Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04969939
Sponsor trial ID:	NN9775-4708
Official title of study:	Investigation of efficacy and safety of NNC0165-1875 as add-on to semaglutide for weight management in subjects with obesity
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Protocol

Protocol title: Investigation of efficacy and safety of NNC0165-1875 as add-on to semaglutide for weight management in subjects with obesity

Substance: NNC0165-1875

Universal Trial Number: U1111-1254-9046

EudraCT Number:

IND Number: 139,592

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	*Date*	*Applicable in country(-ies) and/or site(s)*
Protocol version 4.0	05 April 2022	USA
Protocol version 3.0	03 November 2021	USA
Original Protocol version 2.0	11 March 2021	

Protocol version 4.0 (05 April 2022)

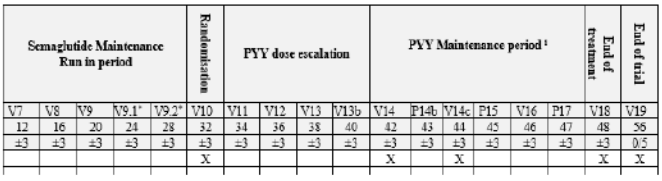
Overall rationale for preparing protocol, version 4.0:

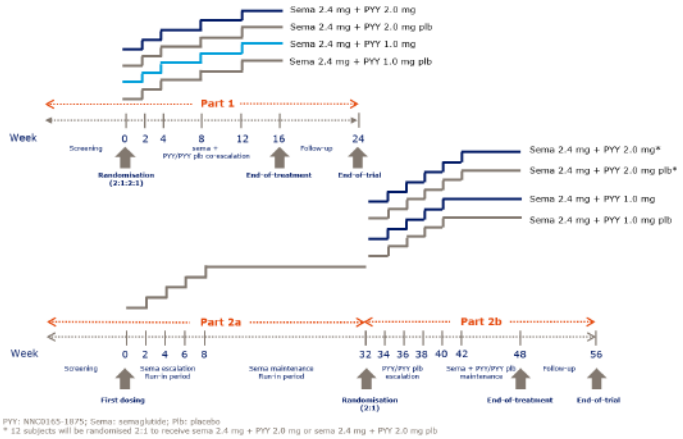
The overall rationale for this protocol amendment was to update the dose and dosing regimen for part 2b, following the safety and tolerability evaluation of part 1.

Safety data for the 2.0 mg dose of NNC0165-1875 were not available from part 1 of the trial due to treatment discontinuation attributed to tolerability issues with the dose escalation regimen used in part 1. The lower starting dose and the dose escalation regimen used for the 1.0 mg NNC0165-1875 dose group appeared tolerable. Based on part 1, the Novo Nordisk Safety Committee has decided to update part 2b by lowering the starting dose to 0.05 mg NNC0165-1875/placebo, by adding extra steps in the dose escalation regimen and by changing the maintenance dose to 1.0 mg from 2.0 mg NNC0165-1875/placebo. In addition, two extra treatment arms have been added for safety evaluation of the 2.0 mg dose of NNC0165-1875, in which 12 subjects will be randomised 2:1 to 2.0 mg NNC0165-1875/placebo. The same low starting dose (0.05 mg) and dose escalation regimen will be used for the 1.0 mg and the 2.0 mg NNC0165-1875/placebo treatment arms. Based on the changes to the dose escalation regimen, two additional site visits (V13b and V14c) and one additional phone visit (P14b) have been added to part 2b. Furthermore, the run-in period with semaglutide has been extended, because the additional visits V9.1 and V9.2 have been activated.

Additionally, the protocol has been updated with the information that four of the laboratory assays used in the trial are for research use only, hence data will not be shared with the sites but will be transferred directly to Novo Nordisk.

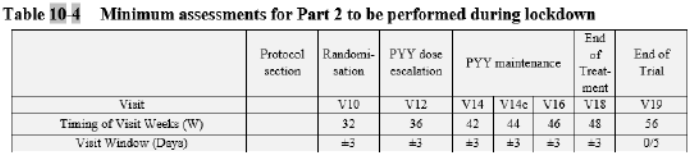
Section # and name	Description of change	Brief rationale
Throughout the protocol	NNC0165-1875/placebo ~~2.0 mg~~ **1.0 mg** *Visit 10 (randomisation):* ~~Week 24~~ **Week 32** *End-of-treatment visit:* ~~Week 40~~ **Week 48**	Part 2b has been updated to a lower maintenance dose of 1.0 mg NNC0165-1875/placebo for efficacy and safety evaluation of NNC0165-1875. Furthermore, at small cohort will be randomised to the 2.0 mg dose of NNC0165-1875/placebo for safety evaluation of NNC0165-1875 2.0 mg.

Section # and name	Description of change	Brief rationale
		The additional run-in visits V9.1 and V9.2 have been activated, hence week numbers and durations of part 2 have been updated.
Section 1.1 Synopsis	To compare the safety and tolerability of NNC0165-1875 **1.0 mg and NNC0165-1875 2.0 mg** added on to semaglutide s.c. 2.4 mg … Part 2 is a ~~40~~ **48**-week, ~~randomised~~ **four-armed**, double-blinded **(within arms), randomised**, placebo-controlled, ~~two-armed,~~ multi-centre, proof-of-principle trial comparing once weekly NNC0165-1875 as add on to once-weekly semaglutide s.c. 2.4 mg versus placebo as add on to once weekly semaglutide s.c. 2.4 mg in subjects with obesity. **In part 2b, 12 subjects will be randomised 2:1 to the 2.0 mg NNC0165-1875/placebo arms, for safety evaluation of the 2.0 mg dose. The remaining subjects will be randomised 2:1 to the 1.0 mg NNC0165-1875/placebo arms for evaluation of efficacy and safety of NNC0165-1875.** At ~~week 24~~ **visit 10**, the subjects enter Part 2b; in addition to receiving semaglutide s.c. 2.4 mg, eligible subjects fulfilling all randomisation criteria ~~at visit 2~~ will be randomised as follows: **12 subjects will be randomised 2:1 to receive NNC0165-1875 2.0 mg or placebo 2.0 mg and the reminder of subjects will be randomised** (2:1) to receive NNC0165-1875 ~~2.0 mg~~ **1.0 mg** or ~~2.0 mg~~ placebo **1.0 mg**. The starting dose of NNC0165-1875 is ~~0.25 mg~~ **0.05 mg** and dose escalation with NNC0165-1875 or ~~NNC0165-1875~~ placebo will be performed every second week to **reach** the maintenance dose~~s~~ of **1.0 mg or 2.0 mg**.	Safety evaluation of the 2.0 mg dose of NNC0165-1875 was not possible in part 1, due to treatment discontinuation in the 2.0 mg dose group. For that reason two extra treatment arms have been added to part 2b, in which 12 subjects will be randomised 2:1 to the 2.0 mg dose of NNC0165-1875/placebo for safety evaluation.
Section 1.2 Flowchart	 **Semaglutide Maintenance Run in period** | **Randomisation** | **PYY dose escalation** | **PYY Maintenance period [i]** | **End of treatment** | **End of trial** V7 V8 V9 V9.1* V9.2* V10 V11 V12 V13 V13b V14 P14b V14c P15 V16 P17 V18 V19 12 16 20 24 28 32 34 36 38 40 42 43 44 45 46 47 48 56 ±3 ±3 ±3 ±3 ±3 ±3 ±3 ±3 ±3 ±3 ±3 ±3 ±3 ±3 ±3 ±3 ±3 0.5 X X X X X *~~If visit~~ **Additional visits** 9.1 and 9.2 **have been activated** ~~are needed both visits will mimic visit 9~~. **[i] PYY maintenance period for 1.0 mg NNC0165-1875/placebo and PYY dose escalation and maintenance period for 2.0 mg NNC0165-1875/placebo**	To match the new dosing regimen in part 2b, two new site visits (V13b and V14c) and one new phone visit (P14b) have been added to the flowchart, and the phone visits P15 and P17 have been moved to occur one week after a site visit instead of two weeks after. Furthermore, the week numbers have been updated to reflect that V.9.1 and V9.2 have been activated.
Section 2.1 Trial rationale	The initial run-in period in Part 2 of the trial (Part 2a) allows for weight loss to be obtained with semaglutide s.c. 2.4 mg, before the addition of NNC0165-1875 ~~2.0 mg~~ **1.0 mg** thus allowing for any additional weight loss obtained by this addition to be compared with the weight loss obtained with continuing semaglutide s.c. 2.4 mg only. **Furthermore, safety evaluation of the NNC0165-1875 2.0 mg dose will be performed in a in a small cohort**. This trial will provide proof of principle **and safety evaluation** to guide further clinical development.	

Section # and name	Description of change	Brief rationale
Section 3.2.1 Primary endpoint	**Primary endpoint for NNC0165-1875 1.0 mg as an add on to semaglutide 2.4 mg versus placebo 1.0 mg as an add on to semaglutide 2.4 mg:**	Primary endpoint will be evaluated for the 1.0 mg dose of NNC0165-1875
Section 3.2.2.2 Supportive secondary endpoints	**Supportive secondary endpoints for NNC0165-1875 1.0 mg as an add on to semaglutide 2.4 mg versus placebo 1.0 mg as an add on to semaglutide 2.4 mg:** **Supportive secondary endpoints for NNC0165-1875 1.0 mg or 2.0 mg as an add on to semaglutide 2.4 mg versus placebo 1.0 mg or 2.0 mg as an add on to semaglutide 2.4 mg:**	Table with supportive secondary endpoints has been divided in two to distinguish between endpoints relevant for the 1.0 mg dose, and endpoints relevant for both 1.0 mg and 2.0 mg doses of NNC0165-1875.
Section 4.1 Overall design	Part 2 is a ~~40~~ **48**-week, ~~randomised~~ **four-armed**, double-blinded **(within arms), randomised**, placebo-controlled, ~~two-armed,~~ multi-centre, proof-of-principle trial comparing once weekly NNC0165-1875 ~~2.0 mg~~… **Part 2 will evaluate efficacy and safety for NNC0165-1875 1.0 mg, and safety for NNC0165-1875 2.0 mg.** At week ~~24~~ **32**, subjects… will enter Part 2b and be randomised in a 2:1 manner to receive either once-weekly NNC0165-1875 ~~2.0~~ **1.0** mg or ~~NNC0165-1875~~ placebo **1.0 mg** as add-on to once-weekly semaglutide 2.4 mg. Part 2b includes ~~6~~ **8** weeks of NNC0165-1875 ~~2.0mg/NNC0165-1875~~ placebo **1.0 mg** dose escalation followed by ~~10~~ **8** weeks of NNC0165-1875 ~~2.0 mg/NNC0165-1875~~ placebo **1.0 mg** maintenance until end-of-treatment. **In part 2b, a small cohort (12 subjects) will be randomised 2:1 to NNC0165-1875/placebo 2.0 mg, these subjects will have 10 weeks of dose escalation followed by 6 weeks on NNC0165-1875/placebo 2.0 mg maintenance until end-of-treatment. For all groups,** ~~V~~visits will take place every 2 weeks during ~~NNC0165-1875 2.0 mg/NNC0165-1875 placebo~~ dose escalation and alternating visits/phone contacts will take place every ~~2~~ weeks~~s~~ for the remaining period until end-of-treatment.  **In protocol version 4.0, the two additional run-in visits (V9.1 and V9.2) have been activated.**	The trial design description and figure have been updated with the new dose and dose escalation regimen for NNC0165-1875/placebo in part 2b. Two extra treatment arms have been added for the 2.0 mg dose NNC0165-1875/placebo. Furthermore, the week numbers have been updated to reflect that V9.1 and V9.2 have been activated.

