that leads to a long duration of action supporting once-weekly dosing by s.c. injection.

In nonclinical studies, NNC0480-0389 alone and in combination with semaglutide has shown to reduce blood glucose levels as well as body weight. To support initiation of phase 2, repeat dose toxicity studies have been performed where NNC0480-0389 alone has been dosed to rats for up to 26 weeks and to dogs for up to 39 weeks. The combination of semaglutide and NNC0480-0389 has been dosed to rats for up to 13 weeks. No significant safety or toxicity findings were observed from the nonclinical safety studies.

Co-administration of semaglutide and NNC0480-0389 is being investigated in an ongoing first human dose (FHD) study NN9389-4536 with a single ascending dose (SAD) part and a multiple ascending dose (MAD) part. The SAD part has been completed and consisted of 4 cohorts with ascending single doses of 1.7-60 mg NNC0480 0389 (or matched placebo) co-administered with a fixed dose of 0.5 mg semaglutide (or matched placebo) as separate s.c. injections. Unblinded data from the SAD part demonstrated that co-administration of semaglutide and NNC0480-0389 was well-tolerated, with no safety concerns identified. The ongoing MAD part consists of 3 sequential cohorts and an additional proof-of-concept cohort with planned doses of 8.6-60 mg NNC0480-0389 (or matched placebo) co-administered with 1.0 mg semaglutide (or matched placebo).

The study population in this phase 2 study will consist of participants with T2D who are in inadequate glycaemic control following treatment with diet and exercise with or without metformin. This study population is expected to benefit from the anti-diabetic treatment and additional benefits that GLP-1:GIP RA combination treatment is expected to provide. Only women of non-childbearing potential are included since embryo-foetal development studies remain to be conducted.

2.3 Benefit-risk assessment

The main benefits and risks related to participation in the study are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of semaglutide and/or NNC0480-0389 may be found in the current version of the NN9389 investigator's brochure.

2.3.1 Risk assessment

The risk assessment for this study is presented in Table 2-1.

Table 2-1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention (semaglutide and NNC0480-0389)		
Hypersensitivity and allergic reactions	As it is the case with all peptide and protein-based drugs, there is a risk of hypersensitivity and allergic reactions. This is the case for both semaglutide and NNC0480-0389. Hypersensitivity reactions may show as local injection site reactions, local allergic reactions or may also occur as severe or serious systemic reactions, including angioedema and anaphylactic reactions.	As a precaution, participants with known or suspected hypersensitivity to study interventions or related products will not be enrolled in this study. In addition, participants will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the trial product occurs.
Semaglutide s.c. risks		
Gastrointestinal disorders	Consistent with other GLP-1 RAs, the most frequent adverse events (AEs) with semaglutide are gastrointestinal (such as nausea, vomiting and diarrhoea). In general, these reactions are mild or moderate in severity, of short duration, and dose dependent. In participants treated with GLP-1 RAs, nausea, vomiting and diarrhoea may lead to significant dehydration.	Clinical studies have shown that a low starting dose and gradual dose escalation mitigates the risk of developing gastrointestinal symptoms. Participants with gastrointestinal (GI) symptoms are recommended to drink plenty of fluids to avoid volume depletion.
Cholelithiasis	Events of cholelithiasis were the most frequently reported gallbladder events in the clinical development programme for semaglutide s.c. 2.4 mg for weight management. In the phase 3a studies, cholelithiasis was reported in 1.6% and led to cholecystitis in 0.6% of participants treated with semaglutide 2.4 mg.	If cholelithiasis is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion.
Hypoglycaemia	There is a low risk of hypoglycaemic episodes when semaglutide is used as monotherapy. NNC0480-0389 is not expected to increase the risk of hypoglycaemia. Participants treated with semaglutide in combination with a sulphonylurea (SU) or insulin have an increased risk of hypoglycaemia.	Participants are not allowed to use SU or insulin during the study. A discontinuation criterion on hypoglycaemic events has been implemented (Section 7.1).

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Diabetic retinopathy complications	In a 2-year clinical study with semaglutide s.c. (NN9535-3744) involving 3,297 participants with T2D, high CV risk, long duration of diabetes and poorly controlled blood glucose, EAC-confirmed events of diabetic retinopathy complications occurred in more participants treated with 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 were 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 with uncontrolled and potentially unstable diabetic retinopathy or maculopathy are excluded from the study.
Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 RAs. In the completed phase 3 studies with semaglutide s.c. in T2D and oral semaglutide in T2D, 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. For obese and overweight subjects treated with semaglutide s.c. 2.4 mg, the frequency of adjudication-confirmed acute pancreatitis reported in phase 3a clinical studies was 0.2% for semaglutide 2.4 mg and <0.1% for placebo, respectively.	Participants should be informed of the characteristic symptoms of acute pancreatitis and if pancreatitis is suspected, study intervention should be discontinued. If confirmed, study intervention should not be restarted. Participants with a history or presence of chronic or acute pancreatitis within 180 days prior to screening are excluded from the study.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Neoplasms (malignant and non-malignant)	People with T2D, as well as people 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. No imbalance was observed in the semaglutide s.c. 2.4 mg for weight management phase 3a trials with regards to the proportions of participants with neoplasms (malignant and non-malignant).	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 or squamous cell skin cancer, in situ carcinomas of the cervix or in situ prostate cancer are allowed.
Pancreatic cancer	People with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is currently no support from nonclinical 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 RAs 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 presence or history of malignant neoplasm within 5 years prior to the day of screening will not be enrolled in this study.
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 13-fold above the clinical plasma exposure at 2.4 mg/week. 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.	To mitigate this risk, participants with a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2) are excluded from this study.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
NNC0480-0389 risks		
Increased heart rate	Nonclinical studies have shown a transient increase in heart rate after administration of NNC0480-0389. A trend towards a post-dose, transient, self-limiting heart rate increase was observed in humans after a single dose of NNC0480-0389 alone and in combination with semaglutide.	Vital signs are measured at each on-site visit. At weeks 0, 2, 4, 6, 8, 10 and 22 dosing will be performed on-site and participants monitored on-site with vital signs and ECG measurements at least 4 hours after dosing.
Reddening of skin and gums	Nonclinical studies have shown an increase in the occurrence of reddening of skin and gums in dogs. A single dose of NNC0480-0389 alone or in combination with semaglutide did not induce a similar response in humans.	No mitigations considered needed.
Decreased blood pressure	Nonclinical studies have shown a transient decrease in blood pressure after administration of NNC0480-0389. A single dose of NNC0480-0389 alone or in combination with semaglutide did not induce a similar response in humans.	Vital signs are measured at each on-site visit. At weeks 0, 2, 4, 6, 8, 10 and 22 dosing will be performed on-site and participants monitored on-site with vital signs and ECG measurements at least 4 hours after dosing.
Study procedures		
Discomfort related to invasive study procedure	Discomfort may occur around the site of blood sampling.	Experienced and properly trained site personnel will ensure minimisation of discomfort caused by study procedures.
Risk of COVID-19 infection in relation to participation in the 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 country at the time of study conduct.	The risk of COVID-19 transmission in relation to site visits is overall considered to be low. To minimise the risk as much as possible, the following measures have been taken: • On-site visits will be well-prepared and as short as possible. Physical contact between participants and site staff will be limited to the extent possible, and protective measures will be implemented (e.g. use of masks, sanitizers, no aerosol-generating procedures etc. according to local practice) • Appendix 9 (Section 10.9) includes mitigations that can be implemented to ensure participant safety and data integrity in case a major emergency (e.g. COVID-19 outbreak) leads to lock-down of sites which affects the ability to perform study-related procedures.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Other		
Pregnancy and fertility	Studies in animals have shown reproductive toxicity with semaglutide. NNC0480-0389 has not yet been tested in relation to pregnancy or fertility. There are limited data from the use of semaglutide in pregnant women.	Only female not of childbearing potential are enrolled in this study

Abbreviations: AE; adverse event; CV: cardiovascular; EAC: event adjudication committee; GI: gastrointestinal; GLP-1 RA: glucagon-like peptide-1 receptor agonist; MEN2: multiple endocrine neoplasia type 2; SU: sulphonylurea; T2D: type 2 diabetes

2.3.2 Benefit assessment

In this study, participants with T2D on diet and exercise ± metformin will be randomised to a 34-week intervention period with either co-administered semaglutide and NNC0480-0389, placebo, NNC0480-0389 monotherapy or semaglutide monotherapy. Treatment with co-administered semaglutide and NNC0480-0389 or semaglutide monotherapy is expected to provide additional benefits on glycaemic control and weight loss on top of the anti-diabetic background treatment of diet and exercise ± metformin.

All participants, including participants randomised to placebo or NNC0480-0389 monotherapy, are expected to benefit from the frequent medical evaluations/examinations.

Furthermore, the data obtained from the present study will form the basis for future development of the semaglutide:NNC0480-0389 combination treatment in people with T2D.

2.3.3 Overall benefit-risk conclusion

Taking into account the measures taken to minimise risk and burden to participants participating in this study, the potential risks identified in association with semaglutide and/or NNC0480-0389 are justified by the anticipated benefits that may be afforded to participants with T2D.

3 Objectives, endpoints and estimands

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	Title	Time frame	Unit
To demonstrate superiority of subcutaneously co-administered semaglutide and NNC0480-0389 (in different dose ratios) versus placebo on change in HbA_{1c} (%-point) from baseline to week 34 in participants with T2D inadequately controlled on diet and exercise with or without metformin.	*Primary*		
	Change in HbA_{1c}	From baseline (week 0) to visit 24 (week 34)	%-point
Secondary			
Secondary objective 1: To demonstrate superiority of subcutaneously co-administered semaglutide and NNC0480-0389 (in different dose ratios) versus NNC0480-0389 and versus semaglutide on change in HbA_{1c} (%-point) from baseline to week 34 in participants with T2D inadequately controlled on diet and exercise with or without metformin.			
Secondary objective 2: To compare the effect of subcutaneously administered NNC0480-0389 monotherapy versus placebo on change in HbA_{1c} (%-point) from baseline to week 34 in participants with T2D inadequately controlled on diet and exercise with or without metformin.			

Objectives	Endpoints		
Secondary objective 3: To compare the effect of subcutaneously co-administered semaglutide and NNC0480 0389 (in different dose ratios) versus placebo, versus NNC0480-0389 and versus semaglutide on change in fasting plasma glucose as well as body weight-related and cardio-metabolic parameters from baseline to week 34 in participants with T2D inadequately controlled on diet and exercise with or without metformin.	Title	Time frame	Unit
	Supportive secondary		
	Change in fasting plasma glucose (FPG)	From baseline (week 0) to visit 24 (week 34)	mmol/L
	Change in body weight (kg)	From baseline (week 0) to visit 24 (week 34)	kg
	Change in body weight (%)	From baseline (week 0) to visit 24 (week 34)	%
	Change in waist circumference	From baseline (week 0) to visit 24 (week 34)	cm
	Change in systolic blood pressure (SBP)	From baseline (week 0) to visit 24 (week 34)	mmHg
	Relative change in total cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in high-density lipoprotein (HDL) cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in low-density lipoprotein (LDL) cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in very-low-density lipoprotein (VLDL) cholesterol	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in triglycerides	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in free fatty acids	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in Apolipoprotein B (ApoB)	From baseline (week 0) to visit 24 (week 34)	Ratio
	Relative change in high sensitivity C-Reactive Protein (hsCRP)	From baseline (week 0) to visit 24 (week 34)	Ratio
Secondary objective 4: To compare the safety and tolerability of subcutaneously co-administered semaglutide and NNC0480 0389 (in different dose ratios) versus placebo, versus NNC0480-0389 and versus semaglutide in participants with T2D inadequately controlled on diet and exercise with or without metformin.	*Supportive secondary*		
	Number of treatment-emergent adverse events (TEAEs)	From baseline (week 0) to visit 25 (week 39)	Count of events

For the primary objective, a primary estimand and an additional estimand are defined. Two intercurrent events are identified: premature discontinuation of randomised treatment and initiation of any rescue medication (anti-diabetic medication). The primary and additional estimands will be used to address both the primary and secondary objectives for the primary endpoint. The estimands are summarised below and the attributes of the estimands are presented in Table 3-2.

Primary estimand

The primary estimand addresses the main question of interest: What is the effect of subcutaneously co-administered semaglutide and NNC0480-0389 versus placebo on change in HbA_{1c} (%-point) from baseline to week 34 in participants with T2D, with or without metformin, had all participants remained on randomised treatment without use of rescue medication (anti-diabetic medications)?

A hypothetical strategy is applied for both the intercurrent event of initiation of any rescue medication and for the intercurrent event of premature discontinuation of randomised treatment. The population-level summary is difference in means.

Results based on the primary estimand quantifies the achievable treatment effect if all participants remain on the randomised treatment without use of rescue medication. This is considered relevant to find the optimal dose ratio from an efficacy perspective.

Additional estimand for the primary objective

The additional estimand addresses an additional question of interest: What is the effect of subcutaneously co-administered semaglutide and NNC0480-0389 versus placebo on change in HbA_{1c} (%-point) from baseline to week 34 in participants with T2D, with or without metformin, regardless of premature discontinuation of randomised treatment and initiation of rescue medication (anti-diabetic medications)?

For the additional estimand, the treatment policy strategy is applied for both the intercurrent event of initiation of any rescue medication and for the intercurrent event of premature discontinuation of randomised treatment. The population-level summary is difference in means.

Results based on the additional estimand are expected to mirror the clinical practice scenario because the estimand considers both the efficacy and tolerability of subcutaneously co-administered semaglutide and NNC0480-0389.

Table 3-2 Estimand attributes

Estimand category	Treatment condition	Variable / endpoint	Population of interest	Intercurrent events and strategy	Population-level summary measure
Primary	The effect of s.c. co-administered semaglutide and NNC0480-0389 without rescue medication with or without metformin versus the effect of placebo without rescue medication with or without metformin, both as add-on to diet and exercise	Change in HbA_{1c} (%-point) from baseline to week 34	Participants with T2D. Further details can be found in Section 5.	Hypothetical strategy is applied for the 2 intercurrent events: 'initiation of any rescue medication' and 'premature discontinuation of randomised treatment'	Difference in means
Additional	The effect of s.c. co-administered semaglutide and NNC0480-0389 with or without metformin versus the effect of placebo with or without metformin, both as add-on to diet and exercise, and both regardless of initiation of rescue medication			Treatment policy strategy is applied for the 2 intercurrent events: 'initiation of any rescue medication' and 'premature discontinuation of randomised treatment'.	

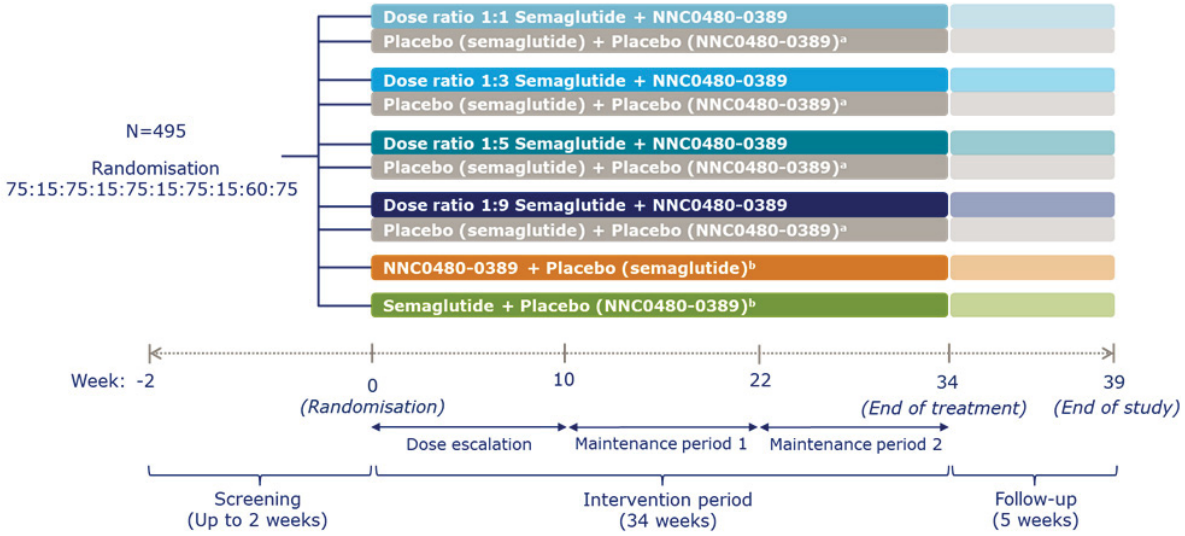
Abbreviations: s.c.: subcutaneously; T2D : type 2 diabetes

4 Study design

4.1 Overall design

This is an interventional, 34-week, randomised, parallel-group, volume-matched placebo-controlled, ten-armed, multi-centre, multi-national dose finding phase 2 study (Figure 4-1). It will be double-blinded between each dose ratio arm and volume-matched placebo arm or volume matched active comparator arm. The study will compare four different dose ratios of semaglutide and NNC0480 0389 (using a fixed dose of semaglutide and varying doses of NNC0480-0389) versus placebo, versus NNC0480-0389 and versus semaglutide, respectively, as an adjunct to diet and exercise ± metformin in participants with T2D.