Section # and name	Description of change	Brief rationale
Section 4.2 Scientific rationale for trial design	**Furthermore, the trial design will allow for evaluation of safety, tolerability and PK properties in the NN0165-1875 2.0 mg dose group.**	The new treatment arms in part 2b, with 2.0 mg NNC0165-1875/placebo will contribute to evaluation of the safety, tolerability and PK properties for NNC0165-1875.
Section 4.3 Justification for dose	**In part 1 of this trial (NN9775-4708), safety, tolerability and PK properties were to be explored for both 1.0 mg and 2.0 mg NNC0165-1875/placebo. However, data for the 2.0 mg dose of NNC0165-1875 were not available from part 1 of the trial, due to treatment discontinuation attributed to tolerability issues with the dose escalation regimen used in part 1. The lower starting dose and the dose escalation regimen used for the 1.0 mg NNC0165-1875 dose group appeared tolerable. Based on part 1, the following changes are made for part 2b in Protocol version 4.0: the Novo Nordisk Safety Committee has decided to update part 2b by lowering the starting dose to 0.05 mg NNC0165-1875/placebo, by adding extra steps in the dose escalation regimen and by changing the maintenance dose to 1.0 mg NNC0165-1875/placebo. In addition, two extra treatment arms have been added for safety evaluation of the 2.0 mg dose of NNC0165-1875, in which 12 subjects will be randomised 2:1 to 2.0 mg NNC0165-1875/placebo.**	The justification for dose section has been updated to include information about the changes made to part 2b.
Section 6.1 Treatments administered	**Table 6-5 Part 2b. Dosing details for NNC0165-1875 and corresponding placebo arms during the escalation and maintenance phases using the NovoPen®4** Target dose / Unit / Visit 10 Randomisation Week 32 / Visit 11 Week 34 / Visit 12 Week 36 / Visit 13 Week 38 / Visit 13b Week 40 / Visit 14 Week 42 & until End of treatment 1.0 mg / Dose in mg / 0.05 / 0.1 / 0.25 / 0.5 / 1.0 / 1.0 mg/ml / 5.0 / 5.0 / 5.0 / 5.0 / 5.0 / 5.0 Volume in mL / 0.01 / 0.02 / 0.05 / 0.1 / 0.2 / 0.2 **Value shown in dose counter** / **1** / **2** / **5** / **10** / **20** / **20** 2.0 mg / Dose in mg / 0.05 / 0.1 / 0.25 / 0.5 / 1.0 / 2.0 mg/ml / 5.0 / 5.0 / 5.0 / 5.0 / 5.0 / 5.0 Volume in mL / 0.01 / 0.02 / 0.05 / 0.1 / 0.2 / 0.4 **Value shown in dose counter** / **1** / **2** / **5** / **10** / **20** / **40** … dose escalation may be postponed by ~~one~~ **1-2** weeks at the discretion of the investigator. **For part 1;** both NNC0165-1875/placebo and semaglutide should be reduced if the subject does not tolerate the randomised target dose. **For part 2b; NNC0165-1875/placebo should be reduced if the subject does not tolerate the randomised target dose. Semaglutide should preferably stay at 2.4 mg but is allowed to be reduced, as per investigator's discretion**	In Table 6-5, dosing details for NNC0165-1875/placebo in part 2b, have been updated to the new dosing regimen and new week numbers for the 1.0 mg and 2.0 mg arms. Clarification of the different dose reduction approaches for part 1 compared with part 2b of the trial.
Section 6.3 Measure to minimise bias: Randomisation and blinding	**As subjects on treatment with NNC0165-1875/placebo 2.0 mg need to be closely monitored for safety and tolerability, the randomisation of the 2.0 mg dose groups will be restricted to 1-3 sites.**	To ensure safety monitoring of subjects receiving 2.0 mg NNC0165-1875, randomisation of subjects for the 2.0 mg arms will be restricted to 1-3 sites.

Section # and name	Description of change	Brief rationale
Section 6.6 Dose modification	Not applicable for this trial. Please refer to Section 6.1 for description of missed dose(s) **and for guidance on dose reduction in case the subject does not tolerate the randomised target dose.**	The reference to Section 6.1 has been updated to include dose reductions in case the subject does not tolerate the randomised target dose.
Section 7.1 Discontinuation of trial treatment	**6. An unacceptable AE defined as any severe AE and/or serious AE (SAE) judged as probably or possibly related to trial product by the investigator**	A new discontinuation criterion has been added for consideration of safety and tolerability.
Section 8.2.4 Electrocardiograms	**Part 2 only:** • **At visits where PK samples are collected the ECG recordings must be performed prior to PK sample collection**	This was stated for part 1, but is also applicable for part 2.
Section 8.2.5.1 Urine samples	Neutrophil gelatinase-ass**ociated** lipocalin/**creatinine**	The name of the laboratory parameter neutrophil gelatinase-ass lipocalin was updated to neutrophil gelatinase-associated lipocalin/creatinine, because these results are reported as a ratio.
Section 8.8 Biomarkers	**The assays used for Soluble Leptin Receptor and Leptin are for research use only, these results will be reported directly to Novo Nordisk.**	The list of biomarkers was updated with bullet indents for clarification. It was added that the data for soluble leptin receptor and leptin will be reported directly to Novo Nordisk.
Section 9.1 Statistical hypotheses	Part 2 For the primary endpoint percentage weight change from randomisation (week ~~24~~ **32**) to end-of-treatment (week ~~40~~ **48**), the superiority test for NNC0165-1875 **1.0 mg** and semaglutide s.c. 2.4 mg versus placebo **1.0 mg** and semaglutide s.c. 2.4 mg will be carried out as follows. As all subjects will receive semaglutide s.c. 2.4 mg and to ease notation, semaglutide s.c. 2.4 mg is ignored in the notation. Let $\mu_{\text{NNC0165-1875 , 1.0 mg ~~2.0 mg~~}}$ and $\mu_{\text{placebo, 1.0 mg}}$ denote the true mean of percentage weight change for dose level NNC0165-1875 **1.0 mg** ~~2.0 mg~~ and the placebo **1.0 mg** group, respectively.	Text updated to clarify that efficacy evaluations for part 2 will be performed using the population of subjects randomised to the 1.0 mg dose of NNC0165-1875/placebo.
Section 9.2 Sample size determination	**In protocol version 4.0, the additional run-in visits (V9.1 and V9.2) have been activated, this means that the subjects will be 8 weeks longer on semaglutide 2.4 mg before randomisation. However, this does not affect the power.**	New text added to clarify that the activation of V9.1 and V9.2 does not affect the power.
Section 9.4.3 Secondary endpoint	TEAEs and treatment emergent SAEs will be summarised by descriptive statistics **for both 1.0 mg NNC0165-1875/placebo and 2.0 mg NNC0165-1875/placebo**.	Safety evaluation will be done for both 1.0 mg and 2.0 mg doses.

Section # and name	Description of change	Brief rationale
Section 9.5 Database lock	**Section 9.5 Database lock** **Part 1:** **DBL 1 of part 1 will be performed after LPLV (week 16). The data in scope are pharmacokinetic and safety lab data until week 16, which will be used for the initial safety committee decision. After DBL 1, data will be unblinded for part 1. Unblinding after DBL 1 is not of any concern for continuing part 2, as sites and subjects are dissimilar for part 1 and part 2 of the trial.** **DBL 2 of part 1 will be performed after the rest of the data has been collected. The data in scope are pharmacokinetic and safety lab data (until week 24) and antibody data.** **Part 2:** **DBL of part 2 will be performed after LPLV. After the DBL has been completed, the data will be unblinded for part 2.**	To clarify that unblinding of data from part 1 at DBL 1 concerns data from part 1 (until week 16) only.
Section 10.2 Appendix 2: Clinical laboratory tests	*A footnote have been added to Appendix 2, Table 10-1:* **[1] Results obtained using assays for research use only will be reported directly to Novo Nordisk.** *Footnotes have been added to Appendix 2, Table 10-2 :* **[2] Results from biomarker assays related to hunger and satiety, for research use only, will be reported directly to Novo Nordisk.** **[3] Results obtained using assay for research use only will be reported directly to Novo Nordisk.** **Furthermore, the assays used for glucagon, neutrophil gelatinase-associated lipocalin/creatinine, soluble leptin receptor and leptin are for research use only, hence these results will not be reported to the sites, but will be reported directly to Novo Nordisk.** Neutrophil gelatinase-associated lipocalin **/creatinine**	The following laboratory assays are for research use only: • Glucagon • Neutrophil gelatinase-associated lipocalin/creatinine • Soluble leptin receptor • leptin For these 4 laboratory parameters, the results are not distributed to sites but directly to Novo Nordisk. In Table 1-2, **/creatinine** was added to the parameter name, because these results are reported as a ratio.
Section 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	*Indents have been added to the bullet list with females not considered woman of childbearing potential (WOCBP).*	The bullet list with categories of females not considered WOCBP was missing several indents. This has been updated to clarify the categories. No changes were made to the content of the text.
Section 10.8 Appendix 8: Retention of human biosamples	at V10, V14, **V14c** and V18 • Serum and plasma (for analyses of circulating biomarkers)	Human biosamples will also be collected at the new visit (V14c).
Section 10.9 Appendix 9: Mitigations to ensure subject safety and data integrity during epidemics/pandemics (e.g. COVID-19)	**Table 10-4 Minimum assessments for Part 2 to be performed during lockdown** 	Visit 14c has been added to flowchart of minimum assessments for part 2 to be performed during lockdown

	Protocol section	Randomi-sation	PYY dose escalation	PYY maintenance			End of Treat-ment	End of Trial
Visit		V10	V12	V14	V14c	V16	V18	V19
Timing of Visit Weeks (W)		32	36	42	44	46	48	56
Visit Window (Days)		±3	±3	±3	±3	±3	±3	0/3

Section # and name	Description of change	Brief rationale
Section 10.11 Protocol amendment history	**Appendix 11: Protocol amendment history …**	The previous amendment rationale and description has been moved to Appendix 11.

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1 Protocol summary

1.1 Synopsis

Rationale:

The present trial is designed to investigate efficacy and safety of NNC0165-1875 subcutaneous (s.c.) once weekly as an add on to semaglutide s.c. 2.4 mg once weekly compared to continuing semaglutide s.c. 2.4 mg once weekly alone for weight management in subjects with obesity. The trial consists of two parts, Part 1 and Part 2. In Part 1, safety and tolerability will be assessed during co-escalation of NNC0165-1875 and semaglutide. In Part 2, NNC0165-1875 will be added on to semaglutide s.c. 2.4 mg at steady state to compare the efficacy and safety of NNC0165-1875 added on to semaglutide s.c. 2.4 mg versus continuing semaglutide s.c. 2.4 mg alone. The initial run-in period in Part 2 of the trial (Part 2a) allows for weight loss to be obtained with semaglutide s.c. 2.4 mg before the addition of NNC0165-1875 (Part 2b), thus allowing for weight loss obtained by this addition to be compared with the weight loss obtained with continuing semaglutide s.c. 2.4 mg only. This trial will provide proof of principle to guide further clinical development.

Objectives and endpoints:

Part 1

Primary objective

To evaluate the safety and tolerability of co-escalation of once-weekly doses of NNC0165-1875 and semaglutide s.c. 2.4 mg administered simultaneously as separate doses in subjects with obesity.

Part 2

Primary objective

To compare the effect of NNC0165-1875 1.0 mg added on to semaglutide s.c. 2.4 mg at steady state versus continuing semaglutide s.c. 2.4 mg alone on body weight in subjects with obesity.

Secondary objective

To compare the effect of NNC0165-1875 1.0 mg added on to semaglutide s.c. 2.4 mg at steady state versus continuing semaglutide s.c. 2.4 mg alone in subjects with obesity on:

- Glycaemic control
- Waist circumference
- Cardiovascular risk factors

To compare the safety and tolerability of NNC0165-1875 1.0 mg and NNC0165-1875 2.0 mg added on to semaglutide s.c. 2.4 mg versus continuing semaglutide s.c. 2.4 mg alone in subjects with obesity.

Primary endpoint

Part 1

Endpoint title	Time frame	Unit
Number of treatment-emergent adverse events (TEAEs)	From time of dosing (day 1) to follow-up (week 24)	Number of events

Part 2

Endpoint title	Time frame	Unit
Change in body weight	From randomisation (week 32) to end of treatment (week 48)	Percentage

Estimands

Estimands apply for statistical analysis of Part 2.

Primary estimand

The estimand will quantify the average treatment of NNC0165-1875 1.0 mg as an add on to semaglutide s.c. 2.4 mg relative to placebo 1.0 mg as an add on to semaglutide s.c. 2.4 mg regardless of treatment discontinuation and rescue interventions (anti-obesity drugs or devices or bariatric surgery) with respect to relative change in body weight from week 32 to week 48. The subject population is all subjects randomised to 1.0 mg NNC0165-1875/placebo, who are able to reach the target dose of semaglutide 2.4 mg during 32 weeks of run-in with escalating semaglutide doses.