Figure 4-1 Schematic overview of the study design



[a] The 4 placebo arms will be pooled into one placebo group in the main analyses
[b] Volume-matched to the dose ratio 1:9 arm

The study consists of an up to 2-week screening period followed by a 34-week intervention period and a 5-week follow-up period. The 34-week intervention period includes a 10-week dose escalation followed by two 12-week maintenance periods until end-of-treatment (week 34/V24). For each participant, the maximum intervention duration is 34 weeks and the maximum study duration is 41 weeks.

All arms in the study will contain once-weekly s.c. co-administered separate injections of semaglutide (or semaglutide matched placebo) and NNC0480-0389 (or NNC0480-0389 matched placebo). For each dose ratio, the active treatment arm and the corresponding volume-matched placebo arm will be blinded towards each other. The four dose ratios will not be blinded towards each other as different injection volumes are used. The active comparator arms (NNC0480-0389 monotherapy and semaglutide monotherapy) as well as the dose ratio 1:9 and corresponding placebo arm will use the same injection volumes and will be blinded.

The 10 study arms consist of 6 active treatment arms and 4 placebo arms, as follows:

- Dose ratio 1:1; 2.4 mg semaglutide and 2.4 mg NNC0480-0389 (75 participants)
- Dose ratio 1:3; 2.4 mg semaglutide and 7.2 mg NNC0480-0389 (75 participants)
- Dose ratio 1:5; 2.4 mg semaglutide and 12.0 mg NNC0480-0389 (75 participants)
- Dose ratio 1:9; 2.4 mg semaglutide and 21.6 mg NNC0480-0389 (75 participants)
- NNC0480-0389 21.6 mg and semaglutide matched placebo (volume-matched to the dose ratio 1:9 arm) (60 participants)
- Semaglutide 2.4 mg and NNC0480-0389 matched placebo (volume-matched to the dose ratio 1:9 arm) (75 participants)
- 4 placebo arms matching the dose ratio arms: each with semaglutide matched placebo and NNC0480-0389 matched placebo (15 participants in each arm, 60 participants on placebo in total)

The 4 placebo arms have different injection volumes to match the different dose levels of the corresponding dose ratio arms. The injection volumes to be administered in each placebo arm is outlined in Table 6-2. For the main analyses, the 4 placebo arms will be pooled into one placebo group.

For each dose ratio, participants will be randomised 75:15 to the active treatment arm and the corresponding placebo matched arm. Moreover, participants will be randomised 60:75 to the NNC0480-0389 monotherapy arm and the semaglutide monotherapy arm. This will result in an overall randomisation scheme of 75:75:75:75:60:75:60 for the four dose ratios, NNC0480-0389 monotherapy, semaglutide monotherapy, and the pooled placebo group. Randomisation will be stratified according to treatment with metformin at screening (yes/no), country (Japan/Other), and HbA_{1c} at screening (<8.5%/≥8.5%).

4.2 Scientific rationale for study design

A randomised, volume-matched placebo-controlled, double-blinded study design with four different dose ratios is applied for this study. The randomisation and double-blinded design are chosen to increase the validity of the study and to avoid bias.

The relatively homogeneous study population of participants with T2D who are in inadequate glycaemic control following treatment with diet and exercise with or without metformin limits the variability. Including participants with HbA_{1c} of 7.0-10.0% and BMI of ≥25 and <40 kg/m^2 in this study allows for an evaluation of glucose and weight management parameters.

The dose ratio for the FDC of semaglutide and NNC0480-0389 developed for phase 3 will be selected based on results from this study. To allow for exploration of the dose ratio, semaglutide and NNC0480-0389 are thus to be co-administered in separate s.c. injections in this study. The co-formulation will be ready for evaluation in phase 3.

Semaglutide and NNC0480-0389 are chosen as active comparators to compare the co-administration of semaglutide and NNC0480-0389 with each individual component. The placebo group (pool of the 4 placebo arms matching each dose ratio arm) is included to compare the co-administration of semaglutide and NNC0480-0389 versus placebo and, furthermore, to compare

NNC0480-0389 monotherapy versus placebo to evaluate the efficacy, safety and tolerability of NNC0480-0389.

The dose escalation regimen and two maintenance periods (see Table 6-2) are included to generate data on each dose level of semaglutide and NNC0480-0389 and to investigate the effect of dose escalation on the overall AE profile of the combination of semaglutide and NNC0480-0389. The study intervention duration of 34 weeks is expected to ensure adequate time for reaching steady state exposure and for comparing the effect on HbA_{1c} in accordance with the study objectives.

The follow-up period is 5 weeks to accommodate washout of at least 5 half-lives of NNC0480-0389, which is approximately 1 week based on data from the first human dose study NN9389-4536 (see the current version of the NN9389 IB). As the half-life of semaglutide is also around 1 week[6], washout of semaglutide is sufficiently covered by the follow-up period of 5 weeks.

4.3 Justification for dose

A maximum target dose of 2.4 mg semaglutide and a dose range of 2.4-21.6 mg NNC0480-0389 have been selected for this dose finding study. This dose range is selected to allow adequate exploration of the added benefits upon combining GLP-1 RA treatment with a GIP RA, while still maintaining an acceptable safety and tolerability profile. The dose ratio for the FDC of semaglutide and NNC0480-0389 developed for phase 3 will be selected based on results from this study.

Semaglutide s.c. 0.5 mg and 1.0 mg are already approved for treatment of people with T2D (Ozempic®). To evaluate a 3rd maintenance dose of semaglutide s.c. for additional glycaemic control in people with T2D, a phase 3b study investigated the efficacy and safety of semaglutide s.c. 2.0 mg compared to semaglutide s.c. 1.0 mg in participants with T2D (NN9535-4506). In addition, a phase 3a study (NN9536-4374) has compared semaglutide s.c. 2.4 mg to placebo and to semaglutide s.c. 1.0 mg in participants with overweight or obesity (BMI $\geq$ 27.0 kg/m^2) and T2D. The studies demonstrated that semaglutide 2.0 mg and 2.4 mg were well-tolerated, with safety and tolerability profiles comparable to semaglutide 1.0 mg and to the GLP-1 RA class in general.

Based on predictions from nonclinical PKPD modelling, once-weekly NNC0480-0389 doses ranging from 2.4 to 21.6 mg are expected to yield NNC0480-0389 exposures sufficient for assessing efficacy and safety to support the dose and ratio selection for the FDC. The highest planned dose of 21.6 mg NNC0480-0389 is predicted to yield steady-state exposures approximately 2.9-fold below the observed exposure in cohort 4 of the SAD part of the FHD study (NN9389-4536), in which a single dose of 60 mg NNC0480-0389 was evaluated. Overall, the SAD part of study NN9389-4536 demonstrated that single doses of 1.7-60 mg NNC0480-0389 co-administered with 0.5 mg semaglutide were well-tolerated, with no safety concerns identified.

Semaglutide and NNC0480-0389 will be administered s.c. in the study as this is the intended route of administration for the market. Semaglutide is already approved as a s.c. injection for treatment of people with T2D (Ozempic®) and NNC0480-0389 is formulated as a solution for s.c. injection. The once-weekly dosing regimen is consistent with the half-life of approximately 1 week for both semaglutide and NNC0480-0389 (based on data from the FHD study NN9389-4536).

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 last visit (end-of-study visit 25).

The primary endpoint is evaluated at visit 24 (week 34). The primary completion date (PCD) is defined as the date of visit 24 (week 34) on which the last participant in the clinical study has an assessment for the primary endpoint. If the last participant is withdrawn early, the PCD is considered the date when the last participant would have completed visit 24.

5 Study population

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

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

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all of 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 of non-childbearing potential. See Appendix 4 (Section 10.4) for the definition of a woman of non-childbearing potential.
3. Aged 18-75 years (both inclusive) at the time of signing informed consent.
   For Japan only: Age 20-75 years (both inclusive) at the time of signing informed consent.
4. Diagnosed with type 2 diabetes mellitus ≥ 180 days before screening.
5. Participants treated with diet and exercise as monotherapy or in combination with stable daily dose(s) ≥ 90 days before screening of any metformin formulations ≥ 1500 mg or maximum tolerated or effective dose.
6. HbA_{1c} 7.0-10.0% (53-86 mmol/mol) (both inclusive)
7. BMI ≥25 and <40 kg/m^2

5.2 Exclusion criteria

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

1. Known or suspected hypersensitivity to study intervention(s) or related products.
2. Previous participation in this study. Participation is defined as signed informed consent.
3. Male participants who are not surgically sterilised (vasectomy) and are sexually active with female partner(s) of childbearing potential and not using condom and/or intend to donate sperm in the period from randomisation visit (V2) until 5 weeks after administration of the investigational medicinal product.
4. Participation (i.e. signed informed consent) in any interventional, clinical study within 90 days before screening.
5. Receipt of an approved COVID-19 vaccine within 14 days prior to screening or planned COVID-19 vaccination between screening and randomisation
6. Any disorder, which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.
7. Anticipated change in lifestyle (e.g. eating, exercise or sleeping pattern) during the study.
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[a]
10. History or presence of chronic pancreatitis[a]
11. Presence of acute pancreatitis within 180 days before screening[a]

12. Myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within 180 days before screening
13. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.
14. Planned coronary, carotid or peripheral artery revascularisation.
15. Renal impairment with estimated Glomerular Filtration Rate (eGFR) < 60 mL/min/1.73 m^2
16. Impaired liver function, defined as Alanine Aminotransferase (ALT) ≥ 2.5 times or Bilirubin >1.5 times upper normal limit at screening
17. Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8.
18. Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator.
19. Inadequately treated blood pressure defined as systolic ≥180 mmHg or diastolic ≥110 mmHg at screening.
20. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days before screening. However, short term insulin treatment for a maximum of 14 days and prior insulin treatment for gestational diabetes are allowed.
21. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).
22. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within 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.
23. 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.
24. Presence or history of any clinically relevant respiratory, metabolic, renal, hepatic cardiovascular, gastrointestinal, or endocrinological conditions (except conditions associated with T2D)
25. Use of any medication with unknown or unspecified content within 90 days before screening.

[a] As declared by the participants or in the medical records

5.3 Lifestyle considerations

5.3.1 Meals and dietary restrictions

- Participants must attend several visits in a fasting state, as indicated in the flowchart.
- Fasting is defined as at least 8 hours prior to the visit without food or liquids, except for water.
- Any medication which should be taken with or after a meal should be withheld on the day of the visit until blood samples have been obtained.
- If the participant is not fasting as required, the participant should be called in for a new visit within the visit window to have the fasting procedures done.
- Assessments requiring participants to fast are listed in Appendix 2 (Section 10.2)

5.3.2 Caffeine, alcohol and tobacco

Participants should avoid caffeine and tobacco use for at least 30 minutes prior to measuring vital signs (Section 8.3.2).

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

5.3.3 Activity

Participants should avoid physical activity for at least 30 minutes prior to measuring the vital signs (Section 8.3.2).

5.4 Screen failures

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

A screen failure session must be made in the interactive web response system (IWRS).

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

5.5 Randomisation criteria

To be randomised, the randomisation criteria must be answered ‘yes’.

1. No receipt of an approved COVID-19 vaccine between screening and randomisation

6 Study intervention(s) and concomitant therapy

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

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

6.1 Study intervention(s) administered

Table 6-1 provides an overview of the IMPs in the study. The doses and injections volumes of the IMPs to be administered in each study arm during dose escalation steps and the maintenance period are presented in Table 6-2.

Table 6-1 Investigational medicinal products

Full intervention name incl. trial product strength	Semaglutide B 1.34 mg/mL PDS290	Semaglutide B 3.0 mg/mL PDS290	NNC0480-0389 A 10 mg/mL	NNC0480-0389 A 30 mg/mL	Semaglutide placebo (1.34 mg/mL)	Semaglutide placebo (3.0 mg/mL)	Placebo A (for NNC0480-0389)
Intervention type	IMP, test product	IMP, test product	IMP, test product	IMP, test product	IMP, reference therapy	IMP, reference therapy	IMP, reference therapy
Pharmaceutical form	Solution for injection						
Route of administration	Subcutaneous						
Medical device	Not applicable See 'Packaging' for device constituent	Not applicable See 'Packaging' for device constituent	NovoPen® 4 The medical device is not under investigation.	NovoPen® 4 The medical device is not under investigation.	Not applicable See 'Packaging' for device constituent	Not applicable See 'Packaging' for device constituent	NovoPen® 4 The medical device is not under investigation.
Dose and dose frequency	Once-weekly dosing. For dose, see Table 6-2						
Sourcing	Manufactured and supplied by Novo Nordisk A/S						
Packaging	1.5 mL PDS290 pre-filled pen injector. The device constituent is not under investigation.	3 mL PDS290 pre-filled pen injector. The device constituent is not under investigation.	3 mL cartridge (to be administered with NovoPen® 4)	3 mL cartridge (to be administered with NovoPen® 4)	1.5 mL PDS290 pre-filled pen injector. The device constituent is not under investigation.	3 mL PDS290 pre-filled pen injector. The device constituent is not under investigation.	3 mL cartridge (to be administered with NovoPen® 4)
Labelling	Labelled and packaged by Novo Nordisk A/S Labelled in accordance with Annex 13,[7] local regulations and study requirements						

Abbreviation: IMP: investigational medicinal product

The investigator must document that directions for use was given to the participant verbally and in writing as directions for use (DFU) documents at the first dispensing visit and at V4, V12 and V18 (as specified in the flowchart). The investigator should remind participants of dosing instructions throughout the study, as applicable, and a dose reminder card will be handed out to the participants at each visit to remind the participant of the dose to be taken until next site visit. A pen differentiation guide and training in how to use the guide should also be provided to the participants at the first dispensing visit.

Investigational medicinal products (IMP)

The investigational medicinal products (IMPs, test products) are listed in Table 6-1.

Two different strengths of semaglutide and NNC0480-0389, respectively, will be used to administer the planned doses in this study as outlined in Table 6-2. Accordingly, two different semaglutide placebo products will be used to match 1.34 mg/mL and 3.0 mg/mL semaglutide, respectively. Placebo A will be used for NNC0480-0389 and is visually identical to both the 10 mg/mL and 30 mg/mL strength; however, the packaging of placebo A will be blinded towards 10 mg/mL and 30 mg/mL NNC0480-0389, respectively.

Dosing instructions

Participants will be instructed to inject semaglutide/semaglutide placebo and NNC0480-0389/placebo A once-weekly at any time of the day, with or without meals, on the same day of the week (to the extent possible) throughout the study. At V2, V4, V6, V8, V10, V12, and V18 the semaglutide/semaglutide placebo and NNC0480-0389/placebo A injections must be administered during the site visit.

The semaglutide/semaglutide placebo and NNC0480-0389/placebo A injections should be administered together by using separate injection areas. The injection site can be changed from week to week between the abdomen, thigh and upper arm, and injections should not be administered intravenously or intramuscularly.

The administration of semaglutide/semaglutide placebo should be performed first and must be performed in the left side of the participant's abdomen, thigh or upper arm.