Attribute	
Treatment	NNC0165-1875 as an add on to semaglutide s.c. 2.4 mg versus continuing on placebo as an add on to semaglutide s.c. 2.4 mg
Population	All subjects randomised to 1.0 mg NNC0165-1875/placebo for whom semaglutide has been escalated to the target dose with semaglutide 2.4 mg at week 28 and at target dose at the randomisation visit (week 32)
Endpoint	Percent change in body weight from week 32 to week 48
Intercurrent events	Treatment discontinuation: treatment policy strategy Rescue interventions (anti-obesity drugs or devices or bariatric surgery): treatment policy/effectiveness policy strategy
Population-level summary	Difference in average percent change in body weight between NNC0165-1875 1.0 mg as an add on to semaglutide s.c. 2.4 mg vs. placebo 1.0 mg as an add on to semaglutide s.c. 2.4 mg

Additional estimand

The estimand will quantify the average treatment of NNC0165-1875 1.0 mg as an add on to semaglutide s.c. 2.4 mg relative to placebo 1.0 mg as an add on to semaglutide s.c. 2.4 mg in all subjects who remain on randomised treatment for the entire planned duration of the treatment period and do not start any rescue intervention (anti-obesity drugs or devices or bariatric surgery) with respect to relative change in body weight from week 32 to week 48. The subject population is all subjects randomised to 1.0 mg NNC0165-1875/placebo, who are able to reach the target dose of semaglutide 2.4 mg during 32 weeks of run-in with escalating semaglutide doses.

Attribute	
Treatment	NNC0165-1875 as an add on to semaglutide s.c. 2.4 mg versus continuing placebo as an add on to semaglutide s.c. 2.4 mg
Population	All subjects randomised to 1.0 mg NNC0165-1875/placebo for whom semaglutide has been escalated to the target dose with semaglutide 2.4 mg at week 28 and at target dose at the randomisation visit (week 32)
Endpoint	Relative change in body weight from week 32 to week 48
Intercurrent events	Treatment discontinuation: hypothetical strategy Rescue interventions (anti-obesity drugs or devices or bariatric surgery): hypothetical/efficacy strategy
Population-level summary	Difference in average percent change in body weight between NNC0165-1875 1.0 mg as an add on to semaglutide s.c. 2.4 mg vs. placebo as an add on to semaglutide s.c. 2.4 mg

Overall design:

Part 1

Part 1 is a 16-week, four-armed, double-blinded (within arms), randomised, placebo-controlled single-site trial comparing co-escalation of two doses of NNC0165-1875 as an add on to semaglutide s.c. 2.4 mg versus placebo added on to semaglutide s.c. 2.4 mg in subjects with obesity. In total, 24 subjects will be randomised 2:1:2:1 to receive NNC0165-1875 1.0 mg/ NNC0165-1875 placebo or NNC0165-1875 2.0 mg/ NNC0165-1875 placebo. All subjects will receive semaglutide 2.4 mg. The follow-up period is 8 weeks (please see Figure 4-1).

Part 2

Part 2 is a 48-week, four-armed, double-blinded (within arms), randomised, placebo-controlled, multi-centre, proof-of-principle trial comparing once weekly NNC0165-1875 as add on to once-weekly semaglutide s.c. 2.4 mg versus placebo as add on to once weekly semaglutide s.c. 2.4 mg in subjects with obesity. In total, 90 subjects are planned to be enrolled in Part 2a to ensure approximately 75 subjects eligible for randomisation in Part 2b. The follow-up period is 8 weeks. In part 2b, 12 subjects will be randomised 2:1 to the 2.0 mg NNC0165-1875/placebo arms for safety evaluation of the 2.0 mg dose. The remaining subjects will be randomised 2:1 to the 1.0 mg NNC0165-1875/placebo arms for evaluation of efficacy and safety of NNC0165-1875.

Key inclusion criteria

Subjects are eligible to be included in the trial only if all of the following criteria apply:

- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
- Male or female, age above or equal to 18 years at the time of signing informed consent.
- Body Mass Index (BMI) 30.0 – 45.0 kg/m^2 (both inclusive) at the screening visit.

Key exclusion criteria

- $HbA1_c \geq 48$ mmol/mol (6.5%) as measured by a central laboratory at screening.
- History of type 1 or type 2 diabetes mellitus.

Number of subjects:

Part 1

Approximately 75 subjects will be screened to achieve 24 subjects randomly assigned to trial product.

Part 2

Based on NN9536-4376 it is expected that 17% subjects will drop out before randomisation in week 32 or not be able to meet the eligibility criteria at week 32. To account for this, it is planned to allow approximately 90 patients to enter (treatment or run-in period) at Visit 2 to ensure that 75 subjects are randomized at week 32. Further, approximately 106 subjects will be screened to ensure approximately 90 eligible subjects (complete Visit 2 or successfully enter run-in period).

Treatment groups and duration:

Part 1

The total trial duration for the individual subject will be approximately 26 weeks. The trial includes a screening period of approximately 2 weeks. Eligible subjects fulfilling all randomisation criteria at visit 2 will be randomised in a 2:1:2:1 manner to receive target doses of NNC0165-1875 1.0 mg, NNC0165-1875 1.0 mg placebo, NNC0165-1875 2.0 mg or NNC0165-1875 2.0 mg placebo. All subjects will receive semaglutide s.c. 2.4 mg. The starting dose of semaglutide is 0.25 mg in all arms. The starting dose of NNC0165-1875 is 0.05 mg or 0.1 mg, depending on treatment arm (please see Figure 4-1). The treatment continues until the 'end of treatment' visit followed by an 8-week follow-up period.

Part 2

The total trial duration for the individual subject will be approximately 58 weeks. Part 2 consists of a screening period of approximately 2 weeks followed by two treatment parts: a 32-week open-label run-in part with dose escalation of semaglutide alone (Part 2a), and a 16-week second part (Part 2b), where NNC0165-1875 or NNC0165-1875 placebo is added to semaglutide s.c. 2.4 mg. In Part 2a, all subjects will receive semaglutide with dose escalation every 2 weeks for 8 weeks from 0.25 mg semaglutide to the target dose of 2.4 mg. At visit 10, the subjects enter Part 2b; in addition to receiving semaglutide s.c. 2.4 mg, eligible subjects fulfilling all randomisation criteria will be randomised as follows: 12 subjects will be randomised 2:1 to receive NNC0165-1875 2.0 mg or placebo 2.0 mg and the reminder of subjects will be randomised (2:1) to receive NNC0165-1875 1.0 mg or placebo1.0 mg. The starting dose of NNC0165-1875 is 0.05 mg and dose escalation with NNC0165-1875 or placebo will be performed every second week to reach the maintenance dose of 1.0 mg or 2.0 mg. The treatment continues until the 'end of treatment' visit followed by an 8-week follow-up period.

The following trial products will be supplied by Novo Nordisk for the duration of the trial:

- NNC0165-1875 A 0.2 mg/mL/Placebo A, 3 mL cartridge for use in NovoPen®4 (durable device)
- NNC0165-1875 A 5.0 mg/mL/Placebo A, 3 mL cartridge for use in NovoPen®4 (durable device)

- Semaglutide B 3.0 mg/mL 3 mL PDS290 pre-filled pen-injector

Data monitoring committee:

Not applicable in this trial.

1.2 Flowchart

Part 1

	Protocol Sections	Screening	Randomisation		PYY and Sema dose escalation and maintenance period											End of treatment	Post treatment	End of trial
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17
Timing in Weeks (W)		-1	0		2		4		6	8		10	12		14	16	18	24
Timing of Visit (Days)		-7	1	4*	15	18*	29	32*	43	57	60*	71	85	88*	99	113	127	169
Visit Window (Days)		-7/0	±0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	0/5
Attend Visit Fasting	5.3.1		X							X						X		X
Informed Consent and Demography[a]	10.1.3	X																
Eligibility Criteria	5.1,5.2	X	X															
Randomisation Criteria and Randomisation	7.1		X															
Discontinuation Criteria	7.1			X	X	X	X	X	X	X	X	X	X	X	X			
Concomitant Medication	6.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History/Concomitant Illness	8.2	X																
Weight History	8.2	X																
Risk Factors	8.2	X																
Tobacco Use[c]	8.2	X																
Childbearing Potential	10.4	X																
Highly sensitive urine pregnancy Test[b]	10.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Measurements	8.1.1																	
Height	8.1.1	X																
Body Weight	8.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BMI	8.1.1	X	X															
Waist Circumference	8.1.1		X													X		
Physical Examination	8.2.2	X					X			X			X			X	X	X
Adverse Event	8.3,10.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Requiring Additional Data	10.3.3																	
Acute Gallbladder Disease	10.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Acute Pancreatitis	10.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Acute Kidney Injury	10.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Protocol Sections	Screening	Randomisation		PYY and Sema dose escalation and maintenance period											End of treatment	Post treatment	End of trial
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17
Timing in Weeks (W)		-1	0		2		4		6	8		10	12		14	16	18	24
Timing of Visit (Days)		-7	1	4*	15	18*	29	32*	43	57	60*	71	85	88*	99	113	127	169
Visit Window (Days)		-7/0	±0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	0/5
Hepatic Event	10.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Malignant Neoplasm	10.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection Site Reaction	10.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication Error, Misuse and Abuse	10.3.3		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
Laboratory Assessments	10.2																	
Biochemistry	10.2	X		X		X		X			X			X		X	X	X
Antibodies[d]	10.2		X		X		X			X			X			X		X
Prostate Specific Antigen in serum[f]	10.2	X								X						X		X
Coagulation Parameter	10.2	X				X		X			X			X		X	X	X
Glucose Metabolism	10.2	X[e]	X							X						X		X
Haematology	10.2	X		X		X		X			X			X		X	X	X
Hormones	10.2		X				X			X			X			X		X
Lipids	10.2		X													X		X
Urinalysis	10.2		X				X			X			X			X		X
24-hour urine	10.2		X													X		
PK	8.5.8.6																	
Semaglutide plasma					X		X			X			X			X		X
NNC0165-1875 plasma				X	X	X	X	X	X	X	X	X	X	X	X	X		X
ECG[g]	8.2.4		X	X		X		X			X			X		X	X	X
Vital Signs	8.2.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biosamples for Future Analysis[h]	10.8		X													X		
Clinical Outcome Assessments	8.2.1																	
C-SSRS Baseline	8.2.1	X																
C-SSRS Since Last Visit	8.2.1		X							X						X		
Patient Health Questionnaire - 9 (PHQ-9)	8.2.1	X	X							X						X		
Administration of trial product	6		X		X		X		X	X		X	X		X	X		

	Protocol Sections	Screening	Randomisation		PYY and Sema dose escalation and maintenance period											End of treatment	Post treatment	End of trial
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17
Timing in Weeks (W)		-1	0		2		4		6	8		10	12		14	16	18	24
Timing of Visit (Days)		-7	1	4*	15	18*	29	32*	43	57	60*	71	85	88*	99	113	127	169
Visit Window (Days)		-7/0	±0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	0/5
Drug accountability					X		X		X	X		X	X		X	X		
Hand Out ID Card		X																
Hand Out Dose Reminder Card	8		X		X		X			X			X					
Hand Out and Instruct in Diary	8		X		X		X			X		X	X		X			
Collect, Review and Transcribe Diaries	8				X		X			X			X			X		
Information about urine collection and dispensing of urine container	8.2.5.1	X													X			
Training in Devices	6.1.1.1		X		X		X		X	X		X	X		X			

*Visit must be at least two days after or max four days after previous dosing visit

[a] Demography consists of date of birth, sex, ethnicity and race (according to local regulation).

[b] For female subjects of childbearing potential.

[c] Smoking is defined as smoking at least one cigarette or equivalent daily.

[d] Antibody samples must be taken pre-dose.

[e] Only HbA_{1c}

[f] Male subjects only

[g] Three consecutive ECG recordings must be performed after the subject has been placed in a supine position for at least 10 minutes

[h] DNA sample will only be collected at visit 2. Serum and plasma samples will be collected at all the marked visits.

Part 2

	Protocol Sections	Screening	Sema dose escalation Run in period					Semaglutide Maintenance Run in period					Randomisation	PYY dose escalation				PYY Maintenance period [i]						End of treatment	End of trial
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V9.1*	V9.2*	V10	V11	V12	V13	V13b	V14	P14b	V14c	P15	V16	P17	V18	V19
Timing of Visit Weeks (W)		-1	0	2	4	6	8	12	16	20	24	28	32	34	36	38	40	42	43	44	45	46	47	48	56
Visit Window (Days)		-7/0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0/5
Attend Visit Fasting	5.3.1		X										X					X		X				X	X
Informed Consent and Demography[a]	10.1.3	X																							
Eligibility Criteria	5.1,5.2	X	X																						
Randomisation Criteria and Randomisation	7.1												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		
Concomitant Medication	6.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History/ Concomitant Illness	8.2	X																							
Weight History	8.2	X																							
Risk factors	8.2	X																							
Tobacco Use[c]	8.2	X																							
Childbearing Potential	10.4	X																							
Highly sensitive urine pregnancy Test[b]	10.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X
Body Measurements	8.1.1																								
Height	8.1.1	X																							
Body Weight	8.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X
BMI	8.1.1	X	X																						
Waist Circumference	8.1.1		X										X					X		X				X	
Physical Examination	8.2.2	X											X											X	
Adverse Event	8.3,10.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Requiring Additional Data	10.3.3																								
Acute Kidney Injury	10.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Protocol Sections	Screening	Sema dose escalation Run in period					Semaglutide Maintenance Run in period					Randomisation	PYY dose escalation				PYY Maintenance period [i]						End of treatment	End of trial
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V9.1*	V9.2*	V10	V11	V12	V13	V13b	V14	P14b	V14c	P15	V16	P17	V18	V19
Timing of Visit Weeks (W)		-1	0	2	4	6	8	12	16	20	24	28	32	34	36	38	40	42	43	44	45	46	47	48	56
Visit Window (Days)		-7/0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0/5
Acute Gallbladder Disease	10.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Acute Pancreatitis	10.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatic Event	10.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Malignant Neoplasm	10.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication Error, Misuse and Abuse	10.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection Site Reaction	10.3.3		X	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	X	X	X
Laboratory Assessments	10.2																								
Biochemistry	10.2	X											X		X			X		X		X		X	X
Antibodies[d]	10.2		X										X	X	X			X		X		X		X	X
Biomarkers	10.2	X[f]	X[g]										X[fg]					X[fg]		X[fg]				X[fg]	X[fg]
Coagulation Parameter	10.2	X											X		X			X		X		X		X	X
Glucose Metabolism	10.2	X[e]	X										X					X		X				X	X
Haematology	10.2	X											X		X			X		X		X		X	X
Hormones	10.2		X										X		X			X		X				X	X
Lipids	10.2		X										X					X		X				X	X
Urinalysis	10.2		X										X		X			X		X		X		X	X
24-hour urine	10.2												X											X	
PK	8.5,8.6																								
Semaglutide plasma													X					X		X				X	X
NNC0165-1875 plasma														X	X	X	X	X		X		X		X	X
ECG	8.2.4		X										X					X		X				X	X
Vital Signs	8.2.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X
Clinical Outcome Assessments	8.2.1																								
C-SSRS Baseline	8.2.1	X																							

	Protocol Sections	Screening	Sema dose escalation Run in period					Semaglutide Maintenance Run in period					Randomisation	PYY dose escalation				PYY Maintenance period [i]						End of treatment	End of trial
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V9.1*	V9.2*	V10	V11	V12	V13	V13b	V14	P14b	V14c	P15	V16	P17	V18	V19
Timing of Visit Weeks (W)		-1	0	2	4	6	8	12	16	20	24	28	32	34	36	38	40	42	43	44	45	46	47	48	56
Visit Window (Days)		-7/0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	0/5
C-SSRS Since Last Visit	8.2.1		X										X					X		X				X	
Patient Health Questionnaire – 9 (PHQ-9)	8.2.1	X	X										X					X		X				X	
Biosamples for Future Analysis[h]	10.8		X										X					X		X				X	
IWRS Session	6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	
Treatment Compliance	6.4		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	
Drug Dispensing	6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	
Hand Out ID Card		X																							
Hand Out Dose Reminder Card	8		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X					
Hand Out and Instruct in Diary	8		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X			
Collect, Review and Transcribe Diaries				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X				X	
Information about Urine collection and dispensing of urine container	8.2.5.1											X										X			
Training in Devices	6.1.1.1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X			

*Additional visits 9.1 and 9.2 have been activated.

[a] Demography consists of date of birth, sex, ethnicity and race (according to local regulation).

[b] For female subjects of childbearing potential.

[c] Smoking is defined as smoking at least one cigarette or equivalent daily.

[d] Antibody samples must be taken pre-dose.

[e] Only HbA_{1c}

[f] Prostate Specific Antigen in serum - only male subjects

[g] Leptin and Soluble Leptin Receptor

[h] DNA sample will only be collected at visit 2. Serum and plasma samples will be collected at all the marked visit

[i] PYY maintenance period for 1.0 mg NNC0165-1875/placebo and PYY dose escalation and maintenance period for 2.0 mg NNC0165-1875/placebo

2 Introduction

The prevalence of obesity has been increasing during the last 30 years[1], with a current estimated worldwide prevalence of more than 600 million people[2]. Obesity is associated with an increased risk of type 2 diabetes (T2D)[3, 4], dyslipidaemia, hypertension[5], cardiovascular disease[6], obstructive sleep apnoea[7], non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH)[8], urinary incontinence[9], several types of cancers[10], and increased mortality[11, 12]. In addition to these pathophysiologic changes, individuals with obesity experience reduced health-related quality of life, including reduced physical function[13-15]. In recognition of the serious and extensive consequences of obesity, several professional associations and organisations worldwide now classify obesity as a disease[16-19].

The risk of obesity-related complications and comorbidities increases with increasing BMI. A weight loss of 5–10% has been shown to have significant health benefits in individuals with obesity in terms of decreasing the risk of T2D progression[20], improving hypertension[21], dyslipidaemia[22], and NAFLD/NASH[23]. In addition, improvements in patient-reported health-related quality of life including physical function have been demonstrated with weight loss[24]. Therefore, achieving and maintaining weight loss in individuals with obesity is crucial. Current standard of care consists of lifestyle counselling including reduced-calorie diets and increased physical activity. However, with this first-line treatment for obesity, only one in five individuals successfully achieve a significant long-term weight loss[25].

Pharmacotherapy may therefore serve as a valuable adjunct to lifestyle intervention for individuals with obesity to achieve and sustain a clinically relevant weight loss, improve comorbid conditions, and facilitate a healthier lifestyle. Few weight management medications are currently available and there is a need for more effective and safe therapeutic options for the treatment of obesity, especially treatments targeting weight maintenance and the treatment and prevention of comorbidities[16, 26-31].

2.1 Trial rationale

The present trial is designed to investigate efficacy and safety of NNC0165-1875 (s.c.) once-weekly as added to semaglutide s.c. 2.4 mg once weekly compared to continuing semaglutide s.c. 2.4 mg once weekly alone for weight management in subjects with obesity. NNC0165-1875 is a long-acting peptide YY $(PYY)_{3-36}$ analogue and a selective Y_2 receptor agonist, intended for chronic weight management by s.c. administration in combination with semaglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist (RA). As PYY and GLP-1 are co-secreted from intestinal L-cells upon feeding, there is considerable interest in investigating the effect of these 2 hormones in combination. Co-infusion of PYY_{3-36} and GLP-1 has been shown to exert a synergistic suppressive effect on energy intake in humans and non-human species[32, 33].

The trial consists of two parts, Part 1 and Part 2. In Part 1, safety and tolerability will be assessed during co-escalation of NNC0165-1875 and semaglutide. In Part 2, NNC0165-1875 1.0 mg will be added to semaglutide s.c. 2.4 mg at steady state to compare the efficacy and safety of NNC0165-1875 added on to semaglutide s.c. 2.4 mg versus continuing semaglutide s.c. 2.4 mg alone. The initial run-in period in Part 2 of the trial (Part 2a) allows for weight loss to be obtained with semaglutide s.c. 2.4 mg, before the addition of NNC0165-1875 1.0 mg thus allowing for any

additional weight loss obtained by this addition to be compared with the weight loss obtained with continuing semaglutide s.c. 2.4 mg only. Furthermore, safety evaluation of the NNC0165-1875 2.0 mg dose will be performed in a small cohort. This trial will provide proof of principle and safety evaluation to guide further clinical development.

2.2 Background

2.2.1 Peptide YY (NNC0165-1875)

Endogenous PYY is secreted together with GLP-1 by L-cells in the distal gut in response to nutrient intake. After secretion, PYY is cleaved into its active form PYY_{3-36}, which has been shown to reduce food intake and lower body weight in several animal species and in humans[34]. The mechanism of action is most likely activation of the Y2 receptor expressed in the hypothalamus, a key region of the brain for regulation of energy homeostasis[35].

One phase 1 trial with NNC0165-1875 has recently been completed. A comprehensive review of results from the non-clinical and clinical studies of NNC0165-1875 can be found in the current edition of the Investigator's Brochure[36] and any updates hereof.

2.2.2 Glucagon-like peptide-1 (semaglutide)

GLP-1 RA is a physiological regulator of appetite and GLP-1 receptors are present in several areas of the brain involved in appetite regulation[37]. Semaglutide is a once-weekly GLP-1 analogue approved for the treatment of adults with T2D at a dose of 1.0 mg (Ozempic®) and is currently under development by Novo Nordisk for weight management with once-weekly semaglutide s.c. doses of 2.4 mg.

A global phase 3a clinical development programme with once-weekly semaglutide s.c. 2.4 mg has been completed in subjects with overweight or obesity (STEP programme). The programme consisted of four trials and enrolled approximately 4,500 adults with overweight or obesity. The largest trial (NN9536-4373; STEP 1) investigated the efficacy and safety of once-weekly semaglutide s.c. 2.4 mg on body weight over 68 weeks compared to placebo in 1,961 adults with overweight or obesity with comorbidities, both in conjunction with lifestyle intervention. Subjects treated with semaglutide s.c. 2.4 mg achieved a mean weight loss of 14.9%, from a baseline body weight of 105.3 kg, compared to a 2.4% weight loss with placebo. In addition, 86.4% of those who received semaglutide s.c. 2.4 mg reached a weight loss of 5% or more after 68 weeks, compared to 31.5% with placebo. Semaglutide s.c. 2.4 mg appeared to be a safe and well tolerated profile in line with what has previously been observed for semaglutide (ref). The most common adverse events (AEs) among subjects treated with semaglutide s.c. 2.4 mg were gastrointestinal events. Most were transient and mild or moderate in severity.

A comprehensive review of results from the non-clinical and clinical studies of semaglutide can be found in the current edition of the Investigator's Brochure and any updates hereof[38].

2.2.3 Trial population

The trial population will consist of subjects with obesity (BMI 30.0-45.0 kg/m^2, both inclusive). These subjects represent a clinically relevant population for pharmacological weight management

as they are at significant risk for weight-related comorbidities and mortality and are likely to benefit from weight reduction.

2.3 Benefit-risk assessment

Main benefits and risks are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected AEs of NNC0165-1875 may be found in the current edition of the Investigator's Brochure[36] and any updates hereof.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of semaglutide may be found in the current edition of the investigator's brochure and any updates hereof[38].

The potential risks described in the below section are based on findings in non-clinical studies with NNC0165-1875 and NNC0165-1875 in combination with semaglutide. The identified and potential risks described in the below section are based on findings in non-clinical studies and clinical trials with semaglutide as well as other GLP-1 RAs. For each of these risks, mitigating actions have been implemented to minimise the risks for subjects enrolled in this trial.