The administration of NNC0480-0389/placebo A should be performed immediately after completion of the administration of semaglutide/semaglutide placebo and must be performed in the right side of the participant's abdomen, thigh or upper arm. To administer the 2nd maintenance dose in the dose ratio 1:9, volume-matched placebo, NNC0480-0389 monotherapy and semaglutide monotherapy study arms, participants need to administer 2 injections (Table 6-2). The 2nd injection of NNC0480-0389/placebo A should be administered immediately after the first injection of NNC0480-0389/placebo A and the 2 injections should be administered in the same injection area, i.e. in the abdomen, thigh or upper arm.

Dose escalation

Dose escalation should take place during the first 10 weeks after randomisation, followed by an 12-week maintenance period 1 and subsequent dose escalation to an 12-week maintenance period 2. Doses, numbers to be dialled on pen and strength of trial products used during the study are

specified in Table 6-2. A simplified table showing only the numbers to be dialled on the PDS290 pen-injector and NovoPen® 4, respectively, is provided in Table 6-3. Deviations from the planned dose regimen are not allowed. If dose escalation is not tolerated, participants are to discontinue the randomised treatment.

Table 6-2 Escalation and maintenance dose, numbers to be dialled on pen and strength

			Dose escalation			Maintenance	
Duration			2 weeks	4 weeks	4 weeks	12 weeks	12 weeks
Study arms – dose ratio 1:1							
Dose ratio 1:1	Semaglutide 2.4 mg	Dose Dial on pen Strength	0.25 mg 0.25 mg 1.34 mg/mL	0.5 mg 0.5 mg 1.34 mg/mL	1.0 mg 1.0 mg 1.34 mg/mL	2.0 mg 67 3.0 mg/mL	2.4 mg 80 3.0 mg/mL
	NNC0480-0389 2.4 mg	Dose Dial on pen Strength	0.3 mg 3 10 mg/mL	0.5 mg 5 10 mg/mL	1.0 mg 10 10 mg/mL	2.0 mg 20 10 mg/mL	2.4 mg 24 10 mg/mL
Volume-matched placebo	Semaglutide placebo	Dial on pen Matching	0.25 mg 0.25 mg of 1.34 mg/mL	0.5 mg 0.5 mg of 1.34 mg/mL	1.0 mg 1.0 mg of 1.34 mg/mL	67 2.0 mg of 3.0 mg/mL	80 2.4 mg of 3.0 mg/mL
	Placebo A (NNC0480-0389)	Dial on pen Matching	3 0.3 mg of 10 mg/mL NNC0480-0389	5 0.5 mg of 10 mg/mL NNC0480-0389	10 1.0 mg of 10 mg/mL NNC0480-0389	20 2.0 mg of 10 mg/mL NNC0480-0389	24 2.4 mg of 10 mg/mL NNC0480-0389
Study arms – dose ratio 1:3							
Dose ratio 1:3	Semaglutide 2.4 mg	Dose Dial on pen Strength	0.25 mg 0.25 mg 1.34 mg/mL	0.5 mg 0.5 mg 1.34 mg/mL	1.0 mg 1.0 mg 1.34 mg/mL	2.0 mg 67 3.0 mg/mL	2.4 mg 80 3.0 mg/mL
	NNC0480-0389 7.2 mg	Dose Dial on pen Strength	0.8 mg 8 10 mg/mL	1.5 mg 15 10 mg/mL	3.0 mg 30 10 mg/mL	6.0 mg 60 10 mg/mL	7.2 mg 24 30 mg/mL
Volume-matched placebo	Semaglutide placebo	Dial on pen Matching	0.25 mg 0.25 mg of 1.34 mg/mL	0.5 mg 0.5 mg of 1.34 mg/mL	1.0 mg 1.0 mg of 1.34 mg/mL	67 2.0 mg of 3.0 mg/mL	80 2.4 mg of 3.0 mg/mL
	Placebo A (NNC0480-0389)	Dial on pen Matching	8 0.8 mg of 10 mg/mL	15 1.5 mg of 10 mg/mL	30 3.0 mg of 10 mg/mL	60 6.0 mg of 10 mg/mL	24 7.2 mg of 30 mg/mL
Study arms - dose ratio 1:5							
Dose ratio 1:5	Semaglutide 2.4 mg	Dose Dial on pen Strength	0.25 mg 0.25 mg 1.34 mg/mL	0.5 mg 0.5 mg 1.34 mg/mL	1.0 mg 1.0 mg 1.34 mg/mL	2.0 mg 67 3.0 mg/mL	2.4 mg 80 3.0 mg/mL
	NNC0480-0389 12 mg	Dose Dial on pen Strength	1.3 mg 13 10 mg/mL	2.5 mg 25 10 mg/mL	5.0 mg 50 10 mg/mL	10.0 mg 33 30 mg/mL	12.0 mg 40 30 mg/mL
Volume-matched placebo	Semaglutide placebo	Dial on pen Matching	0.25 mg 0.25 mg of 1.34 mg/mL	0.5 mg 0.5 mg of 1.34 mg/mL	1.0 mg 1.0 mg of 1.34 mg/mL	67 2.0 mg of 3.0 mg/mL	80 2.4 mg of 3.0 mg/mL
	Placebo A (NNC0480-0389)	Dial on pen Matching	13 1.3 mg of 10 mg/mL	25 2.5 mg of 10 mg/mL	50 5.0 mg of 10 mg/mL	33 10.0 mg of 30 mg/mL	40 12.0 mg of 30 mg/mL

			Dose escalation			Maintenance	
Duration			2 weeks	4 weeks	4 weeks	12 weeks	12 weeks
Study arms – dose ratio 1:9							
Dose ratio 1:9	Semaglutide 2.4 mg	Dose Dial on pen Strength	0.25 mg 0.25 mg 1.34 mg/mL	0.5 mg 0.5 mg 1.34 mg/mL	1.0 mg 1.0 mg 1.34 mg/mL	2.0 mg 67 3.0 mg/mL	2.4 mg 80 3.0 mg/mL
	NNC0480-0389 21.6 mg	Dose Dial on pen Strength	2.3 mg 23 10 mg/mL	4.5 mg 45 10 mg/mL	9.0 mg 30 30 mg/mL	18.0 mg 60 30 mg/mL	21.6 mg 36+36 30 mg/mL
Volume-matched placebo	Semaglutide placebo	Dial on pen Matching	0.25 mg 0.25 mg of 1.34 mg/mL	0.5 mg 0.5 mg of 1.34 mg/mL	1.0 mg 1.0 mg of 1.34 mg/mL	67 2.0 mg of 3.0 mg/mL	80 2.4 mg of 3.0 mg/mL
	Placebo A (NNC0480-0389)	Dial on pen Matching	23 2.3 mg of 10 mg/mL	45 4.5 mg of 10 mg/mL	30 9.0 mg of 30 mg/mL	60 18.0 mg of 30 mg/mL	36+36 21.6 mg of 30 mg/mL
Study arm – NNC0480-0389 monotherapy							
NNC0480-0389 mono	NNC0480-0389 21.6 mg	Dose Dial on pen Strength	2.3 mg 23 10 mg/mL	4.5 mg 45 10 mg/mL	9.0 mg 30 30 mg/mL	18.0 mg 60 30 mg/mL	21.6 mg 36+36 30 mg/mL
	Semaglutide placebo	Dial on pen Matching	0.25 mg 0.25 mg of 1.34 mg/mL	0.5 mg 0.5 mg of 1.34 mg/mL	1.0 mg 1.0 mg of 1.34 mg/mL	67 2.0 mg of 3.0 mg/mL	80 2.4 mg of 3.0 mg/mL
Study arm – semaglutide monotherapy							
Sema-glutide mono	Semaglutide 2.4 mg	Dose Dial on pen Strength	0.25 mg 0.25 mg 1.34 mg/mL	0.5 mg 0.5 mg 1.34 mg/mL	1.0 mg 1.0 mg 1.34 mg/mL	2.0 mg 67 3.0 mg/mL	2.4 mg 80 3.0 mg/mL
	Placebo A (NNC0480-0389)	Dial on pen Matching	23 2.3 mg of 10 mg/mL	45 4.5 mg of 10 mg/mL	30 9.0 mg of 30 mg/mL	60 18.0 mg of 30 mg/mL	36+36 21.6 mg of 30 mg/mL

Numbers to be dialled on pen: the dose of semaglutide 1.34 mg/mL / semaglutide placebo and the increments (pen injector units) of semaglutide 3.0 mg/mL / semaglutide placebo and NNC0480-0389/placebo A.

In each study arm, participants should co-administered separate injections of semaglutide/semaglutide placebo using the PDS290 pen-injector and NNC0480-0389/placebo A using NovoPen® 4. Two types of semaglutide placebo trial products will be used to match 1.34 mg/mL and 3.0 mg/mL semaglutide, respectively. Placebo A is used for NNC0480-0389, and the packaging of placebo A will be blinded towards 10 mg/mL and 30 mg/mL NNC0480-0389, respectively.

To administer the 2nd maintenance dose in the dose ratio 1:9, volume-matched placebo, NNC0480-0389 monotherapy and semaglutide monotherapy study arms, participants need to administer 2 injections of NNC0480-0389/placebo A.

With the trial product strength and injection volume that can be delivered with the PDS290 pen-injector for semaglutide 3.0 mg/mL, the actual dose administered is 2.01 mg; however, this is written as 2.0 mg throughout the protocol.

Table 6-3 Numbers to be dialled on PDS290 pen-injector and NovoPen® 4 during dose escalation and maintenance

	Dose escalation			Maintenance	
Duration	2 weeks	4 weeks	4 weeks	12 weeks	12 weeks
Dose ratio 1:1 or volume-matched placebo					
PDS290 pen-injector (blue pen) Semaglutide or semaglutide placebo	0.25 mg (light blue pen)	0.5 mg (light blue pen)	1.0 mg (light blue pen)	67 (dark blue pen)	80 (dark blue pen)
NovoPen® 4 (grey pen) NNC0480-0389 or placebo A	3 (green box label)	5 (green box label)	10 (green box label)	20 (green box label)	24 (green box label)
Dose ratio 1:3 or volume-matched placebo					
PDS290 pen-injector (blue pen) Semaglutide or semaglutide placebo	0.25 mg (light blue pen)	0.5 mg (light blue pen)	1.0 mg (light blue pen)	67 (dark blue pen)	80 (dark blue pen)
NovoPen® 4 (grey pen) NNC0480-0389 or placebo A	8 (green box label)	15 (green box label)	30 (green box label)	60 (green box label)	24 (white box label)
Dose ratio 1:5 or volume-matched placebo					
PDS290 pen-injector (blue pen) Semaglutide or semaglutide placebo	0.25 mg (light blue pen)	0.5 mg (light blue pen)	1.0 mg (light blue pen)	67 (dark blue pen)	80 (dark blue pen)
NovoPen® 4 (grey pen) NNC0480-0389 or placebo A	13 (green box label)	25 (green box label)	50 (green box label)	33 (white box label)	40 (white box label)
Dose ratio 1:9 or volume-matched placebo, NNC0480-0389 monotherapy or semaglutide monotherapy					
PDS290 pen-injector (blue pen) Semaglutide or semaglutide placebo	0.25 mg (light blue pen)	0.5 mg (light blue pen)	1.0 mg (light blue pen)	67 (dark blue pen)	80 (dark blue pen)
NovoPen® 4 (grey pen) NNC0480-0389 or placebo A	23 (green box label)	45 (green box label)	30 (white box label)	60 (white box label)	36+36 (white box label)

Numbers to be dialled on pen: the dose of semaglutide 1.34 mg/mL / semaglutide placebo and the increments (pen injector units) of semaglutide 3.0 mg/mL / semaglutide placebo and NNC0480-0389/placebo A

Missed doses

If a single dose of trial product (semaglutide and/or NNC0480-0389) is missed, it should be administered as soon as noticed, provided the time to next scheduled dose is at least 2 days (48 hours). If a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the participant should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week or the dose escalation regimen outlined in Table 6-2.

If ≥ 2 consecutive doses of trial product (semaglutide and/or NNC0480-0389) are missed, and the participant does not meet any of the discontinuation criteria, the participant should be encouraged to re-commence the treatment if considered safe as per the investigator's discretion. The trial product should be continued as early as the situation allows. The missed doses should not affect the scheduled dosing day of the week. In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk global medical experts.

Non-investigational medicinal products (NIMP)

Anti-diabetic background medication (metformin) and rescue medication are considered non-investigational medicinal products and will not be supplied by Novo Nordisk.

Auxiliary supplies including medical device(s) not under investigation

Auxiliary supplies (Table 6-4) will be provided by Novo Nordisk.

Table 6-4 Auxiliary supplies

Auxiliary supply	Details
Needles	Needles for PDS290 pen-injector and NovoPen® 4. Details will be provided in the Trial Materials Manual (TMM). Only needles provided by Novo Nordisk and with a maximum length of 6 mm must be used for administration of trial product.
Direction for use (DFU)	DFUs for PDS290 pen-injectors and NovoPen® 4, respectively. DFUs are not included in the dispensing unit and must be handed out separately.
Blood glucose (BG) meters and related auxiliaries	A FreeStyle Optium Neo BG meter (in RS: FreeStyle Precision Neo; in RU: FreeStyle Libre Reader; in US: Precision Xtra BG meter) will be handed out at the randomisation visit (V2). Participants will be instructed in how to use the BG-meter and the instructions will be repeated during the study as needed.
NovoPen® 4	NovoPen® 4 for s.c. administration of NNC0480-0389 and placebo A. NovoPen® 4 has been packed and labelled specifically for the present study.

NovoPen® 4 (medical device) is used for administration of NNC0480-0389 and placebo A and is a durable device which is not under investigation in this study. NovoPen® 4 is a reusable dial-a-dose pen-injector designed to be used with Novo Nordisk Penfill 3 mL cartridges. It can deliver doses of 1-60 pen-injector units in increments of 1 unit. One unit (increment) is equivalent to 10 µl thus the pen-injector can deliver volumes of 10-600 µl. The user can dial up and down in order to adjust a dose. NovoPen® 4 was CE marked in 2005 in accordance with Annex II in the Medical Device Directive 93/42 EEC.

Risk assessment has been conducted for NovoPen® 4 in accordance with EN ISO 14971:2012: Medical devices - Application of risk management to medical devices. A study-specific device risk assessment has also been performed to ensure safe and accurate handling and dosing of NNC0480-0389 (and placebo A) when using NovoPen® 4 in participants with T2D. No additional risks were associated with using NovoPen® 4 according to the clinical procedures specified in this protocol, compared with using NovoPen® 4 within its approved intended use and indication for use. The use of NovoPen® 4 in this study is therefore considered to be of non-significant risk.

The PDS290 pen-injector (device constituent) is used for administration of semaglutide and semaglutide placebo and is a pre-filled pen-injector which is not under investigation in this study. The PDS290 pen-injector is a dial-a-dose prefilled device integrated with a 1.5 mL cartridge (filled with semaglutide 1.34 mg/mL or placebo) or a 3 mL cartridge (filled with semaglutide 3.0 mg/mL or placebo). The PDS290 pen-injector for semaglutide 1.34 mg/mL can deliver the doses of 0.25 mg, 0.5 mg and 1.0 mg (dose dialled on pen-injector) and the PDS290 pen-injector for semaglutide 3.0 mg/mL can deliver the doses of 2.0 mg and 2.4 mg (pen-injector units dialled on pen-injector). The PDS290 pen-injector for semaglutide 3.0 mg/mL can deliver doses of 1-80 units in increments of 1 unit. One unit (increment) is equivalent to 10 µl thus the pen-injector can deliver volumes of 10-800 µl. The user can dial up and down in order to select the correct dose.

Risk assessment has been conducted for the PDS290 pen-injector for semaglutide 1.34 mg/ml and 3.0 mg/ml (and semaglutide placebo) in accordance with EN ISO 14971:2019 when using the PDS290 pen-injector in participants with T2D. All identified risks associated with using the PDS290 pen-injector for semaglutide 1.34 mg/ml and 3.0 mg/ml (and semaglutide placebo) 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. Use of the PDS290 pen-injector for semaglutide 1.34 mg/ml and 3.0 mg/ml (and semaglutide placebo) in this study is therefore considered to be of non-significant risk.

6.2 Preparation, handling, storage and accountability

Only participants enrolled in the study may use trial products and only delegated site staff may supply trial products.

Instructions on how to use the PDS290 pen-injector and NovoPen® 4 will be provided in the DFUs.

Each site will be supplied with sufficient study intervention 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 TMM.

The investigator or designee is responsible for trial product accountability and record maintenance (i.e., receipt, accountability and final disposition records). Japan: For country-specific requirements, please refer to Appendix 10 (Section 10.10).

The investigator or designee must instruct the participant in what to return at next visit.

The investigator or designee must instruct the participant on how to manage the in-use time of the dispensed products.

Drug accountability must be done on a pen level for the PDS290 pen-injector and on a cartridge level for the cartridges supplied for NovoPen® 4. No accountability is performed for NovoPen® 4. Drug accountability must be documented in a drug accountability log and in the IWRS by registering pens/cartridges as used, unused or lost.

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.

6.3 Measures to minimise bias: Randomisation and blinding

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

Randomisation will be stratified according to treatment with metformin at screening (yes/no), country (Japan/Other), and HbA_{1c} at screening (<8.5%/≥8.5%).

At screening, each participant will be assigned a unique 6-digit Subject ID, which will remain the same throughout the study. Each site is assigned a 3-digit number and Subject IDs will start with the site number.

This is a double-blind study in which participants, care providers, investigators and outcome assessors are blinded to trial product allocation. Specifically, the study is double-blinded between each dose ratio arm and the corresponding volume-matched placebo arm. The active comparator arms are blinded towards the dose ratio 1:9 arm and the corresponding volume-matched placebo arm (Section 4.1).

To preserve the blinding of the study in the event of interim evaluation, only a minimum number of Novo Nordisk personnel are allowed to see the randomisation table and treatment assignments before the study is completed.

The IWRS is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's trial product is warranted. Participant safety must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Novo Nordisk prior to unblinding a participant's study intervention unless this could delay emergency treatment of the participant.

If a participant's trial product is unblinded, Novo Nordisk (Global Safety department) must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation. The person breaking the blind must print the blind break confirmation notification generated by the IWRS, sign and date the document. If IWRS is not accessible at the time of blind break, the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

Participants will continue on trial product if there are no safety concerns at the discretion of the investigator.

6.4 Study intervention compliance

Drug treatment compliance

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

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

- Accountability information; counting returned trial product, visual inspection of pens
- Review of diaries

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

6.5 Dose modification

Deviations from the planned doses (see Table 6-2) are not allowed.

6.6 Continued access to study intervention after end of study

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

6.7 Treatment of overdose

Any dose of semaglutide or NNC0480-0389 greater than the planned dose according to dosing schedule (Table 6-2) and which deviate from the intended dose to an extent where clinical consequences for the study participants are likely to happen, as judged by the investigator, will be considered an overdose.

Based on the clinical data available, there is currently no experience with overdose of NNC0480-0389 alone or of co-administered semaglutide and NNC0480-0389. For semaglutide, overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical studies. The most commonly reported adverse event was nausea. All patients recovered without complications.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.4 and Appendix 3 (Section 10.3) for further details.

In the event of an overdose, the investigator should closely monitor the participant for overdose related AEs/SAEs. Appropriate treatment should be initiated according to the participant's clinical signs and symptoms. A prolonged period of observation and treatment for symptoms may be necessary, taking the long half-life of both components into account (approximately 1 week for semaglutide and NNC0480-0389, respectively).

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

For more information on overdose, also consult the current version of the NN9389 investigator's brochure (IB).

6.8 Concomitant therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of the first visit (V1) or receives until end of study must be recorded along with:

- Trade name or generic name
- Primary indication
- Dates of administration including start and stop dates
- Dose (only applicable for anti-diabetic medication)
- Frequency (only applicable for anti-diabetic medication)

Approved COVID-19 vaccines that the participant received within 6 months prior to screening should be recorded in the eCRF at the screening visit (V1).

Changes in concomitant therapy must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 8.4.

After signing the informed consent, participants must continue their anti-diabetic background medication (metformin) throughout the entire study and the background medication dose should remain at the same dose level and with the same frequency during the entire study intervention period unless glycaemic rescue medication is needed (as described in Section 6.8.1) or safety concern related to the use of anti-diabetic background medication arises.

In addition, all background medication:

- is considered to be non-investigational medicinal product (Section 6.1).
- should be used in accordance with standard of care and current approved label in the individual country.
- should not exceed the maximum approved dose in the individual country.

6.8.1 Rescue medicine

Glycaemic rescue medication, i.e. intensification of background OAD treatment and/or initiation of new anti-diabetic treatment, should be implemented at the discretion of the investigator in case of persistent hyperglycaemia. Please see Section 7.1.2 for rescue criteria.

Rescue medication should be selected according to the ADA/EASD guideline[8,9] (preferably excluding GLP-1 RAs, dipeptidyl peptidase-4 (DPP-4) inhibitors and amylin analogues).

Participants that are started on rescue medication should continue to follow the protocol-specified visit schedule and stay on randomised treatment unless the investigator judge that it jeopardises participant's safety.

Rescue medication (intensification of existing background medication and/or initiation of new medication) and any changes to this should be documented in medical records and reported on the concomitant medication form in the eCRF.

7 Discontinuation of study intervention and participant discontinuation/withdrawal

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

7.1 Discontinuation of study intervention

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

Efforts must be made to have participants attend and complete all scheduled visit procedures to collect the required data for the analysis of the primary endpoint. 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 as judged by the investigator (including any clinically relevant changes in vital signs or laboratory parameters)
2. Safety concern due to recurrent symptomatic or severe hypoglycaemic events possibly or probably related to study medication, as judged by the investigator
3. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study
4. Confirmation of acute pancreatitis

Participants who discontinue randomised treatment should continue with the remaining scheduled study visits and assessments until the end of treatment visit (V24) and end of study visit (V25), as per the flowchart (Section 1.2).

If a participant is unwilling to attend any of the scheduled clinic visits, efforts should be made to have the remaining visits converted to phone contacts. However, as a minimum, these participants must be asked to attend V24 in order to collect the required data for the analysis of the primary endpoint, and information about the attempts to follow-up with the participant must be documented in the medical records.

When initiating new anti-diabetic treatment after discontinuation of randomised treatment, the half-life of semaglutide and of NNC0480-0389 of approximately one week should be kept in mind.

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

7.1.1 Temporary discontinuation of study intervention

In case of suspicion of acute pancreatitis, the randomised treatment should promptly be interrupted (treatment discontinuation session should not be made in IWRS before diagnosis of acute pancreatitis is confirmed). Appropriate actions should be initiated, including local measurement of

amylase and lipase (see Appendix 3, Section 10.3 for reporting of AE). If acute pancreatitis is confirmed, randomised treatment should not be restarted, and a treatment discontinuation session should be made in IWRS. If the Atlanta criteria[10] are not fulfilled and thus, the suspicion of acute pancreatitis is not confirmed, randomised treatment may be resumed.

If a participant has discontinued randomised treatment due to temporary safety concern not related to the randomised treatment and is allowed to resume, the participant should follow the guide for missed doses (Section 6.1). Similarly, a participant who discontinues randomised treatment on their own initiative should be encouraged to resume the randomised treatment.

7.1.2 Rescue criteria

If any of the fasting plasma glucose (FPG) values exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified, the participant should be offered treatment intensification (rescue medication, see Section 6.8.1).

Rescue medication should be offered if FPG values exceeds:

- 15.0 mmol/L (270 mg/dL) from randomisation to end of week 5
- 13.3 mmol/L (240 mg/dL) from week 6 to end of week 11
- 11.1 mmol/L (200 mg/dL) from week 12 to end of study

A confirmatory FPG should be obtained by the central laboratory. If the confirmatory FPG exceeds the values described above, the participant should be offered treatment intensification (rescue medication) at the discretion of the investigator and in accordance with the ADA/EASD guideline[8,9] (preferably excluding GLP-1 RAs, DPP-4 inhibitors and amylin analogues). Rescue medication should be prescribed as add-on to randomised treatment and participants should continue to follow the protocol-specified visit schedule.

7.2 Participant discontinuation/withdrawal from the study

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

If a participant withdraws consent prior to randomisation, he/she will not be asked to have any follow-up assessments performed. The following data must be collected: Demography, eligibility criteria, date of informed consent, date of screening and the date when 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 V24. See the flowchart (Section 1.2) for data to be collected.

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

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

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

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

7.2.1 Replacement of participants

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

7.3 Lost to follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, at least three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's source document.
- Should the participant continue to be unreachable by the end of the study (for definition of the end of study, see Section 4.4), 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, is essential and required for study conduct.

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

- Blood sampling
- Other assessments

A visit-specific diary for collection of detailed dosing information, hypoglycaemic episodes, and adverse events must be handed out at each site visit from randomisation (V2) to end of treatment (V24) included.

Review of diaries, ECG, laboratory reports etc. must be documented in the source documents or the participant's medical record. If clarification of entries or discrepancies in the diary 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.

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 Screening assessments

Demography

The following information has to be recorded after informed consent at the screening visit (V1):

- Date of birth, unless not permitted by local regulations (Appendix 10, Section 10.10)
- Sex
- Race, unless not permitted by local regulations
- Ethnicity, unless not permitted by local regulations

Tobacco use

Details of tobacco use must be recorded at screening. Tobacco use is defined as smoking at least one cigarette or equivalent daily.

Smoking status information to be collected:

- Never smoked
- Previous smoker (smoking stop date)
- Current smoker

Woman of non-childbearing potential

The assessment of childbearing potential in female participants should be performed at the screening visit (V1) and recorded as specified in the flowchart (Section 1.2) and Appendix 4 (Section 10.4).

8.2 Efficacy assessments

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

8.2.1 Clinical efficacy laboratory assessments

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

8.2.2 Body measurements

Body measurements (height, weight, waist circumference) are described as part of the physical examinations (Section 8.3.1).

8.3 Safety assessments

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

Medical history is a medical event that the participant experienced prior to the time point from which AEs are collected. Only relevant medical history as judged by the investigator should be reported in the eCRF. However, medical history related to diabetes complications and cardiovascular disease must be specifically reported in the medical history/concomitant illness form in the eCRF.

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

In case of an abnormal and clinically significant finding fulfilling the definition of medical history or concomitant illness, the investigator must record the finding on the medical history/concomitant illness form. The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

Any change to a concomitant illness should be recorded during the study. A clinically significant worsening of a concomitant illness must be reported as an AE (Section 8.4).

Information on hypoglycaemia unawareness will be recorded according to Clarke's questionnaire, question 8.[11] 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.

8.3.1 Physical examinations

A physical examination will be performed as specified in the flowchart (Section 1.2) and will include assessments of:

- general appearance
- skin
- thyroid gland
- respiratory system
- cardiovascular system
- gastrointestinal system including mouth
- central and peripheral nervous system
- lymph node palpation.

Any abnormal, clinically significant findings before first administration of randomised treatment must be recorded as concomitant illness. Any clinically significant worsening from time of first administration of randomised treatment must be reported as an AE (Section 8.4).

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

Body weight should be measured at all on-site visits and should be measured without shoes and only wearing light clothing and recorded in the eCRF in kilogram or pound [kg/lb], with a precision of 1/10 unit, (e.g. 62.2 kg / 137.2 lb). BMI will be calculated in the eCRF. The body weight should be assessed on the same calibrated weighing scale throughout the study. The scale must be calibrated yearly as a minimum, unless the manufacturer certifies that calibration of the weighing scale is valid for the lifetime of the scale.

Height is measured without shoes in centimetres (cm) or inches (in) at V1 and recorded in the eCRF.

Waist circumference is measured in centimetres (cm) or inches (in) at V2, V6, V10, V13, V16, V18, V20, V22 and V24 and recorded in the eCRF. 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 waist circumference should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The participant should be standing with arms down their side and feet together. The tape should touch the skin but not compress soft tissue. The participant should be asked to breathe normally, and the measurement should be taken when the participant is breathing out gently.

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

8.3.2 Vital signs

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

Participants should avoid caffeine and tobacco use and physical activity for at least 30 minutes prior to measuring vital signs. 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 all on-site visits in the study, as specified in the flowchart (Section 1.2). At V2, V4, V6, V8, V10, V12, and V18 vital signs must be measured pre-dose, 2 hours post-dose and 4 hours post-dose. The participant can be discharged if no concerns are raised based on 4-hour assessments. If considered needed by the investigator an additional vital sign assessment can be taken after 6 hours before the participant is discharged from site. These assessments do not need to be performed in a fasting state.

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 two consecutive readings on systolic or diastolic blood pressure differ by >10 mmHg. No more than four measurements should be performed. The last 2 systolic and last 2 diastolic blood pressure measurements should be recorded in the eCRF. The eCRF will calculate the mean systolic blood pressure and mean diastolic blood pressure values based on the last 2 measurements.

Pulse rate will be measured in connection to the blood pressure measurements. The pulse rate for the last 2 measurements should be recorded in the eCRF. The eCRF will calculate the mean pulse rate value based on the last 2 measurements.

Any clinically significant worsening from time of first administration of randomised treatment must be reported as an AE (Section 8.4).

8.3.3 Eye examination

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

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

If the participant had such an eye examination performed within 90 days prior to screening, the investigator may base his/her evaluation upon the results of that examination. The examination must

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

After randomisation an eye examination must be performed according to above as per protocol flowchart. Results must be available at V24 (end of treatment visit). An eye examination performed within 3 weeks prior to V24 is acceptable, provided no clinical symptoms suggestive of eye disease have occurred in the meantime.

The investigator should indicate the outcome of each eye examination. Relevant findings prior to randomisation must be recorded as concomitant illness/medical history, while relevant findings occurring after randomisation should be reported as an AE, if applicable according to Section 8.4.

8.3.4 Electrocardiograms

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

At V2, V4, V6, V8, V10, V12, and V18 ECG must be measured pre-dose and 4 hours post-dose. The participant can be discharged if no concerns are raised based on 4-hour assessments. If considered needed by the investigator an additional ECG assessment can be taken after 6 hours, before the participant is discharged from the site. These assessments do not need to be performed in a fasting state.

The ECG should be recorded after at least 5 minutes resting in supine position. The ECG will be evaluated by the investigator or designee and the outcome must be specified in the eCRF as either “normal” or “abnormal”.

If “abnormal”, a comment must be given together with an assessment of clinical significance (yes/no). The investigator or designee must sign and date the ECG on the day of evaluation. The data will be transferred to the eCRF.

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 deterioration from baseline should be reported as an AE (Section 8.4).

8.3.5 Clinical safety laboratory assessments

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

8.3.6 Plasma glucose measurements

Plasma glucose (PG) should always be measured using a BG meter and recorded in the diary and eCRF when a hypoglycaemic episode is suspected. For more information on reporting of hypoglycaemic episodes, see Appendix 7 (Section 10.7).

When using BG meters, the measurement is performed with capillary blood calibrated to plasma equivalent glucose values, i.e., the measurement is performed on blood while the value is reported as plasma; therefore 'PG' is the term to use as descriptor for the value.

The BG meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display.

The BG meter provided by Novo Nordisk should be used for the measurements required in the protocol (see auxiliary supplies in Section 6.1).

Participants should be instructed in how to record the results of the PG values in the diary. The record of each PG value should include date, time and value. All data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone, and a discrepancy is later detected, the values in the eCRF must be corrected. Occasional review by the investigator of the BG meter values stored in the memory of the BG meter and correct reporting of these in the diary is advised in order to ensure adequacy of the data reported in the study database.

8.3.7 Injection site reactions

All injection site reactions must be reported as AEs according to Section 8.4 and additional data collection will be performed for these events. The area of the injection site reaction should be included in the AE description (right/left abdomen, thigh or upper arm). Additional information on the injection site reaction must be provided in the eCRF injection site reaction form. For the 2nd maintenance dose in the dose ratio 1:9, volume-matched placebo, NNC0480-0389 monotherapy and semaglutide monotherapy study arms, where the dose of NNC0480-0389/placebo A is administered using 2 injections (Table 6-2), one injection site reaction form and associated AE form must be completed for each affected injection site.