2.4 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Trial treatment NNC0165-1875		
Increased blood pressure	Increased blood pressure has been observed in a safety pharmacology study in rats.	Systolic, diastolic blood pressure and pulse rate will be assessed frequently
Papillary necrosis in the kidneys	A bilateral renal papillary necrosis has been observed in one male in a toxicology study in rats.	Exposure cap is based on the highest dose in 16-week pig NOAEL. Kidney function will be monitored by biochemistry assessment and urinalysis. Routine pharmacovigilance will be executed throughout the trial.
Gastric necrosis	Distended stomach at necropsy, inflammation and necrosis in the mucosa and submucosa of the non-glandular stomach has been observed in a dose range finding study in rats. In some animals, the necrosis was transmural, with spreading to other organs and thereby causing local peritonitis.	Frequent site visits with vital signs, physical examination and safety laboratory assessments is included. Routine pharmacovigilance will be executed throughout the trial.
Change in male reproductive organs	Marked decrease in prostate gland and seminal vesicles weights and associated with histopathology findings (epithelial atrophy in the prostate and decreased secretion in the prostate and seminal vesicles) was observed in toxicology studies in rats.	Subjects with a history of prostate disease will not be included in the trial. Hormones (FSH, LH, prolactin, estradiol and testosterone) and prostate specific antigen (PSA) will be assessed.
Increased tidal volume	Increased respiratory rate and minute volume and increased tidal volume has been observed in safety pharmacology studies in rats.	Vital signs including respiratory rate and oxygenation will be monitored.
Nausea, diarrhoea, vomiting and constipation	Nausea, diarrhoea, vomiting and constipation has been observed when treating subjects with NNC0165-1875 and has been observed when treating subjects with PYY_{3-36}.	A low starting dose and dose escalation steps will be implemented. Routine pharmacovigilance will be executed throughout the trial.
Increased urinary calcium concentration	Increased urinary excretion of calcium has been observed in a toxicity study in rats.	Urinary ion concentration will be monitored by frequent urinalysis and by 24-hour urine collections, including assessment of urinary ion excretion.
Immunogenicity (Allergic reactions / antibody formation)	As is the case with all protein-based pharmaceuticals, subjects treated with NNC0165-1875 are at a risk of developing immunogenic and allergic reactions.	NNC0165-1875 is contraindicated in persons with known or suspected hypersensitivity to any of the trial product components, including excipients. Subjects will be closely monitored for hypersensitivity reactions after administration of the trial product

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Injection site reactions	As is the case with all protein-based pharmaceuticals, subject treated with NNC0165-1875 are at risk of developing injection site reactions	Frequent site visits with physical examination is included
Trial treatment NNC0165-1875 in combination with semaglutide		
Decreased gastric emptying and decreased intestinal motility	Enhanced decrease in intestinal motility and gastric emptying when compared to single components	Gastrointestinal signs and symptoms and changes in bowel habits will be monitored by physical examination and AE reporting Routine pharmacovigilance will be executed throughout the trial
Increased urine volume incl. Increased urinary calcium concentration	Increases in urinary volume resulting in lower urinary concentration of calcium, potassium, chloride, phosphorus, creatinine has been observed in a combination toxicity study in rats.	Urine volume will be monitored by 24-hour urine volume collections. Urinary ion concentration will be monitored by frequent urinalysis and by 24-hour urine collections, including assessment of urinary ion excretion.
Trial treatment semaglutide		
Gastrointestinal AE	Consistent with findings with other GLP-1 RAs, the most frequently reported AE in clinical trials with semaglutide were gastrointestinal AEs.	A low starting dose and dose escalation steps will be implemented.
Cholelithiasis	Frequently reported gallbladder events in the phase 2 weight management trial (NN9536-4153) and were in a few instances co-reported with the event adjudication committee confirmed acute pancreatitis.	If cholelithiasis is suspected, appropriate clinical follow-up is to be initiated at the investigator's discretion
Acute pancreatitis	Acute pancreatitis has been observed with the use of GLP-1 RA drug class.	Subjects with a history of chronic pancreatitis or recent pancreatitis will not be enrolled in the trial. In addition, trial product should be discontinued in case of suspicion of pancreatitis in accordance to Section 7.1.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Medullary thyroid cancer (MTC) (based on non-clinical data)	Proliferative thyroid C-cell changes were seen in the mouse and rat carcinogenicity studies after daily exposure to semaglutide for 2 years. No hyperplasia was observed in monkeys after 52 weeks exposure up to 13-fold above the clinical plasma exposure at 2.4 mg/week. In clinical trials with semaglutide, there have been no clinically relevant changes in calcitonin levels. The C-cell changes in rodents are mediated by the GLP-1 receptor, which is not expressed in the normal human thyroid. Accordingly, the risk of GLP-1 receptor-mediated C-cell changes in humans is considered to be low.	Exclusion criteria related to medical history of multiple endocrine neoplasia type 2 (MEN2) or MTC have been implemented.
Pancreatic cancer	There is currently no support from non-clinical studies, clinical trials or post-marketing data that GLP-1 RA based therapies increase the risk of pancreatic cancer, but pancreatic cancer has been classified as a potential class risk of GLP-1 RAs by European Medicines Agency.	Subjects with a history of malignant neoplasms within the past 5 years prior to screening will be excluded from the trial.
Allergic reactions	As is the case with all protein-based pharmaceuticals, subjects treated with semaglutide are at risk of developing immunogenic and allergic reactions.	Subjects with known or suspected hypersensitivity to semaglutide or related products will not be enrolled.

Trial procedures		
Potential risk of clinical significance	**Summary of data/rationale for risk**	**Mitigation strategy**
COVID-19: 1.Risk of COVID-19 infection in relation to participation in trial 2.Extension of semaglutide treatment in Part 2a. 3. Other risks related to COVID-19	1.Subjects may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country 2.Extension of semaglutide treatment for some subjects in Part 2a can be considered in case of an outbreak of COVID-19.	1.The risk of COVID-19 transmission in relation to site visits is overall considered to be low; however, this may vary between geographical area. To minimise the risk as much as possible, the following measures have been taken: Cautious subject recruitment planning ensures controlled subject enrolment at sites where the COVID-19 pandemic is evaluated to be sufficiently under control, and where health care resources are evaluated to be adequate Guidance is provided to site staff to request that onsite visits are planned to be as short as possible. Physical contact between subjects and site staff will be limited to the extent possible, and protective measures will be implemented e.g., use of masks, sanitisers, no aerosol-generating procedures, etc. according to local requirements 2. In case sites in Part 2a are being temporarily closed due to the COVID-19 pandemic, subjects will be allowed to extend treatment with semaglutide before adding NNC0165-1875. This is allowed in order to mitigate that subjects would otherwise have to be discontinued if it was not possible to attend a site visit to add NNC0165-1875 according to the flowchart schedule. 3.To minimise other risks related to COVID-19 the following measures have been taken.
		Eligibility criteria: COVID-19 testing and diagnosis should be done according to local requirements. Co-participation in COVID-19 studies is not allowed Treatment with NNC0165-1875 and semaglutide:

		COVID-19 testing should be performed according to local requirements. In case of a subject has a positive COVID-19 test, the discontinuation of the trial product is at the discretion of the investigator according discontinuation criteria no. 1. Subjects recovered from a COVID-19 infection are allowed to resume trial product at the discretion of the investigator. The subject should follow the guide for missed doses (see Section 6.1) if treatment should be resumed.
Other		
Pregnancy	Semaglutide Studies in animals have shown reproductive toxicity. There is limited data from the use of semaglutide in pregnant women. NNC0165-1875: No non-clinical repro-toxicology data or clinical data are available.	Semaglutide and NNC0165-1875 should not be used during pregnancy. Exclusion and discontinuation criteria related to pregnancy have been implemented. For guidance on contraception for women of childbearing potential; refer to Appendix 4, Section 10.4

2.4.1 Benefit assessment

Subjects will be treated with a regimen anticipated to be better than or equal to the weight management they receive at the time of entry into the trial. In addition, all subjects will undergo thorough medical evaluations/assessments during the trial, including physical exams, blood tests and ECGs.

2.4.2 Overall benefit-risk conclusion

Taking into account the measures taken to minimise risk to subjects participating in this trial, the potential risks identified in association with NNC0165-1875 in combination with semaglutide are justified by the anticipated benefits that may be afforded to subjects with obesity

3 Objectives and endpoints

3.1 Primary, secondary and exploratory objectives and estimands

Objectives

Part 1

Primary objective

To evaluate the safety and tolerability of co-escalation of once-weekly doses of NNC0165-1875 and semaglutide administered simultaneously as separate doses in subjects with obesity.

Part 2

Primary objective

To compare the effect of NNC0165-1875 1.0 mg added on to semaglutide s.c. 2.4 mg at steady state, versus continuing semaglutide s.c. 2.4 mg alone, on body weight in subjects with obesity.

Secondary objective

To compare the effect of NNC0165-1875 1.0 mg added on to semaglutide s.c. 2.4 mg at steady state versus continuing semaglutide s.c. 2.4 mg alone in subjects with obesity on:

- Glycaemic control
- Waist circumference
- Cardiovascular risk factors

To compare the safety and tolerability of NNC0165-1875 1.0 mg and NNC0165-1875 2.0 mg added on to semaglutide s.c. 2.4 mg versus continuing semaglutide s.c. 2.4 mg alone in subjects with obesity.

Estimands

Estimands apply for statistical analysis of Part 2.

Primary estimand

The estimand will quantify the average treatment of NNC0165-1875 1.0 mg as an add on to semaglutide 2.4 mg relative to placebo as an add on to semaglutide 2.4 mg in all randomised subjects regardless of treatment discontinuation and rescue interventions (anti-obesity drugs or devices, or bariatric surgery) with respect to percent change in body weight from week 32 to week 48 in all randomised subjects who are able to reach the target dose of semaglutide during 32 weeks of run-in with escalating semaglutide doses.

Attribute	
Treatment	NNC0165-1875 as an add on to semaglutide 2.4 mg versus placebo as an add on to semaglutide 2.4 mg
Population	All subjects randomised to 1.0 mg NNC0165-1875 for whom semaglutide has been escalated to the target dose with semaglutide 2.4 mg at week 28 and at target dose at the randomisation visit (week 32)
Endpoint	Percent change in body weight from week 32 to week 48
Intercurrent events	Treatment discontinuation: treatment policy strategy Rescue interventions (anti-obesity drugs or devices, or bariatric surgery): treatment policy/effectiveness policy strategy
Population-level summary	Difference in average percent change in body weight between NNC0165-1875 1.0 mg as an add on to semaglutide s.c. 2.4 mg versus placebo as an add on to semaglutide s.c. 2.4 mg

Additional estimand

The estimand will quantify the average treatment of NNC0165-1875 1.0 mg as an add on to semaglutide 2.4 mg relative to placebo as an add on to semaglutide 2.4 mg in all subjects who remain on their randomised treatment for the entire planned duration of the treatment period and do not start any rescue intervention (anti-obesity drugs or devices, or bariatric surgery) with respect to percent change in body weight from week 32 to week 48 in all randomised subjects who are able to reach the target dose of semaglutide during 32 weeks of run-in with escalating semaglutide doses.

Attribute	
Treatment	NNC0165-1875 as an add on to semaglutide 2.4 mg versus placebo as an add on to semaglutide 2.4 mg
Population	All subjects randomised to 1.0 mg NNC0165-1875 for whom semaglutide has been escalated to the target dose with semaglutide 2.4 mg at week 28 and at target dose at the randomisation visit (week 32)
Endpoint	Percent change in body weight from week 32 to week 48
Intercurrent events	Treatment discontinuation: hypothetical strategy Rescue interventions (anti-obesity drugs or devices or bariatric surgery): hypothetical/efficacy strategy
Population-level summary	Difference in average percent change in body weight between NNC0165-1875 1.0 mg as an add on to semaglutide s.c. 2.4 mg versus placebo as an add on to semaglutide s.c. 2.4 mg

3.2 Primary, secondary and exploratory endpoints

3.2.1 Primary endpoint

Part 1

Endpoint title	Time frame	Unit
Number of treatment-emergent adverse events (TEAEs)	From time of dosing (day 1) to follow-up (week 24)	Number of events

Part 2

Primary endpoint for NNC0165-1875 1.0 mg as an add on to semaglutide 2.4 mg versus placebo 1.0 mg as an add on to semaglutide 2.4 mg:

Endpoint title	Time frame	Unit
Change in body weight	From randomisation (week 32) to end of treatment (week 48)	percentage

3.2.2 Secondary endpoints

3.2.2.1 Confirmatory secondary endpoints

Not applicable

3.2.2.2 Supportive secondary endpoints

Part 2

Supportive secondary endpoints for NNC0165-1875 1.0 mg as an add on to semaglutide 2.4 mg versus placebo 1.0 mg as an add on to semaglutide 2.4 mg:

Endpoint title	Time frame	Unit
Change in body weight	From randomisation (week 32) to end of treatment (week 48)	kg
Change in $HbA1_c$	From randomisation (week 32) to end of treatment (week 48)	Percentage point
Change in fasting plasma glucose	From randomisation (week 32) to end of treatment (week 48)	mmol/l
Change in fasting insulin	From randomisation (week 32) to end of treatment (week 48)	pmol/l
Change in waist circumference	From randomisation (week 32) to end of treatment (week 48)	cm
Relative change in total cholesterol	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline
Relative change in HDL cholesterol	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline
Relative change in LDL cholesterol	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline
Relative change in VLDL cholesterol	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline
Relative change in Triglycerides	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline
Relative change in Free fatty acids	From randomisation (week 32) to end of treatment (week 48)	ratio to baseline

Supportive secondary endpoints for NNC0165-1875 1.0 mg or 2.0 mg as an add on to semaglutide 2.4 mg versus placebo 1.0 mg or 2.0 mg as an add on to semaglutide 2.4 mg:

Endpoint title	Time frame	Unit
Number of emergent adverse events (TEAEs)	From baseline at (week 0) to end of trial (week 56)	Count of events
Number of serious treatment emergent adverse events (SAEs)	From baseline at (week 0) to end of trial (week 56)	Count of events

3.2.3 Exploratory endpoints

Not applicable for this trial.