Additional assessments will be performed until resolution, as judged necessary by the investigator. For documentation, digital pictures may be taken of the injection site as often as judged necessary by the investigator. The pictures should include subject ID, date of picture taken, time after dosing, number of associated AEs, and a ruler for scaling. The pictures should be stored as part of source documentation at site. Pictures may be used for a central evaluation by an external dermatologist.

8.4 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 8 (Section 10.8).

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 8 (Section 10.8).

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

Event type	AE requiring additional data collection	Event for adjudication	Other event requiring collection of additional information
Medication error	X		
Misuse and abuse	X		
Hypersensitivity reaction	X		
Injection site reaction	X		
Acute gallbladder disease	X		
Diabetic retinopathy	X		
Acute kidney injury	X		
Hepatic event	X		
Death		X	
Acute Coronary Syndrome (ACS) (acute myocardial infarction and unstable angina pectoris requiring hospitalisation)		X	
Cerebrovascular event (stroke and transient ischaemic attack)[a]		X	
Heart failure (requiring hospitalisation and urgent heart failure visit)		X	
Hypoglycaemic episodes			X

[a] All cerebrovascular events (stroke and transient ischemic attack) are to be reported and sent for adjudication, however the event adjudication committee 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 8 (Section 10.8) for events requiring adjudication.

8.4.1 Time period and frequency for collecting AE information

All AEs and SAEs must be collected from first administration of randomised treatment (V2) and until the end of study (V25) in accordance with the flowchart (Section 1.2) or whenever, within the above time period, the site becomes aware of an AE or SAE.

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

AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3). All SAEs must be recorded and reported to Novo Nordisk 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 IMP or related to study participation, the investigator must promptly notify Novo Nordisk.

8.4.2 Method of detecting AEs

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

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

8.4.3 Follow-up of AEs

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

8.4.4 Regulatory reporting requirements for SAEs

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 (SUSAR).

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

8.4.5 Pregnancy

Only female participants of non-childbearing potential are eligible for inclusion in the study (see Section 5.1 for inclusion criteria). The definition of a woman of non-childbearing potential is provided in Appendix 4 (Section 10.4.1).

Details of pregnancies in female partners of male participants will be collected after the male participant's first exposure to randomised treatment and until the end of study (V25). For details regarding collection and reporting of pregnancy information, please refer to Appendix 4 (Section 10.4).

8.4.6 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.

8.5 Pharmacokinetics and pharmacodynamics

8.5.1 Pharmacokinetics

Samples will be used to evaluate the pharmacokinetics of semaglutide and NNC0480-0389 and will be collected in accordance with the flowchart (Section 1.2). The date, exact time, dose of the latest administration of randomised treatment prior to PK sampling and location of the injection site will be reported in the diary and entered into the eCRF.

Procedures for sampling, handling, storage, labelling, and shipments of samples must be performed in accordance with the laboratory manual.

Residual PK samples may be used for exploratory metabolite analysis and for method development and validation purposes. Potential metabolite analysis will be reported separately from the clinical study report (CSR). Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Bioanalysis of the plasma samples for semaglutide and NNC0480-0389 will be performed at a special laboratory using a validated assay. The PK bioanalysis is outlined in the Special laboratory study plan. Assay descriptions will be provided in a bioanalytical report prepared by the laboratories, and the bioanalytical report must be provided before finalisation of the CSR. Quality controlled data must be available for review by Non Clinical and Clinical Assay Sciences, Novo Nordisk, prior to database lock. After final reporting, study samples will be destroyed (upon approval by Novo Nordisk), and confirmation of destruction must be sent to Novo Nordisk.

Bioanalysis will be performed on all samples from participants randomised to the four dose ratio arms, semaglutide monotherapy or NNC0480-0389 monotherapy. Samples from participants receiving placebo will not be analysed.

8.5.2 Pharmacodynamics

Not applicable.

8.6 Genetics

Not applicable.

8.7 Biomarkers

Collection of samples for biomarker analyses is part of this study. The following samples are required and will be collected from all participants in this study:

- Blood samples at baseline, during maintenance (at V18) and at end of study

The detailed sampling regimen is described in the flowchart (Section 1.2) and as defined in Appendix 2 (Section 10.2). The intent is to capture potential dynamic changes of the biomarkers described in the section below over the duration of the study.

The blood samples are collected to evaluate the association between exploratory systemic biomarkers and the response (including efficacy and safety) of semaglutide, NNC0480-0389 and the co-administration of both trial products at different dose ratios. This evaluation of biomarkers aims to understand how semaglutide and NNC0480-0389 affect downstream biomarkers associated with regulation of disease pathways.

Some of the biomarkers are also defined as supportive secondary endpoints in this study (Section 3) and thus used for efficacy and safety assessments (Sections 8.2 and 8.3); this include markers related to lipid metabolism (e.g. HDL-cholesterol, LDL-cholesterol and triglycerides), inflammation (hsCRP) and SBP. In addition to these, other exploratory biomarkers include markers of bone metabolism (C-terminal telopeptide: CTx and procollagen-1 N-terminal peptide: P1NP) and the adipokine adiponectin (both high-molecular weight and total) and a neuroinflammatory marker (glial fibrillary acidic protein: GFAP). These predefined biomarkers will be analysed prior to database lock (DBL) and reported in the CSR.

The predefined biomarkers are based on current knowledge and technology; however, the biomarker evaluation in this study will not be restricted to the biomarkers and analysis methods described above. Blood samples will also be collected for multiplex quantitative proteomic assessments from commercial vendors to increase knowledge on diseases such as T2D and related complications (e.g. cardiovascular disease, chronic kidney disease and non-alcoholic steatohepatitis). These exploratory analyses will be reported separately from the CSR.

In addition, biosamples are collected for future research and will be stored in a biobank. Refer to Section 8.9 for further details and Appendix 6 (Section 10.6) for retention.

8.8 Immunogenicity assessments

Anti-NNC0480-0389 antibody samples will be collected according to the flowchart (Section 1.2) in all 10 study arms. All samples must be drawn prior to trial product administration if trial product administration is planned on the sampling day.

Assessment of anti-NNC0480-0389 antibodies will be performed at Novo Nordisk A/S for participants randomised to the four dose ratio arms and the NNC0480-0389 monotherapy.

For details on blood sampling, serum preparation and storage, please refer to the laboratory manual.

Analysis for anti-NNC0480-0389 antibodies will be performed in a tiered approach. Anti-NNC0480-0389 positive samples will be further characterised for cross-reactivity towards endogenous GIP. Furthermore, samples from the end of study visit (V25) that are cross-reactive to endogenous GIP will be further characterized for in vitro neutralising effect towards endogenous GIP in a cell based neutralising assay.

The anti-NNC0480-0389 antibody effect can be assessed by correlation to PK, pharmacodynamics (PD) and to potential severe and/or serious AEs that may be related to anti-NNC0480-0389 antibody development. Detailed description of the assay methods will be included in an analytical report. Antibody assays will be validated according to international guidelines and recommendations.

The investigator will not be able to review the results of antibody measurements in relation to AEs as these will be analysed after last participant last visit (LPLV).

Refer to Appendix 6 (Section 10.6) for details on retention of antibody samples for future research.

8.8.1 Hypersensitivity reactions

If suspicion of a hypersensitivity reaction occurs the participants should be instructed to contact the site staff as soon as possible for further guidance.

Hypersensitivity reactions must be reported as AEs according to Section 8.4 and additional data collection will be performed for these events.

The investigator or the participant should take digital pictures of the hypersensitivity reaction at the time of identification 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 should be stored as part of source documentation at site. Pictures may be used for a central evaluation by an external dermatologist.

In case of a **systemic hypersensitivity reaction** (not local hypersensitivity reactions, e.g. injection site reactions) judged as possibly or probably related to randomised treatment by the investigator, additional blood sampling should be performed. If possible, a blood sample should be taken as soon as possible and no later than 1-2 weeks after the reaction. A second sample should be taken 3-4 weeks after the reaction.

Samples will be used for analysing the following parameters:

- Tryptase (optimal 0.5-2 hours post the hypersensitivity reaction)
- Total IgE
- Anti-NNC0480-0389 IgE antibodies
- Anti-semaglutide IgE antibodies
- Anti-NNC0480-0389 binding antibodies

In addition, the baseline antibody sample from the same participant will also be assessed on the above-mentioned assays to compare antibody levels and allergy markers on samples drawn prior to first administration of trial product.

The analyses will be performed by Novo Nordisk or a laboratory assigned by Novo Nordisk A/S.

8.9 Human biosamples for future research

Collection of biosamples for future analysis is a component of this study. The samples will be stored in a biobank and allow for future analyses when new knowledge or improved testing technologies may have become available during or after the study. Participation is optional, and participants must sign a separate informed consent to indicate their participation in the biobank component(s) of the study. Participants who do not wish to participate in the biobank component(s) may still participate in the study. Blood samples will be collected according to Appendix 6 (Section 10.6 and stored for future use.

Genetic analyses may include analysis of selected genes or genetic markers throughout the genome with the purpose of understanding and predicting response to semaglutide, NNC0480-0389 or the combination of the two compounds as well as to understand T2D or other related conditions.

Analyses of circulating biomarkers will measure hormones, metabolites or other non-genetic serum entity with the purpose of understanding and predicting response to semaglutide, NNC0480-0389 or the combination of the two compounds as well as understanding T2D or other related conditions.

The samples may be analysed as part of a multi-study assessment. Results will not be reported to the investigator for assessments of AEs nor will they be part of the clinical study report. The primary objective of the analysis is to investigate on a population level and results are very unlikely to have clinical utility on an individual level. Furthermore, the analyses will be done on pseudonymised data. Therefore, any outcome of the analyses will not be reported directly to participants or sites. The result may be reported in publications, at scientific conferences or to authorities.

The human biosamples for future research will be stored for up to 15 years after end of study at a central laboratory or appropriate storage facility (see Appendix 6 [Section 10.6]).

8.10 Health economics

Not applicable.

9 Statistical considerations

The statistical analysis plan (SAP) will be finalised prior to first unblinding, 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 endpoint.

9.1 Statistical hypotheses

For the primary estimand with primary endpoint, change from baseline to week 34 in HbA_{1c} (%-point), the following hypotheses are planned to be tested.

The primary hypotheses of superiority for the four dose ratios versus placebo are defined as follows; Let x denote the NNC0480-0389 dose in the dose ratio 1:x, let $\mu_{\text{Ratio 1:x}}$ denote the true mean of change in HbA_{1c} (%-point) from baseline to week 34 for dose ratio 1:x, and let μ_{placebo} denote the true mean of change in HbA_{1c} (%-point) from baseline to week 34 for the pooled placebo group. The null and alternative hypotheses tested are:

$$H_0\text{: } \mu_{\text{Ratio 1:x}} \geqslant \mu_{placebo} \text{ vs. } H_A\text{: } \mu_{\text{Ratio 1:x}} < \mu_{placebo}$$

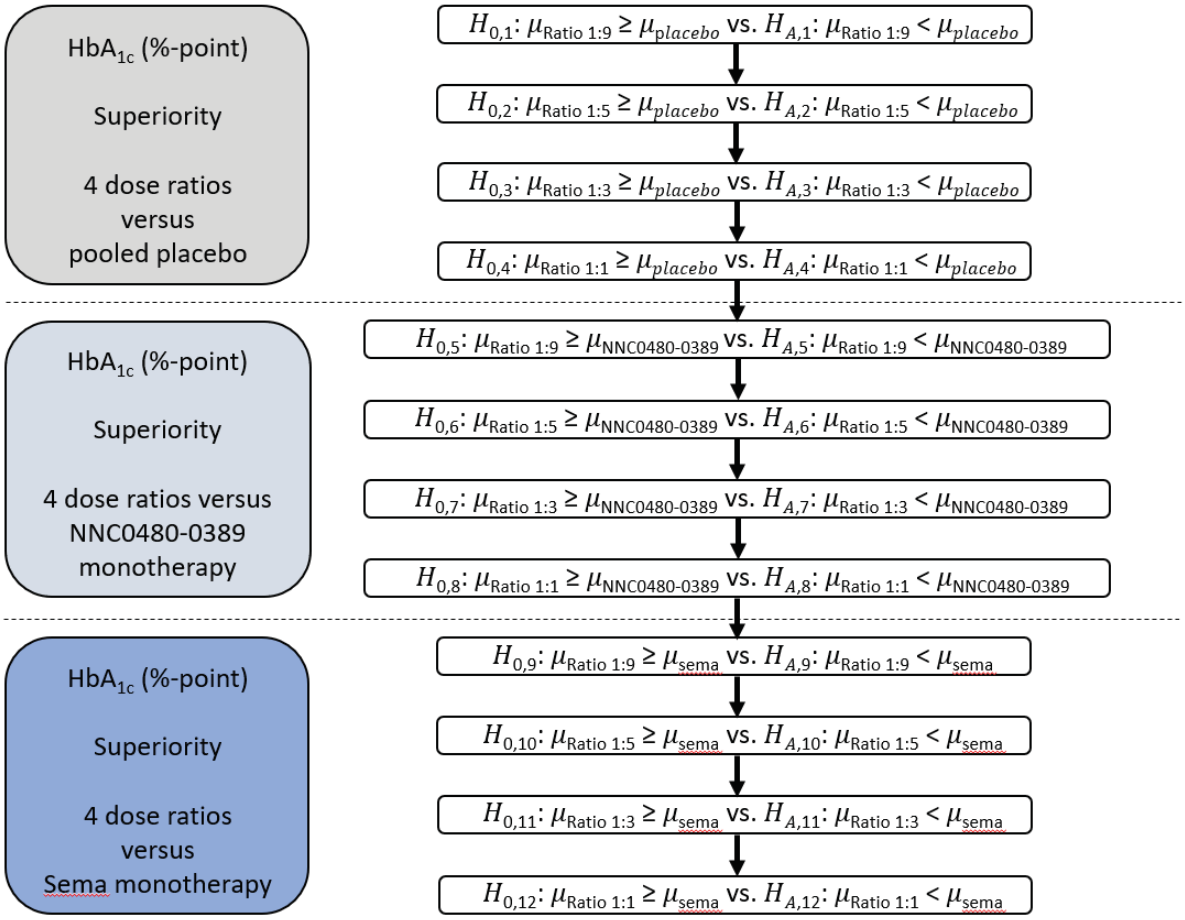
Furthermore, the secondary hypothesis of superiority for each of the four dose ratios versus NNC0480-0389 monotherapy ($\mu_{\text{NNC0480-0389}}$) will be evaluated, and finally evaluated versus semaglutide monotherapy (μ_{sema}). In total, this results in a hierarchical testing procedure with 12 tests for change in HbA_{1c} from baseline to week 34 (see Section 9.1.1).

The null hypothesis will be rejected if the upper limit of the estimated two-sided 95% confidence interval (CI) for the treatment difference is below 0, thereby demonstrating that the lowering of HbA_{1c} for the dose ratio is superior to the comparator.

9.1.1 Multiplicity adjustment

Confirmation of superiority in lowering of HbA_{1c} for each of the four dose ratios versus placebo will be evaluated using a hierarchical testing procedure starting with the treatment difference between the highest dose ratio (1:9) and placebo and ending with the lowest dose ratio (1:1) and placebo. Likewise, the hierarchical testing procedure continues with confirmation of superiority in lowering of HbA_{1c} for each of the four dose ratios versus NNC0480-0389 monotherapy, and lastly versus semaglutide monotherapy. If a study arm is discontinued due to safety/tolerability concerns, the tests associated with that study arm will be omitted from the testing hierarchy. In case of a non-significant treatment difference, the testing procedure will stop. This will protect the family wise type 1 error in the strong sense on a 5% (two-sided) level of significance. The hierarchical testing procedure is shown in Figure 9-1.

Figure 9-1 Hierarchical testing procedure for showing superiority for each of the four dose ratios vs pooled placebo, NNC0480-0389 monotherapy and semaglutide monotherapy, respectively, on change in HbA_{1c} (%-point) from baseline to week 34



9.2 Analysis sets

Two participant analysis sets are defined, see Table 9-1.

Table 9-1 Participant analysis sets

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

The participants to be excluded from the participant analysis sets and the reasons for their exclusion must be documented before unblinding and will be described in the CSR. FAS will be used when analysing efficacy endpoints and assessments and SAS will be used when analysing safety endpoints and assessments.

Three data points sets are defined, see Table 9-2.

Table 9-2 Data points sets

Defined data points set (DPS)	Description
DPS1 – in-study	All observed data from date of randomisation to date of last planned contact with study site will be included in the data point set.
DPS2 – on-treatment	All observed data for which participants are considered exposed to randomised treatment will be included in the data point set. More specifically, this includes observed data from DPS1 excluding data observed after the first date of any of the following: • The date of last dose of randomised treatment + 35 days • The date of the last planned contact with study site.
DPS3 – on-treatment without rescue medication	All observed data for which participants are considered exposed to randomised treatment and have not initiated any rescue medication will be included in the data point set. More specifically this includes observed data from DPS2 excluding data observed after the first date of any of the following: • Initiation of rescue medication • The date of last dose of randomised treatment + 14 days

FAS and DPS3 are used to estimate the primary estimand for the primary objective and for the secondary objectives 1 and 2.

FAS and DPS1 are used to estimate the additional estimand for the primary objective and for the secondary objectives 1 and 2.

SAS and DPS2 are used to analyse safety data.

9.3 Statistical analyses

9.3.1 General considerations

For all analyses and reporting, the four placebo arms will be pooled.

Handling of missing baseline data

The latest available measurement at or prior to randomisation is used as the baseline measurement. If no measurement(s) have been obtained at or prior to randomisation, the mean value at randomisation across all participants is used as the baseline value.

9.3.2 Primary endpoint analysis

The primary endpoint is change from baseline (week 0) to week 34 in HbA_{1c} (%-point).

Analysis addressing the primary estimand

The primary estimand for change in HbA_{1c} (%-point) addresses the effect of the four dose ratios and will be estimated based on the FAS using the on-treatment without rescue medication data point set (DPS3).

The primary analysis for the primary estimand for change in HbA_{1c} (%-point) is an analysis of covariance (ANCOVA) with randomised treatment and strata as factors and baseline HbA_{1c} as a covariate. Strata are defined by treatment with metformin at screening (yes/no) and country (Japan/Other).

The estimated treatment difference between each dose ratio and placebo will be reported together with the associated two-sided 95% CI and corresponding two-sided p-value.

The primary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 34 from the on-treatment without rescue medication data point set (DPS3). Missing data and observations outside the period covered by DPS3 such as week 34 assessments for retrieved dropouts will be imputed using multiple imputation assuming missing at random (MAR). Missing post-baseline data will be imputed sequentially within each randomised treatment using the observed post-randomisation assessments included in DPS3 for visits prior to the one in question. The imputation model will include strata as factors and baseline and post-baseline values prior to the visit in question as covariate. The proportion of HbA_{1c} change data at week 34 that will not be included in the analysis is assumed to be no more than 20%. Initiation of rescue medication is expected to be more frequent with placebo and NNC0480-0389 monotherapy than for the remaining study arms. A higher proportion of participants are expected to discontinue randomised treatment due to AEs in the dose ratio arms and with semaglutide monotherapy compared to the other arms. So, overall, the frequency of data not included in the analysis is expected to be similar across arms. In case of sparse data in some of the groups, a common treatment discontinuation group across randomised treatments will be created, and randomised treatment will be added to the model as a factor. If this is still not sufficient, the model will be thinned in the following order, starting with the one that will be removed first; strata, randomised treatment, and baseline value.

Analyses addressing the additional estimand

The analysis model for change in HbA_{1c} (%-point) is an ANCOVA with randomised treatment and strata as factors and baseline HbA_{1c} as a covariate.

The additional estimand will be estimated based on the FAS using week 34 measurements from the in-study data point set (DPS1). Missing week 34 data will be imputed using multiple imputation assuming MAR. Imputation will be done based on the placebo group. The imputation model will include strata as factors and baseline HbA_{1c} as covariate.

9.3.3 Dose-response modelling

The mean HbA_{1c} (%-point) change will be estimated using dose of NNC0480-0389 as a continuous variable. This is done to evaluate the effect of the four dose ratios versus semaglutide monotherapy on change in HbA_{1c} (%-point) and to characterise the dose-response relationship, where dose is the NNC0480-0389 dose in the given dose ratio and response is the treatment difference in change in HbA_{1c} between the dose ratio and treatment with semaglutide monotherapy.

The dose-response candidate models in Table 9-3 will be fit.

Table 9-3 Dose-response candidate models

Model	Functional form
Emax	$E_0 + E_{max}\frac{d}{ED_{50} + d}$
Linear	$E_0 + \beta d$

E_0: the expected effect on HbA_{1c} when treated with semaglutide monotherapy, ED_{50}: The dose, which produces half of E_{max}, E_{max}: Maximum effect attributable to the drug, d: NNC0480-0389 dose.

The candidate models will be fit to the estimated change in HbA_{1c} (%-point) at week 34 for the employed four dose ratios and semaglutide monotherapy analysed similar to the primary analysis of the primary estimand described above. Thus, all participants in the FAS will be included and the same assumptions regarding missing values and the impact of explanatory variables will be applied.

The model used to evaluate dose-response will be selected among the candidate models based on the best fit to data. The best fit will be evaluated based on convergence, model complexity, Akaike information criterion (AIC) value and visual evaluation.

9.3.4 Secondary endpoints analysis

There are no confirmatory secondary endpoints in the study. For details on the analyses of supportive secondary endpoints, please refer to the SAP.

9.3.5 Exploratory endpoints analysis

Not applicable, as there are no exploratory endpoints in the study.

9.3.6 Safety analyses

All safety analyses will be made on the SAS. 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.

9.3.7 Other analyses

Population PK and exposure-response analyses is described below. For other analyses, please refer to the SAP.

Pharmacokinetic and/or pharmacodynamic modelling

Population PK and exposure-response analyses will be used as supportive evidence for the evaluation of efficacy and safety and to support the recommended dose combinations for the FDC of semaglutide and NNC0480-0389. First, plasma drug concentrations versus time will be analysed using population PK models, quantifying covariate (such as baseline body weight, age, gender, race, ethnicity, and injection site) effects on semaglutide/NNC0480-0839 exposure. Secondly, model-based estimates of steady-state average concentrations will be derived for each participant to facilitate subsequent exposure-response analyses. Relevant efficacy and safety endpoints will be related to steady-state average concentrations and subjected to model-based analysis. Exploratory PKPD models may be developed for longitudinal analysis of relevant endpoints.

The PK model analyses will be conducted for participants with PK sampling in this study, while exposure-response and PKPD model analysis will be conducted using all exposed participants (safety analysis set). A modelling analysis plan will be prepared before first database lock in the study, outlining details of the analyses. The modelling will be reported separately from the CSR.

9.4 Interim analysis

There may be up to two interim evaluations for this study, and the first may occur when approximately 80% of participants have completed Visit 18 (week 22) for early guidance of dose selection for phase 3. This interim evaluation will include available safety, efficacy, and PK data. A

limited number of Novo Nordisk personnel will be unblinded to perform the interim evaluations and will not be involved in study conduct after unblinding. No change in study design can occur and the study will not be stopped for either positive efficacy or futility at the interim evaluation. It is not considered a protocol deviation if the interim evaluation is not performed. Further information on the interim evaluation will be specified in an interim charter or the SAP before unblinding.

In addition, an interim evaluation conducted as a partial database lock will be performed at the end of the intervention period for all participants, i.e. after the date of the last participant last treatment (LPLT) visit. The database will be updated after the partial database lock to include remaining PK data and any additional safety information. The full database lock will be performed after the date of the LPLV.

Novo Nordisk will become unblinded at the time of the partial database lock, whereas participants and investigators will remain blinded until after LPLV. 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 and PK data will be performed after the full database lock. This approach is implemented to support further development activities for the combination of semaglutide and NNC0480-0389. A detailed plan for data handling and operational aspects of the partial database lock and the database update will be finalised before the first interim evaluation or before the partial DBL if the first interim evaluation is not conducted.

There will be no data monitoring committee established in this study.

9.5 Sample size determination

To characterise the shape of the curve for the dose-response relationship, it is considered adequate to test four dose ratios and the sample size for each dose ratio is determined in order to achieve a sufficient precision on this relationship. Furthermore, sample size estimation is based on addressing assumptions corresponding to the analyses addressing the primary estimand. Here, measurements of the primary endpoint from participants that have discontinued randomised treatment prematurely but continue in the study (retrieved dropouts) are not included in the primary analysis.

Participants are randomised 75:15:75:15:75:15:75:15:60:75 to each study arm as described in Section 4.1.

Assumptions for the power calculations:

- The significance level is 5%
- As a hypothetical strategy is applied for discontinuation of randomised treatment when addressing the primary estimand, data collected after discontinuation of randomised treatment will not be used, but imputed sequentially based on treatment completers within the same study arm. Hence, it is not necessary to account for withdrawals in the power calculations.
- A standard deviation (SD) of 1.0%-point for the change in HbA_{1c} from baseline to week 34 is assumed for the sample size calculation. The SD is based on the observed %-point change from studies NN9535-3623, NN9535-3626, NN9535-3624 and NN9535-4506. It is assumed that co-administration of semaglutide and NNC0480-0389 improves efficacy without changing the SD of change in HbA_{1c}.

- An expected HbA_{1c} treatment effect as assessed by the primary estimand of
  - -0.2%-point when treated with placebo is assumed based on results from study NN9924-4233.
  - -0.2%-point when treated with NNC0480-0389 monotherapy is assumed based on results from animal studies.
  - -2.0%-point when treated with semaglutide monotherapy is predicted based on exposure-response modelling of data from studies NN9535-3623, NN9535-3626 and NN9535-3624.
- When characterising the shape of the curve for the dose-response relationship, estimates for the assumed changes are obtained using an E_{max} model (see Table 9-3), where dose is the NNC0480-0389 dose in the given dose ratio and response is the treatment difference in change in HbA_{1c} between the dose ratio and semaglutide monotherapy. Based on PK/PD model analysis of weight loss data in mice, it is assumed that $ED_{50} = 1.3$. If $E_0 = -2.0$ denotes the expected effect on HbA_{1c} when treated with semaglutide monotherapy, as stated above, and if assuming a response for the maximal investigated dose ratio vs. semaglutide monotherapy of R = -0.5, the estimates for the changes from baseline in HbA_{1c} are as follows:
  - -2.50%-points for dose ratio 1:9
  - -2.48%-points for dose ratio 1:5
  - -2.45%-points for dose ratio 1:3
  - -2.34%-points for dose ratio 1:1

Both the marginal and the combined power for the 12 hypotheses will be evaluated. The combined power is calculated under the assumptions that hypotheses are independent which is a conservative assumption.

For the primary hypothesis of superiority for each of the four dose ratios versus placebo in terms of change from baseline to week 34 in HbA_{1c}, there will be >99% marginal power and >99% combined power of detecting a true treatment difference in HbA1c with the assumptions listed above.

For the secondary hypotheses of superiority for each of the four dose ratios versus NNC0480-0389 monotherapy in terms of change from baseline to week 34 in HbA_{1c}, there will also be >99% marginal power and >99% combined power of detecting a true treatment difference in HbA_{1c} with the assumptions listed above.

For the secondary hypotheses of superiority for each of the four dose ratios versus semaglutide monotherapy in terms of change from baseline to week 34 in HbA_{1c}, the marginal power and combined power of detecting a true treatment difference in HbA_{1c} is as shown below:

- 86.0% marginal power and 86.0% combined power for dose ratio 1:9
- 82.9% marginal power and 71.3% combined power for dose ratio 1:5
- 78.0% marginal power and 55.6% combined power for dose ratio 1:3
- 55.3% marginal power and 30.7% combined power for dose ratio 1:1

A sample size of 75 participants in each of the four dose ratio arms and in the semaglutide monotherapy arm compared with a pooled placebo group of 60 participants allows the 95% CI of the treatment difference between any active arm and placebo to be contained within ±0.36%-points of the estimate with 80% probability. This is considered to be a sufficient precision to characterise

the dose-response relationship and for determining which dose ratio to use for the FDC of semaglutide and NNC0480-0389.

With 60 participants in the NNC0480-0389 monotherapy arm and in the pooled placebo group, respectively, the 95% confidence interval for the estimated treatment difference will with 89% probability be contained within ±0.39%-points of the estimate, assuming SD=1.0%.

With respect to the secondary hypotheses of superiority for each of the four dose ratio versus semaglutide monotherapy in terms of change from baseline to week 34 in HbA_{1c}, the sample size of 75 participants in each arm allows the 95% CI of the treatment difference between each of the four dose ratio arms and semaglutide monotherapy to be contained within ±0.34%-points of the estimate with 83% probability.

Sensitivity analysis for the sample size calculation

To elaborate on the sensitivity of the secondary hypothesis of superiority for the 1:9 dose ratio versus semaglutide monotherapy in terms of change from baseline to week 34 in HbA_{1c}, the marginal power of detecting a true difference is shown for different number of participants in the two arms, an SD of 1.0 and 1.1%-point, and a response R of -0.4, -0.5, and -0.6, respectively. The scenarios can be seen in Table 9-4 and Figure 9-2.

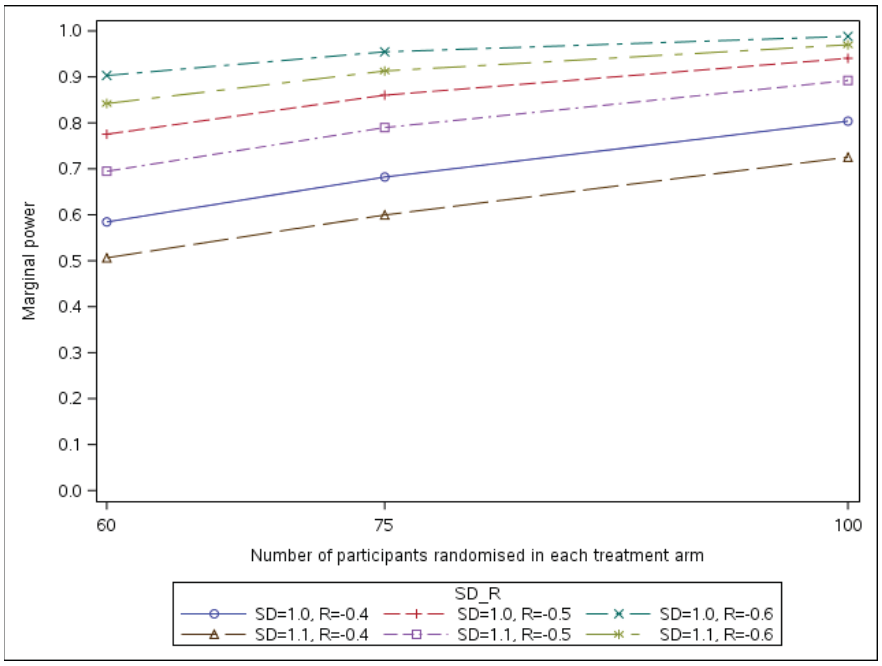
Furthermore, the sensitivity of the secondary hypotheses of superiority for each of the four dose ratios versus semaglutide monotherapy in terms of change from baseline to week 34 in HbA_{1c} is explored by calculating the marginal power of detecting a true treatment difference in HbA_{1c} for different scenarios assuming R = -0.5 and SD = 1.0. The four scenarios correspond to the number of participants in each of the four dose ratio arms and in the semaglutide monotherapy arm being either 60, 75 or 100 participants. The scenarios can be seen in Figure 9-3.