4 Trial design

4.1 Overall design

Part 1

Part 1 is a 16-week, four-armed, double-blinded (within arms), randomised, placebo-controlled, single-site trial comparing co-escalation of two doses of NNC0165-1875 as an add on to semaglutide s.c. 2.4 mg versus placebo added on to semaglutide s.c. 2.4 mg in subjects with obesity.

Part 1 includes a screening visit to assess subject's eligibility. At visit 2 (randomisation) eligible subjects will enter a 12-week dose escalation period followed by a 4-week maintenance period until end-of-treatment. Visits will take place every 2 weeks. Following each dose escalation, 5 additional visits will take place corresponding to the predicted T_{max} of NNC0165-1875. The follow-up period is 8 weeks to account for the long half-life of NNC0165-1875 and semaglutide. To assess subject safety during and after wash-out of trial product, two visits are scheduled 2 weeks (visit 16) and 8 weeks (visit 17) after end-of-treatment.

NNC0165-1875/NNC0165-1875 placebo will be co-escalated with semaglutide every 2 weeks for the first 4 weeks, and every 4 weeks for the next 8 weeks until final target dose levels are reached. The starting dose of NNC0165-1875/NNC0165-1875 placebo is 0.05 mg or 0.1 mg and the final target dose of NNC0165-1875/NNC0165-1875 placebo is 1.0 mg or 2.0 mg, depending on the treatment arm. The starting dose semaglutide is 0.25 mg and the final target dose of semaglutide is 2.4 mg in all arms. Further information on dose regimens is presented in Section 6.1.

Approximately 24 subjects will be randomised 2:1:2:1 to receive NNC0165-1875 1.0 mg / NNC0165-1875 1.0 mg placebo or NNC0165-1875 2.0 mg / NNC0165-1875 2.0 mg placebo in combination with semaglutide. Each NNC0165-1875 treatment arm will administer different dose volumes but is blinded towards placebo with matching injection volumes.

Part 1 will be conducted by a CRO.

Part 2

Part 2 is a 48-week, four-armed, double-blinded (within arms), randomised, placebo-controlled, multi-centre, proof-of-principle trial comparing once weekly NNC0165-1875 as add on to once-weekly semaglutide s.c. 2.4 mg versus placebo as add on to once-weekly semaglutide s.c. 2.4 mg in subjects with obesity. Part 2 will evaluate efficacy and safety for NNC0165-1875 1.0 mg, and safety for NNC0165-1875 2.0 mg.

Part 2 consists of two parts: an open-label run-in part (Part 2a) where all subjects are treated with once-weekly semaglutide and a second part (Part 2b) where once-weekly NNC0165-1875 or NNC0165-1875 placebo is added to semaglutide s.c. 2.4 mg.

Part 2a includes a screening visit to assess the subject's eligibility. At visit 2 eligible subjects will enter a 32-week run-in period with 8 weeks of semaglutide dose-escalation and 24 weeks of semaglutide s.c. 2.4 mg maintenance. Semaglutide will be escalated every 2 weeks. Visits will take

place every 2 weeks during semaglutide dose escalation and every 4 weeks during semaglutide maintenance.

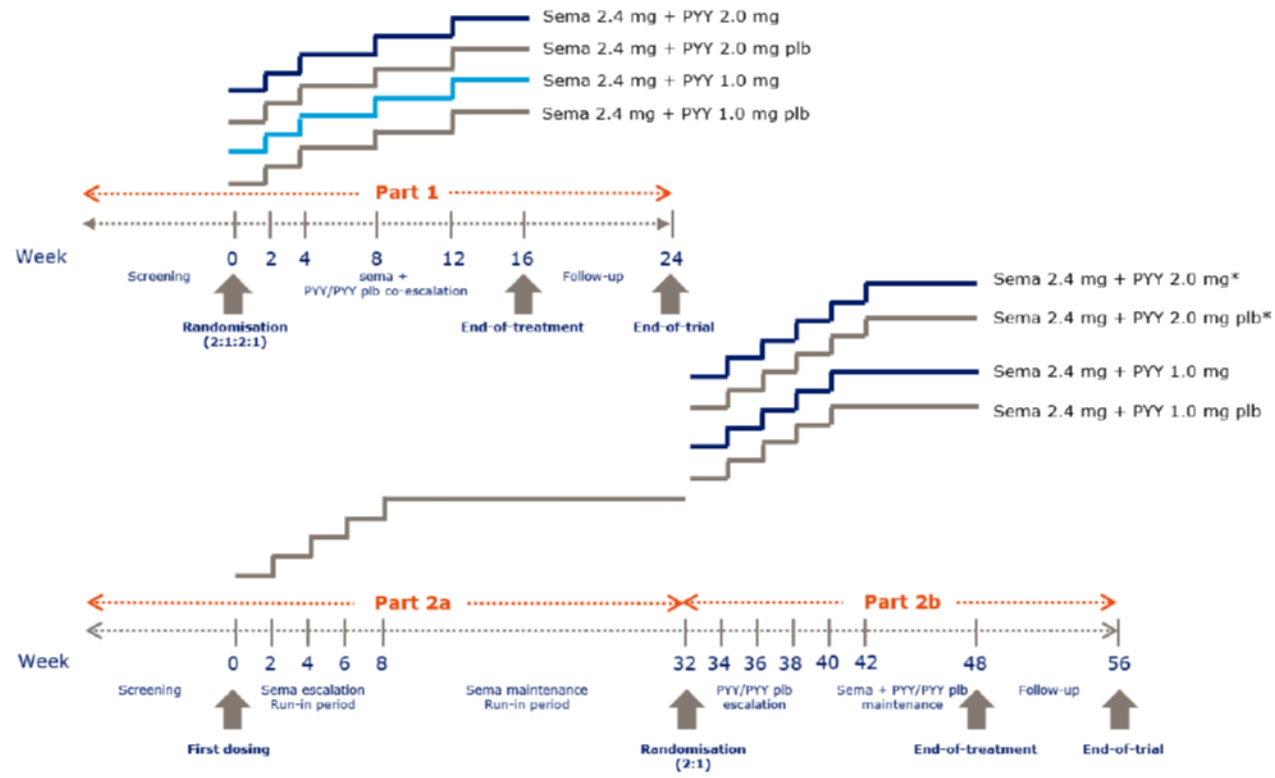
At week 32, subjects who have reached the target dose of semaglutide s.c. 2.4 mg during the run-in period and fulfil the randomisation criteria (see Section 5.5.2) will enter Part 2b and be randomised in a 2:1 manner to receive either once-weekly NNC0165-1875 1.0 mg or placebo 1.0 mg as add-on to once-weekly semaglutide 2.4 mg. Part 2b includes 8 weeks of NNC0165-1875/placebo 1.0 mg dose escalation followed by 8 weeks of NNC0165-1875/placebo 1.0 mg maintenance until end-of-treatment. In part 2b, a small cohort (12 subjects) will be randomised 2:1 to NNC0165-1875 2.0 mg/placebo 2.0 mg, these subjects will have 10 weeks of dose escalation followed by 6 weeks on NNC0165-1875/placebo 2.0 mg maintenance until end-of-treatment. For all groups, visits will take place every 2 weeks during dose escalation and alternating visits/phone contacts will take place every week for the remaining period until end-of-treatment. A follow-up visit ('end of trial visit') for safety assessments is scheduled 8 weeks after end of treatment to account for the long half-life of NNC0165-1875 and semaglutide. Information on dose regimens is presented in Table 6-2, Table 6-3, Table 6-4, Table 6-5.

The trial duration of Part 2 will be approximately 58 weeks; 2 weeks of screening, 32 weeks of semaglutide run-in, 16 weeks of NNC0165-1875 or NNC0165-1875 placebo add on to semaglutide s.c. 2.4 mg. The follow-up is 8 weeks.

Ninety subjects are planned to be enrolled in Part 2a to ensure approximately 75 subjects eligible for randomisation in Part 2b.

An overview of the trial design for Part 1 and Part 2 is presented in Figure 4-1.

Figure 4-1 Overview of the trial design



PYY: NNC0165-1875; Sema: semaglutide; Plb: placebo
* 12 subjects will be randomised 2:1 to receive sema 2.4 mg + PYY 2.0 mg or sema 2.4 mg + PYY 2.0 mg plb

In Part 1, according to 'the internal Novo Nordisk safety oversight group charter', a blinded internal Novo Nordisk safety oversight group will monitor the trial continuously for safety, tolerability and PK properties on the individual subject level and dose group level. Following LPLV in Part 1, the internal Novo Nordisk safety oversight group will evaluate the totality, pattern and severity of observed AEs, laboratory parameters and PK properties of NNC0165-1875 based on unblinded data.

Part 1 and Part 2a will be conducted in semi-parallel, as the recruitment for the two parts will be separated in time allowing for a conclusion to be made on Part 1 before subjects from Part 2a are randomised into Part 2b. The decision to progress into Part 2b will be taken by the Novo Nordisk safety committee based on a recommendation from the Novo Nordisk safety oversight group. The safety committee may decide whether:

- the trial should proceed into Part 2b
- the Part 2b protocol specified frequency of visits and/or clinical and laboratory monitoring should be adjusted
- the Part 2b protocol specified dose escalation should be adjusted and/or the once weekly target dose of 2 mg of NNC0165-1875 should be reduced

If changes to the protocol for Part 2b are required based on the outcome of Part 1, and if the protocol amendment is not finalised before the first subjects in Part 2a reach the randomisation visit (V10) at week 24, subjects are allowed to continue in Part 2a on once-weekly semaglutide s.c. 2.4 mg until randomisation can be initiated. The maximum allowed additional time in Part 2a is 8 weeks where additional visits (V9.1 and V9.2) will take place approximately every 4 weeks.

If the maximum allowed additional time in Part 2a is used, the trial duration of Part 2 will be approximately 58 weeks (2 weeks of screening, 32 weeks of semaglutide run-in, 16 weeks of NNC0165-1875 2.4 mg/NNC0165-1875 placebo add on to semaglutide s.c. 2.4 mg and 8 weeks of follow-up).

In protocol version 4.0, the two additional run-in visits (V9.1 and V9.2) have been activated.

4.2 Scientific rationale for trial design

The trial design in Part 1 will allow for the evaluation of safety, tolerability and PK properties of two different dose levels of once-weekly NNC0165-1875 co-escalated in combination with once-weekly semaglutide. The visit structure will allow for frequent interaction between subject and investigator hereby ensuring monitoring of subject safety, AE handling and reporting.

The trial design in Part 2 will allow for the comparison of once-weekly NNC0165-1875 1.0 mg versus placebo 1.0 mg as add on to once-weekly semaglutide s.c. 2.4 mg. The 32-week run-in period (Part 2a) of the trial allows for weight loss to be obtained with semaglutide s.c. 2.4 mg before the add on of NNC0165-1875 1.0 mg. The design allows for identifying any additional weight loss by the combination treatment compared to the effect of continuing with semaglutide s.c. 2.4 mg treatment. Furthermore, the trial design will allow for evaluation of safety, tolerability and PK properties in the NN0165-1875 2.0 mg dose group.

A treatment duration of 16 weeks (Part 2b) is considered appropriate to evaluate proof-of-principle for once-weekly NNC0165-1875 for weight loss effects and will provide information on the safety and tolerability profile of NNC0165-1875.

4.2.1 Subject input into design

There has been no interaction with subjects for input to design of the current trial; however, experience from previous obesity trials has been implemented to the extent possible.

4.3 Justification for dose

NNC0165-1875

The dose levels of 1.0 and 2.0 mg of NNC0165-1875 have been selected based on clinical and non-clinical findings.

In trial NN9775-4398, the safety, tolerability, and PK/PD properties of a single s.c dose of NNC0165-1875 were tested. Single s.c dose of NNC0165-1875 up to 2.1 mg as monotherapy, and single s.c dose of NNC0165-1875 up to 1.7 mg in combination with semaglutide 0.25 mg was shown to be safe and tolerable. Based on data from NN9775-4398, the half-life of NNC0165-1875 is estimated to be approximately 10 days, supporting once-weekly dosing.