Table 9-4 Marginal power of the 1:9 dose ratio versus semaglutide monotherapy for different N, R, and SD

R	SD	Marginal power for confirming superiority of the 1:9 dose ratio versus semaglutide monotherapy		
		N: 60	**N: 75**	**N: 100**
-0.4	1.1	50.6%	60.0%	72.5%
	1.0	58.4%	68.2%	80.4%
-0.5	1.1	69.5%	79.0%	89.2%
	1.0	77.5%	86.0%	94.0%
-0.6	1.1	84.2%	91.3%	97.0%
	1.0	90.3%	95.5%	98.8%

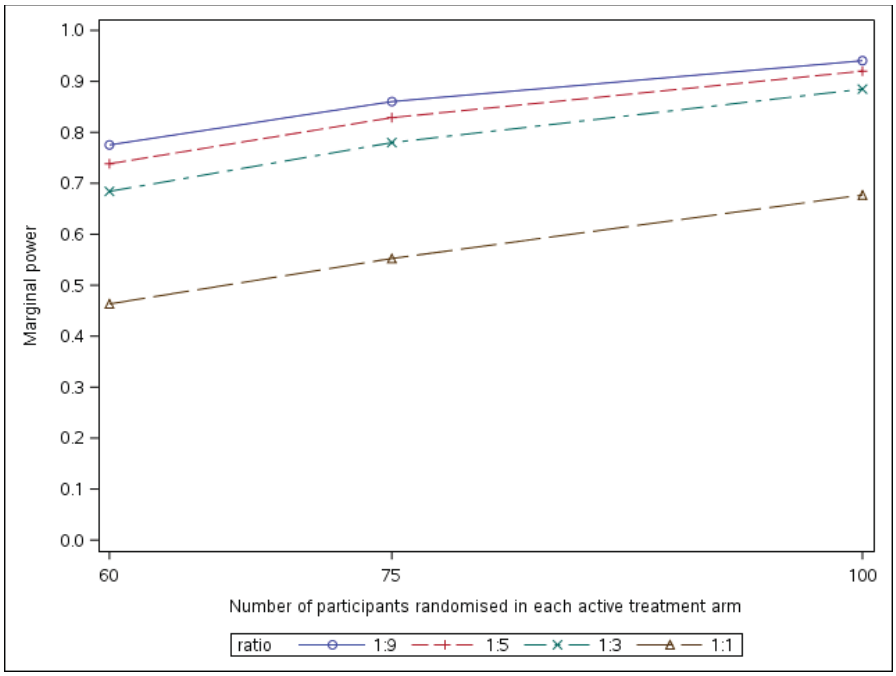
N: number of participants in the four dose ratio arms and the semaglutide monotherapy arm. SD: Standard deviation, R: Expected response for the maximal investigated dose ratio vs. semaglutide monotherapy. The scenario shown in grey highlight represents the marginal power for confirming superiority of the 1:9 dose ratio versus semaglutide monotherapy with the sample size and assumptions for SD and R applied in the study.

Figure 9-2 Sensitivity analysis showing the marginal power of the 1:9 dose ratio versus semaglutide monotherapy for different N, R, and SD



N: number of participants in the 1:9 dose ratio arm and the semaglutide monotherapy arm, respectively. R: Expected response for the maximal investigated dose ratio vs. semaglutide monotherapy, SD: Standard deviation

Figure 9-3 Sensitivity analysis showing the marginal power of the hypotheses of superiority for each of the four dose ratios vs semaglutide monotherapy, R = -0.5, SD = 1.0



R: Expected response for the maximal investigated dose ratio vs. semaglutide monotherapy, SD: Standard deviation

The sensitivity of the precision of the estimate for the treatment difference in HbA_{1c} for a fixed sample size of 60 participants in the NNC0480-0389 monotherapy arm and in the pooled placebo group is presented in Table 9-5 for different number of participants in the four dose ratio arms, with a SD of 1.0 and 1.1%-point. The table is also used when comparing the pooled placebo group to the NNC0480-0389 monotherapy arm, hence two situations are highlighted in the table.

Table 9-5 Width of the 95%CI with corresponding probability for different scenarios

$N_{comparison}$	$N_{placebo}$	SD	Width of 95%CI (probability)
60	60	1.1	±0.42%-point (81.1%)
		1.0	±0.39%-point (88.9%)
75		1.1	±0.40%-point (84.6%)
		1.0	±0.36%-point (80.2%)
100		1.1	±0.38%-point (89.9%)
		1.0	±0.34%-point (83.6%)

$N_{comparison}$: number of participants in each of the four dose ratio arms or in the NNC0480-0389 monotherapy arm, $N_{placebo}$: number of participants in the pooled placebo group, SD: Standard deviation, CI: Confidence interval. The scenarios shown in grey highlight represent the width of the 95% CI for the comparison between NNC0480-0389 monotherapy and pooled placebo and between one of the four dose ratios and pooled placebo with the sample size and assumptions for SD and R applied in the study.

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[12] and applicable ICH Good Clinical Practice (GCP) Guideline[13]
- Applicable laws and regulations.
  Bulgaria: For country-specific requirements, please refer to Appendix 10 (Section 10.10).

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.

For US sites: 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[13] guidelines, Declaration of Helsinki,[12] privacy and data protection requirements, where applicable, and the IRB/IEC or site. For country-specific requirements, please refer to Appendix 10 (Section 10.10).

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

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

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

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

A separate informed consent form intended for collection of additional blood samples for future research (circulating biomarkers) is available for this study (see Section 8.9).

A separate informed consent form intended for a female partner of a male participant in case of an abnormal pregnancy is available for this study (Appendix 4, Section 10.4).

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) Appendix 8, Section 10.8).

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,[12] the International Committee of Medical Journal Editors (ICMJE),[14] the Food and Drug Administration Amendment Act (FDAAA),[15] European Commission Requirements[1, 16, 17] 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.

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

The following will be provided as paper CRFs:

- Pregnancy forms

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

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

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

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

10.1.8.2 Monitoring

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the study. If the electronic source data does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone).

Study monitors will perform ongoing source data verification of critical data points to confirm that data entered into the eCRF by authorised site personnel are accurate, complete and verifiable from source documents. Study monitors will perform ongoing source data review to ensure that the study is being conducted in accordance with the current approved protocol and any other study agreements, ICH GCP[13], and all applicable regulatory requirements, evaluating the adequacy of critical processes at site for the execution of the protocol, collection of study data, to ensure that the safety and rights of participants are being protected.

Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.

Quality tolerance limits (QTLs) will be predefined in the relevant monitoring plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.

10.1.8.3 Protocol compliance

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

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

10.1.9 Source documents

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

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

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

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

Data that is transcribed into the eCRF from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

It must be possible to verify participant's medical history in source documents, such as participant's medical record.

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

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

10.1.10 Retention of clinical study documentation

Records and documents, including signed informed consent forms, pertaining to the conduct of this study must be retained by the investigator for 25 years after end of study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.

The investigator 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 supplied by Novo Nordisk. Site-specific eCRFs and other participant data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.

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

United States of America: For country-specific requirements, please refer to Appendix 10 (Section 10.10).

10.1.11 Study and site closure

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

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

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

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

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

10.1.12 Responsibilities

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

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

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

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

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

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

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

10.1.13 Indemnity statement

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

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

10.1.14 Publication policy

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

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

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

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

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

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of studies regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

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

At the end of the study, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases, the study results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the

content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

10.1.14.2 Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the study concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[18]

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, Table 10-2, Table 10-3 and Table 10-4 will be performed by the central laboratory unless otherwise noted.

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

The central lab will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their laboratory SOPs. These data will not be transferred to the study database. The investigator should review such values for AEs and report these according to this protocol.

The investigator must review all laboratory results for concomitant illnesses and AEs.

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

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

Human biosamples for future research will be stored as described in Appendix 6 (Section 10.6).

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.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism Assessments performed at V2, V14 V16, V18, V20, V22, V24 unless otherwise indicated	• Fasting insulin[a] • Fasting plasma glucose[a,b] (V2, V4, V8, V12, V13, V14, V16, V18, V20, V22, V24) • Fasting proinsulin[a] • Fasting C-peptide[a] • Fasting glucagon[a] • HbA_{1c} (V1, V2, V4, V8, V12, V14, V16, V18, V20, V22, V24) • HOMA B • HOMA IR
Lipids[a] Assessments performed at V2, V4, V8, V12, V14, V16, V18, V20, V22, V24	• Apolipoprotein B (ApoB) • Cholesterol • Free fatty acids • HDL cholesterol • LDL cholesterol • Triglycerides • VLDL cholesterol
Notes: [a] Assessment to be done in fasting state (see Section 5.3.1) [b] 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). Please also refer to Section 7.1.2 for rescue criteria related to FPG.	

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology Assessments performed at V1, V2, V14, V16, V18, V20, V22, V24	• Basophils • Eosinophils • Erythrocytes • Haemoglobin • Leucocytes • Lymphocytes • Mean corpuscular volume (MCV) • Monocytes • Neutrophils • Thrombocytes

Laboratory assessments	Parameters
Biochemistry[a] Assessments performed at V1, V2, V14, V16, V18, V20, V22, V24	• Alanine aminotransferase (ALT) • Albumin • Alkaline phosphatase • Amylase • Aspartate aminotransferase (AST) • Bilirubin • Calcium • Phosphate • Creatinine • hsCRP • Lipase • Potassium • Sodium
Urinalysis Assessment performed at V1, V2, V14, V16, V18, V20, V24	• Protein/Creatinine
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation • Biosamples for future research (V2, V18, V24)
Antibodies[b, c] Assessments performed at V2, V6, V10, V14, V18, V24, V25	• Anti-NNC0480-0389 antibodies (Positive/Negative) • Anti-NNC0480-0389 antibodies titre (numeric) • Anti-NNC0480-0389 antibodies cross reacting with endogenous GIP (Positive/Negative) • Anti-NNC0480-0389 antibodies with *in vitro* neutralising effect to endogenous GIP (Positive/Negative) (only at V25)
Notes: [a] Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 3 (Section 10.3) (Hy's Law) and Section 7.1. [b] Analysis performed by Novo Nordisk laboratory [c] Results will not be provided to the investigator, as these results will not be used for any clinical evaluation during the study.	

Table 10-3 Protocol-required PK assessments

Laboratory assessments	Parameters
Pharmacokinetics[a, b] Assessments performed at all visits except V1	• NNC0480-0389 plasma concentrations • Semaglutide plasma concentrations
Notes: [a] Analysis performed by special laboratory contracted by Novo Nordisk [b] Results will not be provided to the investigator, as these results will not be used for any clinical evaluation during the study.	

Table 10-4 Protocol-required biomarkers

Laboratory assessments	Parameters
Biomarkers[a] Assessments performed at V2, V18, V24, unless otherwise indicated	• High-molecular weight adiponectin[b] • Total adiponectin[b] • CTx[b] • GFAP (only at V25) • P1NP[b] • Samples for exploratory biomarker analyses
Notes: [a] Results will not be provided to the investigator, as these results will not be used for any clinical evaluation during the study. [b] Assessment to be done in fasting state (see Section 5.3.1)	

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

10.3.1 Definition of AE

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

Events to be reported as AEs:

- Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected
- Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected
- Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition
- Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent

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

Events NOT to be reported as AEs:

- Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions. This includes those conditions identified during screening or identified during other study procedures performed before exposure to IMP.
  Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.
- Medical or surgical procedures (e.g., endoscopy, appendectomy). The condition that leads to the procedure is the AE.
- Medical or surgical procedures not preceded by an AE or worsening of a known condition.

10.3.2 Definition of an SAE

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

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalisation or prolongation of existing hospitalisation**
  - Hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the

physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

- Hospitalisation for elective treatment (e.g., elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE.
  Note: Hospitalisations for administrative, study-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for medical or surgical procedures, planned before study inclusion, are not considered AEs or SAEs

- **Results in persistent or significant disability/incapacity**
  - The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Important medical event:**
  - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
  - The following must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:
    - Suspicion of transmission of infectious agents via IMP
    - Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x UNL and total bilirubin >2x UNL where no alternative aetiology exists (Hy's law)

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

Adverse events requiring additional data collection

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

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 or use of wrong device
    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 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 reaction

- All drug allergies, drug hypersensitivities and autoimmunity. For all hypersensitivity reactions additional information should be collected on a specific event form.

Injection site reaction

- Inflammation in or damage to the tissue surrounding where the drug was administered. For all types of injection site reactions, additional information should be collected on a specific event form including information about the objective findings (e.g. erythema, haematoma, ecchymosis) and local symptoms (e.g. burning, pain, numbness, itching).

Acute gallbladder disease

- Events of symptomatic acute gallbladder disease including gallstones and cholecystitis. For all events additional information should be collected on a specific event form.

Diabetic retinopathy

- New onset or worsening of diabetic retinopathy. For all events additional information should be collected on a specific event form.

Acute kidney injury

- For all events of acute kidney injury, including acute kidney failure, additional information should be collected on a specific event form.

Hepatic event

- ALT or AST > 5 x ULN and total bilirubin ≤ 2 x ULN
- ALT or AST >3 x ULN and total bilirubin > 2 x ULN

Note: Assessments in case of increased levels of aminotransferases, as described above, should prompt repeat testing (at central laboratory) including ALT, AST, alkaline phosphatase (ALP) and total bilirubin and discontinuation of trial product should be considered. Thereafter, repeat testing (at central laboratory) of ALT, AST, ALP and total bilirubin should be done regularly until the

abnormalities return to normal or baseline state. Additional clinical information such as related symptoms, risk factors and contributing conditions (e.g. viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, hepatobiliary or pancreatic disorders) should be gathered to seek a possible cause of the observed laboratory test abnormalities.

- Hepatic event leading to trial product discontinuation.

Other events requiring collection of additional information

Hypoglycaemic episodes

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

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

10.3.4.1 AE and SAE recording

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

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

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

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

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 adverse event 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 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 eCRF.

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

10.3.4.4 Final outcome

The investigator will select the most appropriate outcome:
- **Recovered/resolved**: The participant has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented
- **Recovering/resolving**: The condition is improving, and the participant is expected to recover from the event. This term may also be applicable for AEs ongoing at the time of death (where death was due to another AE).
  Note: For SAEs, this term is only applicable if the participant has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae**: The participant has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.

- **Not recovered/not resolved**: The condition of the participant has not improved, and the symptoms are unchanged, or the outcome is not known. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal**: This term is only applicable if the participant died from a condition related to the reported AE. Outcomes of other reported AEs in a participant before he/she died should be assessed as 'recovered/resolved', 'recovering/resolving', 'recovered/resolved with sequelae' or 'not recovered/not resolved'. An AE with a fatal outcome must be reported as an SAE.
- **Unknown**: This term is only applicable if the participant is lost to follow-up

10.3.4.5 Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g., severe hypersensitivity reactions, Hy's law). This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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. In case an autopsy was not performed, the investigator should provide Novo Nordisk with a death certificate instead.

New or updated information should be recorded in the eCRF.

10.3.5 Reporting of SAEs

AE and SAE reporting via CRF

Relevant forms must be completed in the eCRF.

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

- AE form within 24 hours
- Safety information form within 5 calendar days
- Both forms must be signed within 7 calendar days after first knowledge by the investigator.
- Specific event form within 14 calendar days.
- For timelines related to events for adjudication, refer also to Appendix 8 (Section 10.8).

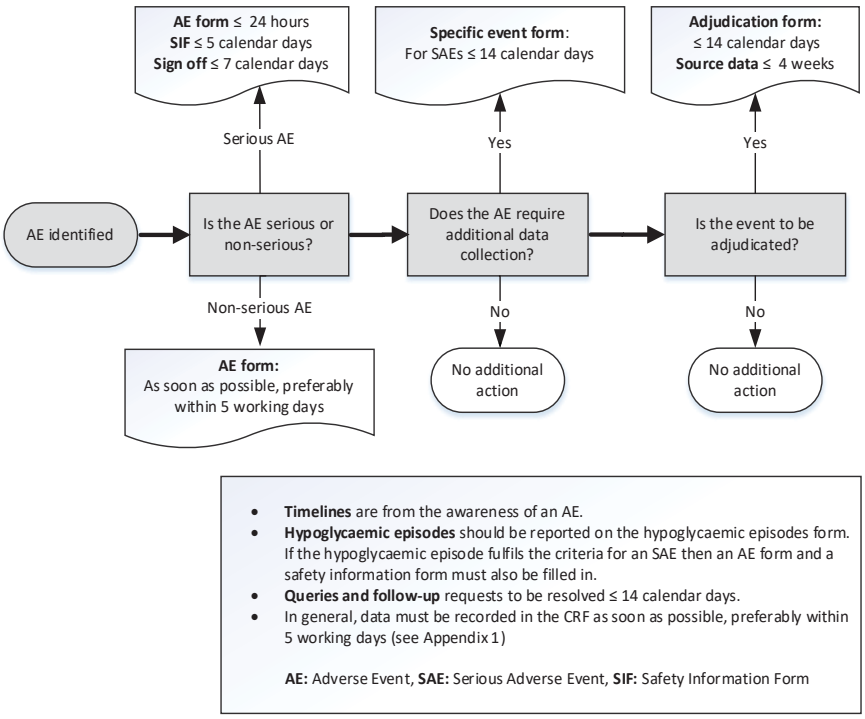
If the eCRF is unavailable for more than 24 hours, then the sites will use the paper AE form, and if the eCRF is unavailable for more than 5 calendar days, then the site will use the paper safety information form. The site should enter the SAE data in the eCRF as soon as it becomes available.

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

After the study is completed, the study database will be locked, and the eCRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a

report of a new SAE from a participant or receives updated information on a previously reported SAE after eCRF 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 8 (Section 10.8).
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.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Only women of non-child-bearing potential (WONCBP) are eligible for inclusion in the study. Documentation of non-child-bearing potential must be recorded in the eCRF.

10.4.1 Definitions

Females in the following categories are considered WONCBP

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 (HRT) and whose menopausal status is in doubt are considered of childbearing potential and will not be eligible for inclusion in the study.

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

The male participant who are not surgically sterilised (vasectomy) and are sexually active with female partner(s) of childbearing potential should use condom during treatment and until 5 weeks after last dose of IMP.

10.4.3 Collection of pregnancy information

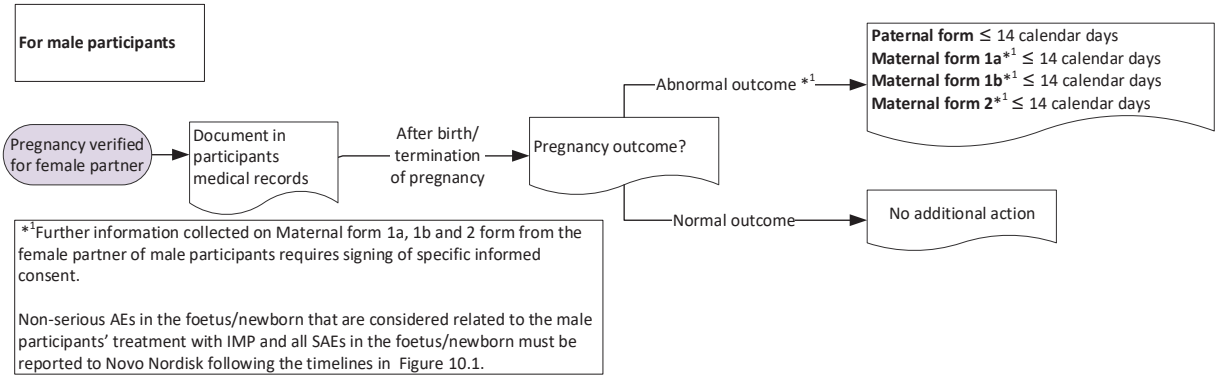
Male participants with partners who become pregnant

Investigator will attempt to collect pregnancy information on any female partner who becomes pregnant while male participant is participating in this study. The pregnancy should be documented in the medical record of the male participant. Only in case of abnormal outcome (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) of the pregnancy and in case the male participant receives IMP, should the investigator inform Novo Nordisk. Abnormal pregnancy outcome is considered an SAE.

After obtaining the necessary signed informed consent from the pregnant female partner, the investigator will record pregnancy information on the appropriate form and submit it to Novo Nordisk within 14 calendar days of learning of the abnormal outcome of the partner's pregnancy (see Figure 10-2). Information on the status of the mother and child will be included.

Generally, follow-up will be 1 month following the delivery date.

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



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

10.5.1 Definition of technical complaint

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

Examples of technical complaints:

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

Time period for detecting technical complaints

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

10.5.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk

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

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

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

Timelines for reporting technical complaints to Novo Nordisk

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

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

If the eCRF 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 eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

Follow-up of technical complaints

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

Collection, storage and shipment of technical complaint samples

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

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the 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 for future research

Human biosamples (also in some cases known as human biospecimen or human biological materials) are samples that have been taken from the human body during life or after death. It includes:

- Primary cells, tissues, organs or cell containing fluids of human origin (for example, whole blood, urine, saliva, synovial fluid)
- Cell free fluids of primary human origin (for example, serum and plasma)
- Extracts or derivatives of the above, when derived by purification (for example, DNA, RNA, proteins, membranes, microsomes and other cellular substructures).

In countries where applicable, this study will involve collection of human biosamples for future research to be stored in a central laboratory facility during the study. Serum, plasma and whole blood samples will be stored, and the timing of sampling and amount of material to be stored are specified in Table 10-5.

Table 10-5 Type of material, timing of sampling and amount of material to be stored for future research

Type of material	Timing of sampling[a]	Material to be stored
Serum	Randomisation (V2), during maintenance (V18) and at End of treatment (V24)	5x 0.5 mL aliquots per sample
Plasma	Randomisation (V2), during maintenance (V18) and at End of treatment (V24)	5x 0.5 mL aliquots per sample
Whole blood[b]	Randomisation (V2) and at End of treatment (V24)	1x 2.5 mL aliquot per sample

[a] Timing of sampling also specified in the flowchart (Section 1.2) and Appendix 2 (Section 10.2).

[b] Whole blood collected for analysis of DNA and RNA

The biosamples will be stored at a central laboratory for up to 15 years after end of study. Only relevant Novo Nordisk, consultants, auditors, research organisations or laboratories working for or collaborating with Novo Nordisk as well as storage facility employees will be able to access the stored biosamples and associated data. The biosamples may be transferred to other countries for analysis and will be destroyed at the latest 15 years after end of study.

The analyses of the biosamples for future research are not intended to identify participant-specific findings, but to understand and predict response to semaglutide, NNC0480-0389 or the combination of the two compounds as well as understanding T2D and related conditions on a population level.

Analysis will be done on the biosamples and associated data (data relating to the test results or results from the main study).

Novo Nordisk will ensure that third party collaborators live up the regulations on data protection, see Appendix 1 (Section 10.1.5).

The participant may request the stored biosamples for future research to be destroyed by withdrawing the designated informed consent at any timepoint during and after the study. For samples that have already been analysed, the results can still be used for scientific research and will not be removed from the datafile.

Residual antibody samples may be analysed for further characterisation of immune responses towards drug, if required by health authorities or for safety reasons, and for further development of antibody assays and to generate reagents for in-study validation or control of future assay performance. In case of a systemic hypersensitivity reaction, the additional blood samples taken in relation to the reaction may be retained to follow up on the hypersensitivity reaction. If deemed relevant by Novo Nordisk, applicable exploratory analyses may be performed, e.g. histamine release test (basophil activation), complement analysis, prick tests and/or intra-dermal tests. The samples will be stored at Novo Nordisk 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.

Residual PK samples may be retained for later exploratory analysis of metabolites and for method development and validation purposes. The samples will be stored at Novo Nordisk 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 10-6 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 IHSG,[19] ADA,[20] ISPAD,[21] type 1 diabetes outcomes program,[22] ATTD.[23] Severe hypoglycaemia as defined by Seaquist[24] and ISPAD.[21]		

Severe hypoglycaemia

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.[24]

Nocturnal hypoglycaemia

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

Reporting of hypoglycaemic episodes

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

Reporting of hypoglycaemic episodes by BG meters:
Plasma glucose (PG) should always be recorded in the diary and eCRF when a hypoglycaemic episode is suspected.

When a participant experiences a hypoglycaemic episode, the participant should record the general information in relation to the hypoglycaemia (timing, PG measurements, symptoms, etc.) as described in the diary. The investigator should ensure correct reporting of the hypoglycaemic episode and report the hypoglycaemic episode to the eCRF. In case a participant is not able to fill in the diary (e.g., in case of hospitalisation), the investigator should still report the hypoglycaemic episode on the hypoglycaemic episodes form.

Upon onset of a hypoglycaemic episode the participant is recommended to measure PG every 15 minutes until the PG value is ≥3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines.[24]

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.[24]

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

Diary review

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

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

1. If a hypoglycaemic episode form in the diary is not completed by the participant within 7 calendar days of the PG measurement, the episode should be described in the source documents and reported by the investigator on a hypoglycaemic episode eCRF with as much information as possible. If the participant did not need help to get a sugary drink, food, or medicine, Novo Nordisk will only ask for start date due to recall bias.[25, 26]

Re-training of participants

The participant must be re-trained in how to report hypoglycaemic episodes if the investigator identifies incomplete or incorrect reporting of hypoglycaemic episodes. The training should be documented by the investigator in source documents.

10.8 Appendix 8: 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 AEs requiring event adjudication

Event type (AE category) (serious and non-serious AEs)	Description
Death	• All cause death
Acute coronary syndrome (ACS) (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)[a]	• 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

[a]All cerebrovascular events (stroke and transient ischemic attack) are to be reported and sent for adjudication, however the event adjudication committee will only confirm strokes.

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 eCRF.
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 eCRF and has the option to report the EAC-identified event.

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

Copies of source documents should be uploaded to the event adjudication system (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.

10.9 Appendix 9: Mitigations to ensure participant safety and data integrity during an emergency situation

10.9.1 Definition and scope of appendix

A major emergency is defined as a situation that causes substantial restrictions to study site access for participants and/or sponsor representatives, i.e. pandemics (e.g., COVID-19) and natural disasters (e.g., hurricanes, floods, and large-scale fires).

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

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

Table 10-8 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.

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

10.9.2 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 V4, V6, V8, V10, V12, V16, V18, V20, V22, V24, and V25 should be performed as on-site visits, if in any way possible. If not, assessments can be conducted remotely as home or off-site visits and if not possible then as video or phone visits to follow up on patient safety.

On-site visits (Visits V13, V14, V15, V17, V19, V21, and V23) can be converted to remote visits (video, phone or similar) or home or off-site visits.

If the end of treatment visit (V24) cannot be performed on-site, using remote (video, phone or similar) or home or off-site visits within the given visit window, the visit window for the assessment can be extended for up to 1 week.

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

10.9.3 Assessments

Assessments used for safety and for the primary endpoint should be prioritised. The preferred order for the method of assessment is: on-site, home visit, video, phone. Specifications regarding how to perform these assessments using remote visits or as home visits will be provided by Novo Nordisk or the vendor.

Local laboratories or diagnostic facilities can be used for haematology, biochemistry, fasting plasma glucose, HbA_{1c}, ECG, eye examination at the investigator's discretion if on-site visits are not possible or in case of temporary lockdown of the central laboratory. Only findings meeting the definition for an AE (refer to Appendix 3 [Section 10.3]) should be reported in the eCRF.

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

Assessments performed as home visits should follow the minimum requirements as shown in Table 10-8 if on-site visits are not possible and if deemed feasible for the patient.

If the assessments indicated in Table 10-8 cannot be performed as on-site visits, remote visits or be analysed at a local laboratory or diagnostic facility, they should be performed at the first possible timepoint following the originally scheduled visit in agreement with Novo Nordisk.

10.9.4 Study intervention

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

Table 10-8 Minimum assessments following randomisation

Procedure	Protocol Section	Intervention period																					End of treatment	End of study
		Dose escalation										Maintenance period 1						Maintenance period 2						
Visit		P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25
Timing of Visit (Weeks)		1	2	3	4	5	6	7	8	9	10	12	14	16	18	20	22	24	26	28	30	32	34	39
Visit Window (Days)[a]		0/1	±3	0/1	±7	0/1	±7	0/1	±7	0/1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	0/7
Discontinuation Criteria	7.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medication	6.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Measurements	8.3.1		X														X						X	X
Physical Examination	8.3.1																X						X	
Adverse Event	8.4 10.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic Episodes	10.7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Assessments	10.2		X				X				X						X		X				X	X
PK Sampling	8.5.1		X				X				X						X		X				X	X
Antibodies	8.8																X						X	X
Attend Visit Fasting	5.3.1		X				X										X		X				X	
ECG	8.3.4																X						X	
Eye Examination	8.3.3																						X	
Vital Signs	8.3.2		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Protocol Section						Intervention period																End of treatment	End of study
							Dose escalation					Maintenance period 1						Maintenance period 2						
Visit		P3	V4	P5	V6	P7	V8	P9	V10	P11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25
Timing of Visit (Weeks)		1	2	3	4	5	6	7	8	9	10	12	14	16	18	20	22	24	26	28	30	32	34	39
Visit Window (Days)[a]		0/1	±3	0/1	±7	0/1	±7	0/1	±7	0/1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	0/7
Samples for biomarker analysis	8.7																X						X	
Biosamples for future research	8.9																X						X	
Drug Dispensing	6.2		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X		
Training in Devices	6.1		X								X						X							

Abbreviations: ECG, electrocardiogram; P, phone contact, PK, pharmacokinetic; V, site visit.

[a] The visit window for the phone contacts (P3, P5, P7, P9, and P11) is in relation to the administration of the study medication, i.e. these phone contacts must be performed either on the day of administration (post-dose) or the next day at the latest.

10.10 Appendix 10: Country-specific requirements

Country	Section(s)	Requirement
Bulgaria	10.1	According to Regulation 31 (for defining the rules of Good Clinical Practice, 12 Aug 2007), art. 4, par. (2): this protocol has been 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 patients that cannot consent personally and other vulnerable groups; 4) description of the procedures for recruiting patients 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 cares for the participants after the study is ended; 6) monitoring procedures; 7) publication policy.
Denmark	5.2, 10.4	Contraception requirements are per the CTFG guideline: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
	10.1.5	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 in the given country of data handling.
Hungary		The participant's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth.
Japan	5.1	Subjects must be aged ≥ 20 years at the time of signing informed consent.
	6.2	The head of the study site or the trial 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.
	10.1.3	A name and seal is accepted as a signature.
United States	10.1.10	In the United States, 21 CFR 312.62(c) and 21 CFR 812.140(d) require clinical study documentation to be retained for 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.
		FDA form 1572: For US sites: • Intended for US sites • Conducted under the IND • All US investigators, as described above, will sign FDA Form 1572 For sites outside the US: • Intended for participating sites outside of the US • Not conducted under the IND • All investigators outside of the US will not sign FDA form 1572 Novo Nordisk will analyse and report data from all sites together.

10.11 Appendix 11: Abbreviations

ADA	American Diabetes Association
AE	adverse event
ACS	acute coronary syndrome
AIC	Akaike information criterion
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoB	apolipoprotein B
AST	aspartate aminotransferase
ATTD	Advanced Technologies & Treatments for Diabetes
BG	blood glucose
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTFG	clinical trial facilitation group
CTx	C-terminal telopeptide
CV	cardiovascular
DBL	database lock
DFU	directions for use
DMC	Data Monitoring Committee
DPP-4	dipeptidyl peptidase-4
DPS	data points set
DUN	dispensing unit number
EAC	Event Adjudication Committee
EAS	event adjudication system
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated Glomerular Filtration Rate
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FDC	fixed dose combination
FHD	first human dose
FPG	fasting plasma glucose

GCP	Good Clinical Practice
GFAP	glial fibrillary acidic protein
GI	gastrointestinal
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycated haemoglobin
HDL	high-density lipoprotein
HOMA B	homeostatic model assessment of beta-cell function
HOMA IR	homeostatic model assessment of insulin resistance
HRT	hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
IB	investigator's brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
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
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LAM	lactational amenorrhoea method
LDL	low-density lipoprotein
LPLT	last participant last treatment
LPLV	last participant last visit
MAD	multiple ascending dose
MAR	missing at random
MCV	mean corpuscular volume
MEN-2	multiple endocrine neoplasia type 2
NIMP	non-investigational medicinal product
NYHA	New York Heart Association
OAD	oral antidiabetic drug
P1NP	procollagen-1 N-terminal peptide
PAS	participant analysis set

PCD	primary completion date
PD	pharmacodynamics
PG	plasma glucose
PK	pharmacokinetics
QTL	quality tolerance limit
RA	receptor agonist
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	safety analysis set
SBP	systolic blood pressure
s.c.	subcutaneously
SD	standard deviation
SU	sulphonylurea
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TEAE	treatment-emergent adverse event
TMM	Trial Materials Manual
VLDL	very-low-density lipoprotein
WONCBP	women of non-child-bearing potential

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9.1.1 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

If applicable, Protocol Attachment II is also located in the Trial Master File.

Content: Global key staff and Country key staff.