In part 1 of this trial (NN9775-4708), safety, tolerability and PK properties were to be explored for both 1.0 mg and 2.0 mg NNC0165-1875/placebo. However, data for the 2.0 mg dose of NNC0165-1875 were not available from part 1 of the trial, due to treatment discontinuation attributed to tolerability issues with the dose escalation regimen used in part 1. The lower starting dose and the dose escalation regimen used for the 1.0 mg NNC0165-1875 dose group appeared tolerable. Based

on part 1, the following changes are made for part 2b in Protocol version 4.0: the Novo Nordisk Safety Committee has decided to update part 2b by lowering the starting dose to 0.05 mg NNC0165-1875/placebo, by adding extra steps in the dose escalation regimen and by changing the maintenance dose to 1.0 mg NNC0165-1875/placebo. In addition, two extra treatment arms have been added for safety evaluation of the 2.0 mg dose of NNC0165-1875, in which 12 subjects will be randomised 2:1 to 2.0 mg NNC0165-1875/placebo.

The exposure limits are based on the exposures observed at the NOAEL non-clinical toxicity study, and the maximum dose of NNC0165-1875 2.0 mg is selected in order not to exceed this. Please refer to the Investigator's Brochure NNC0165-1875 and any updates hereof[36].

Semaglutide

In a phase 3a trial (NN9536-4373; STEP1) comprising 1,961 adults with obesity or overweight with comorbidities, subjects treated with semaglutide s.c. 2.4 mg achieved a mean weight loss of 14.9%, from a baseline body weight of 105.3 kg, compared to a 2.4% weight loss with placebo. In addition, 86.4% of those who received semaglutide 2.4 mg s.c. reached a weight loss of 5% or more after 68 weeks, compared to 31.5% with placebo. Semaglutide 2.4 mg s.c. appeared to have a safe and well tolerated profile in line with what has previously been observed for semaglutide[62]. The most common adverse events among subjects treated with semaglutide 2.4 mg s.c. were gastrointestinal events. Most events were transient, and mild or moderate in severity.

In NN9775-4708 Part 1, semaglutide dosing will be initiated at a once-weekly dose of 0.25 mg and increased to 0.5 mg and 1.0 mg after 2 weeks. At 1.0 mg, dose escalation will occur every 4 weeks to doses of 1.7 and 2.4 mg/week until the target dose is reached after a total of 16 weeks. Fewer expected tolerability issues at lower dose levels allow for faster dose escalation at lower doses compared to higher doses.

In NN9775-4708 Part 2a, semaglutide dosing will be initiated at a once-weekly dose of 0.25 mg and followed by dose increases every 2 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week), until the target dose is reached after 8 weeks. The subjects will continue at semaglutide 2.4 mg once-weekly for the remaining part of the trial (until week 48).

It is well known that to mitigate gastrointestinal side effects with GLP-1 RA treatment, dose escalation to the target dose is required.

4.4 End of trial definition

A subject is considered to have completed the trial if he/she has completed either Part 1 or Part 2b of the trial including the last visit in Part 1 or Part 2b. The end of the trial is defined as the date of the last visit of the last subject in Part 2b.

5 Trial population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted. The inclusion and exclusion criteria listed below apply for both Part 1 and Part 2.

5.1 Inclusion criteria

Subjects are eligible to be included in the trial only if all of the following criteria apply:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age above or equal to 18 years at the time of signing informed consent.
3. BMI 30.0 – 45.0 kg/m^2 (both inclusive) at the screening visit.

5.2 Exclusion criteria

Subjects are excluded from the trial if any of the following criteria apply:

Glycaemia-related

1. $HbA1_c \geq 48$ mmol/mol (6.5%) as measured by a central laboratory at screening.
2. History of type 1 or type 2 diabetes mellitus.
3. Treatment with glucose-lowering agent(s) within 90 days before screening.

Obesity-related

4. A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records.
5. Treatment with any medication indicated for weight management within 90 days before screening.
6. Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed >1 year before screening, (2) laparoscopic banding, if the band has been removed >1 year before screening, (3) intragastric balloon, if the balloon has been removed >1 year before screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year before screening.
7. Uncontrolled thyroid disease per investigators discretion.
8. Treatment with a GLP-1 RA within 180 days before screening.

Mental health-related

9. History of major depressive disorder within 2 years before screening.
10. History of other severe psychiatric disorders (e.g., schizophrenia or bipolar disorder).
11. A lifetime history of a suicidal attempt.
12. Suicidal behaviour within 30 days before screening
13. Suicidal ideation corresponding to type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the past 30 days before screening
14. A Patient Health Questionnaire-9 (PHQ-9) score ≥ 15 at screening

Cardiovascular assessments

15. Sitting blood pressure outside the range of 90-159 mmHg for systolic or 50-99 mmHg for diastolic at screening.
16. Pulse of ≥ 100 beats/min at screening.
17. Presence or history of cardiovascular disease, including myocardial infarction, stroke, stable or unstable angina pectoris, transient ischaemic attack, cardiac decompensation, clinically significant arrhythmias or clinically significant conduction disorders.
18. Subject presently classified as being in New York Heart Association (NYHA) Class IV heart failure.

General safety

19. Presence or history of prostate disease
20. Prostate Specific Antigen > 4 ng/mL as measured by the central laboratory at screening
21. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of < 60 ml/min/1.73 m2 as defined by KDIGO 2012[39] by the central laboratory at screening.
22. Impaired liver function, defined as Alanine Aminotransferase (ALT) ≥2.5 times or Aspartate Aminotransferase (AST) ≥2.5 times or Alkaline Phosphatase ≥2.5 times or Bilirubin >1.5 times upper normal limit (UNL), as measured by the central laboratory at screening.
23. Known or suspected abuse of alcohol or recreational drugs.
24. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.
25. Presence or history of chronic pancreatitis.
26. Presence of acute pancreatitis within 180 days prior to the first screening visit.
27. Presence or history of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed.
28. Surgery scheduled during the duration of the trial, except for minor surgical procedures, per investigator discretion.
29. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.
30. Known or suspected hypersensitivity to trial products or related products.
31. Previous participation in this trial. Participation is defined as signed informed consent.
32. Other subject(s) from the same household participating in any trial testing NNC0165-1875 or semaglutide.
33. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method (see Appendix 4, Section 10.4)
34. COVID-19 vaccinations within 30 days before screening.
35. Any disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.

5.3 Lifestyle considerations

To ensure alignment regarding performance of assessments across subjects and trial sites, the below restrictions apply.

5.3.1 Meals and dietary restrictions

- Subjects must attend visits fasting according to the flowchart (Section 1.2).

- Fasting is defined as:
  - no food or liquid, except for water, for at least 8 hours prior to the visit.
  - no water 2 hours prior to the visit.
- If the subject is not fasting as required, the subject must be called in for a new visit within the visit window to have the fasting procedures performed.
- Procedures requiring the subject to fast include blood sampling of FPG, fasting serum insulin and free fatty acids.

5.3.2 Caffeine, alcohol and tobacco

- Tobacco use is defined as smoking at least one cigarette or equivalent daily.
- Subject should avoid caffeine and smoking at least 30 minutes prior to measurement of blood pressure.

5.3.3 Physical activity

Not applicable for this trial.

5.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Only Part 2 of the trial will be handled by IWRS.

A screen failure session must be made in the interactive web response system (IWRS) for Part 2. For Part 1 the screen failure reason must be entered in the eCRF end of trial form.

Individuals who do not meet the criteria for participation in this trial may not be rescreened. If the subject 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 parameters.

However, if a subject is inadvertently randomised in violation of the inclusion and exclusion criteria (RVIE) the following procedure must be performed:

- Temporary discontinuation of randomised treatment
- Safety risk evaluation by the principal investigator and the medical responsible from Novo Nordisk A/S to determine whether randomised treatment should be restarted or permanently discontinued (a treatment discontinuation session made in IWRS)
- Submission of an important protocol deviation and notification of the IEC/IRB and regulatory authorities according to local requirements.

5.5 Run-in criteria and/or randomisation criteria

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

Re-sampling is not allowed if the subject has failed any of the run-in/randomisation criteria related to laboratory parameters. However, in case of technical issues (e.g., haemolysed or lost), re-sampling is allowed for the affected parameters.

5.5.1 Run-in criteria

Part 2a

To be eligible to enter run-in, all run-in criteria must be answered "yes"

1. A PHQ-9 score of < 15 at week 0
2. No suicidal behaviour in the period between screening and week 0
3. No suicidal ideation corresponding to type 4 or 5 on the C-SSRS in the period between screening and week 0

5.5.2 Randomisation criteria

Part 1

To be randomised, all randomisation criteria must be answered "yes"

1. A PHQ-9 score of < 15 at week 0
2. No suicidal behaviour in the period between screening and week 0
3. No suicidal ideation corresponding to type 4 or 5 on the C-SSRS in the period between screening and week 0

Part 2b

To be randomised, all randomisation criteria must be answered "yes"

1. Attend the randomisation visit (week 32)
2. Have escalated to the target dose with semaglutide s.c. 2.4 mg by week 28
3. Are at target dose at the randomisation visit (week 32)

Subject not fulfilling the randomisation criteria will be considered run-in failure. All run-in failures should attend the 'end of trial' visit 8 weeks +5 days after their week 32 visit.

5.5.3 Dosing day criteria

Not applicable for this trial.

6 Treatments

6.1 Treatments administered

Investigational medicinal products (IMP)

All trial products listed in Table 6-1 are considered IMPs and are supplied by Novo Nordisk.

Table 6-1 Investigational medicinal products provided by Novo Nordisk

Trial product name:	NNC0165-1875 A 0.2 mg/ml	NNC0165-1875 A 5.0 mg/ml	Semaglutide B 3.0 mg/ml	NNC0165-1875 Placebo A
Dosage form	Solution for injection	Solution for injection	Solution for injection	Solution for injection
Route of administration	Subcutaneous	Subcutaneous	Subcutanous	Subcutanous
Dosing instructions	Once-weekly	Once-weekly	Once-weekly	Once-weekly
Packaging	3 ml cartridge for use in NovoPen® 4 (durable device)	3 ml cartridge for use in NovoPen® 4 (durable device)	PDS290 pen injector to be used is with a U100 scale on the scale drum	3 ml cartridge for use in NovoPen® 4 (durable device)

- Semaglutide will be administered as open-label, while NNC0165-1875 is blinded by corresponding placebo.
- Dosing must be administered on site at all site visits, for both Part 1 and Part 2. On site the dose should be administered by the investigator or delegated staff. The investigator must document that directions for use (DFU) are given to the subject verbally and in writing
- For the dosing at home, subjects will be instructed to inject trial products once weekly on the same day of the week (to the extent possible) throughout the trial.
- In Part 1 and 2b all subjects will be instructed to inject two injections (at the same time) each week; one dose of semaglutide and one dose NNC0165-1875/placebo.
- In Part 2a, all subjects will be instructed to inject one injection with semaglutide each week.
- Trial products can be taken at any time of day, irrespective of timing of meals.
- Trial product injections should be administered subcutaneously in the thigh or abdomen
- The administration of NNC0165-1875/placebo must always be in the right side of the abdomen or the right thigh.
- The administration of semaglutide must always be in the left side of the abdomen or the left thigh.
- Dosing information must be collected in the designated paper dosing diary, entries must be entered in the case report form (CRF) and contains:
  - Date
  - Time of dose
  - Value shown in dose counter or not taken
  - Injection site:
    - thigh or abdomen
  - Injection side
    - left or right

- Dose Value entered by site staff

- If a scheduled dose of any trial product is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 2 days (48 hours). If a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the subject should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week. The scheduled dosing day of the week should remain the same throughout the trial if possible.
- If ≥ 2 consecutive doses of trial product are missed, the subject should be encouraged to recommence the treatment, if considered safe as per the investigator's discretion and if the subject does not meet any of the discontinuation criteria (Section 7.1). The trial product should be continued as soon as the situation allows. The missed doses should not affect the scheduled dosing day of the week. The start dose for re-initiation of trial product is at the investigator's discretion. In case of questions related to re-initiation of trial product, the investigator should consult Novo Nordisk global medical experts.
- To prevent pen mix-up and medication errors, The Pen Differentiation Guide must be used during training of site staff and subjects and handed out to subjects when administering trial products at home (please see Pen Difference Guidance)

Table 6-2 Part 1. Dosing details for NNC0165-1875 and corresponding placebo arms during the escalation and maintenance phases using the NovoPen®4

Target dose	Unit	Visit 2 Randomisation	Visit 4 Week 2	Visit 6 Week 4	Visit 9 Week 8	Visit 12 Week 12 & until End of treatment
1.0 mg	Dose in mg	0.05	0.1	0.25	0.5	1.0
	Product Strength in mg/ml	0.2	0.2	5.0	5.0	5.0
	Volume in mL	0.25	0.5	0.05	0.1	0.2
	Value shown in dose counter	**25**	**50**	**5**	**10**	**20**
2.0 mg	Dose in mg	0.1	0.25	0.5	1.0	2.0
	Product Strength in mg/ml	0.2	5.0	5.0	5.0	5.0
	Volume in mL	0.5	0.05	0.1	0.2	0.4
	Value shown in dose counter	**50**	**5**	**10**	**20**	**40**

Table 6-3 Part 1. Dosing details for semaglutide B 3.0 mg/mL PDS290 during the escalation and maintenance phase

Target dose	Unit	Visit 2 Randomisation	Visit 4 Week 2	Visit 6 Week 4	Visit 9 Week 8	Visit 12 Week 12 & until End of treatment
2.4 mg	Dose in mg	0.25	0.5	1.0	1.7	2.4
	Volume in mL	0.08	0.17	0.34	0.57	0.80
	Value shown in dose counter	**8**	**17**	**34**	**57**	**80**

Table 6-4 Part 2a and 2b. Dosing details for semaglutide B 3.0 mg/mL PDS290 during the escalation and maintenance phase

Target dose	Unit	Visit 2 Week 0	Visit 3 Week 2	Visit 4 Week 4	Visit 5 Week 6	Visit 6 Week 8	Visit 7 Week 12 Maintenance	Visit 10 Week 32 Randomisation & until End of treatment
2.4 mg	Dose in mg	0.25	0.5	1.0	1.7	2.4	2.4	2.4
	Volume in mL	0.08	0.17	0.34	0.57	0.80	0.80	0.80
	Value shown in dose counter	**8**	**17**	**34**	**57**	**80**	**80**	**80**

Table 6-5 Part 2b. Dosing details for NNC0165-1875 and corresponding placebo arms during the escalation and maintenance phases using the NovoPen®4

Target dose	Unit	Visit 10 Randomisation Week 32	Visit 11 Week 34	Visit 12 Week 36	Visit 13 Week 38	Visit 13b Week 40	Visit 14 Week 42 & until End of treatment
1.0 mg	Dose in mg	0.05	0.1	0.25	0.5	1.0	1.0
	mg/ml	5.0	5.0	5.0	5.0	5.0	5.0
	Volume in mL	0.01	0.02	0.05	0.1	0.2	0.2
	Value shown in dose counter	**1**	**2**	**5**	**10**	**20**	**20**
2.0 mg	Dose in mg	0.05	0.1	0.25	0.5	1.0	2.0
	mg/ml	5.0	5.0	5.0	5.0	5.0	5.0
	Volume in mL	0.01	0.02	0.05	0.1	0.2	0.4
	Value shown in dose counter	**1**	**2**	**5**	**10**	**20**	**40**

All subjects should aim to reach the recommended target dose of NNC0165-1875/placebo and semaglutide within their arm.

- In case of unacceptable AEs as judged by the investigator, dose escalation may be postponed by 1-2 weeks at the discretion of the investigator. This should only be allowed if the subject would otherwise discontinue trial product completely and if considered safe to continue the trial product, as per the investigator's discretion.
- If a subject does not tolerate the randomised target dose, the subject may stay at a lower dose level. This should only be allowed if the subject would otherwise discontinue trial product completely and if considered safe to continue on trial product, as per investigator's discretion.
- the lower dose level is at the discretion of the investigator
- For part 1; both NNC0165-1875/placebo and semaglutide should be reduced if the subject does not tolerate the randomised target dose
- For part 2b; NNC0165-1875/placebo should be reduced if the subject does not tolerate the randomised target dose. Semaglutide should preferably stay at 2.4 mg but is allowed to be reduced, as per investigator's discretion
- In case of deviations from the planned dose escalation regimen, it is recommended that the subject make at least one attempt to re-escalate to the recommended target level dose, as per the investigator's discretion.

- It is recommended that the investigator consults Novo Nordisk in case of persistent deviations from the planned escalation regimen.

A dose reminder card will be handed out to the subjects at each site visit during the escalation period. The handout dose reminder card will contain information on:

- The dose to be taken until next site visit
- A reminder for the subject to bring trial product to site for the dosing at site.

Non-investigational medicinal products

Not applicable.

Auxiliary supplies will be provided by Novo Nordisk in accordance with the trial materials manual (TMM) (See Table 6-6).

Table 6-6 Auxiliary supplies provided by Novo Nordisk

Auxiliary supply	Details
Needles	NovoFine Plus 32G, 4 mm NovoFine 32G, 6 mm
Device	NovoPen® 4
Directions for use (DFU)	DFU for NovoPen® 4 DFU for PDS290 pen-injector

Only needles provided and approved by Novo Nordisk must be used for administration of trial product.

6.1.1 Medical devices

6.1.1.1 Investigational medical devices

Not applicable for this trial.

6.1.1.2 Non-investigational medical devices

Non-investigational medical devices are listed in Section 6.1 as auxiliary supplies.

NovoPen® 4 is a durable device which is not under investigation in this trial. 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 from 1 to 60 units in increments of 1 unit. One unit (increment) is equivalent to 10 µL, thus the pen-injector can deliver volumes from 10 µL to 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. The investigator must document that the DFU is given to the subject orally and in writing at the first dispensing visit.

Information about the NovoPen® 4 and PDS290 pre-filled pen-injector may be found in the NNC0165-1875 Investigator's Brochure and any updates hereof[36]. Information about the use of the NovoPen® 4 and the PDS290 pre-filled pen-injector for semaglutide and semaglutide placebo can be found in the DFU.

Training in the medical devices

The subjects must be trained according to the DFU in how to handle the NovoPen® 4 and the PDS290 pen-injector, when handed out the first time.

The investigator must document that training in DFU has been given to the subjects orally and in writing at the first dispensing visit. Training must be repeated during the trial at regular intervals in order to ensure correct use of the medical device. Training is the responsibility of the investigator or a delegate.

6.2 Preparation/handling/storage/accountability

Only subjects randomised to treatment may use trial product and only delegated site staff may supply or administer trial product.

- Each site will be supplied with sufficient trial products for the trial on an ongoing basis. Trial product will be distributed to the sites according to screening 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 subject before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the trial materials manual (TMM).
- The investigator or designee is responsible for drug accountability and record maintenance (i.e., receipt, accountability and final disposition records).
- The investigator or designee must instruct the subject in what to return at next visit.
- Drug accountability should be performed on a pen level and must be documented in the IWRS for Part 2 and the eCRF for Part 1
- The subject must return all used, partly used and unused trial product including empty packaging materials during the trial as instructed by the investigator.
- 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, un-used, expired or damaged trial products (for technical complaint samples, see 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

Randomisation

For Part 2 all subjects will be centrally screened and randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed/allocated at the trial visits summarised in the flowchart. As subjects on treatment with

NNC0165-1875/placebo 2.0 mg need to be closely monitored for safety and tolerability, the randomisation of the 2.0 mg dose groups will be restricted to 1-3 sites.

For Part 1 the specific treatment for a subject will be assigned using a randomisation list. Potential bias will be reduced by central randomisation. All subjects will be assigned a unique number (randomisation number) in ascending numerical order. The randomisation number encodes the subject's assignment to x of y treatment arms in the trial according to the randomisation schedule generated before the trial. For further instruction, see the TMM.

Open-label

- Semaglutide B 3.0 mg/mL

Blinding

The active drug and placebo are visually identical for the following trial products:

- NNC0165-1875 1.0 mg/ NNC0165-1875 1.0 mg placebo
- NNC0165-1875 2.0 mg/ NNC0165-1875 2.0 mg placebo

For Part 2 the IWRS is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment is warranted. Subject 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 subject's treatment unless this could delay emergency treatment of the subject. If a subject's treatment 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 "code 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 help desk should be contacted. Contact details are listed in Attachment I.

For Part 1 Three sets of sealed codes containing treatment information for each subject will be prepared. The sealed codes will be retained by the investigator (CRO), the local Novo Nordisk affiliate and the Novo Nordisk Global Safety department in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subjects' treatment is warranted. Subject 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 (Global Safety department) prior to unblinding a subject's treatment, unless this could delay emergency treatment of the subject. If a subject's treatment is unblinded, Novo Nordisk (Global Safety department) must be notified within 24 hours after breaking the blind. The date when and reason why the blind was broken must be recorded in the source documentation. Once the trial is complete, all hard copy codes (sealed and opened) must be accounted for at the site. The codes will be collected by the monitor at trial closure visit. Treatment allocation will also be accessible to special laboratory responsible for PK analysis.

6.4 Treatment compliance

Drug treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to encourage subject compliance.

Dosing will be administered on site at all site visits, for both Part 1 and Part 2. In between the visits the subjects will self-administer trial product at home.

When dosing at site

When at the site the subjects will be dosed by the investigator or designee, under medical supervision. The date and time of each dose administered at the site will be recorded in the source documents.

When dosing at home

When subjects self-administer trial product(s) 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, apart from occasionally the site must enter into a dialogue with the subject, 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.

- Drug accountability information: counting returned trial product, visual inspection of pens
- Review of dosing diaries
- Questioning of subjects

Treatment date, time, trial product taken, injected dose, dose unit, injection site and location of injection are recorded in the CRF.

6.5 Concomitant medication

Any medication (including over the counter or prescription medicines) other than the trial products that the subject is receiving at the time of the first visit or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dose, Unit and Frequency
- Dates of administration including start and stop dates

During the trial subjects should not initiate any weight management treatment (e.g., medication) which is not part of the trial procedures. If such treatment is initiated, the subject should be instructed to stop the weight management treatment.

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE, then this must be reported according to Appendix 3, Section 10.3.

6.6 Dose modification

Not applicable for this trial. Please refer to Section 6.1 for description of missed dose(s) and for guidance on dose reduction in case the subject does not tolerate the randomised target dose.

6.7 Treatment after end of trial

When discontinuing trial products, either at the scheduled 'end of treatment' visit or if trial product is discontinued, the subject should be treated at the discretion of the investigator.

7 Discontinuation of trial treatment and subject discontinuation/withdrawal

Treatment of a subject may be discontinued at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Efforts must be made to have subjects attend and complete all scheduled visit procedures. Subjects must be informed about the continued scientific importance of their data, even if they discontinue trial product. Only subjects who withdraw consent will be considered as withdrawn from the trial.

7.1 Discontinuation of trial treatment

Discontinuation of trial treatment can be decided by both the investigator and the subject. The trial treatment may be discontinued at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

The subject must be discontinued from trial product, if any of the following applies for the subject:
1. Safety concern as judged by the investigator
2. Pregnancy
3. Intention of becoming pregnant
4. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical trial
5. Suspicion of pancreatitis
6. An unacceptable AE defined as any severe AE and/or serious AE (SAE) judged as probably or possibly related to trial product by the investigator

If acute pancreatitis is suspected appropriate management should be initiated, including local measurement of amylase and lipase (Appendix 3, Section 10.3.3)

Subjects meeting discontinuation of treatment criteria no. 1, 2 and 3 are allowed to resume trial product if the criteria are no longer met.

Subjects meeting discontinuation criterion no. 5 are allowed to resume trial product if the Atlanta criteria[40] are not fulfilled and thus the suspicion of acute pancreatitis is not confirmed.

The primary reason for discontinuation of trial product must be specified in the end-of-treatment-form in the eCRF, and final drug accountability must be performed. For Part 2 a treatment discontinuation session must be made in the IWRS.

Efforts must be made to have subjects in Part 1 and Part 2b, who discontinue trial product, attend and complete all scheduled visit procedures. Only subjects who withdraw consent will be considered withdrawn from the trial. Subjects must be educated about the continued scientific importance of their data, even if they discontinue trial product.

Subjects who discontinue trial product in Part 1 or Part 2b should be encouraged to continue with the scheduled visits and assessments until the time of the originally scheduled end of treatment visit (V15 for Part 1 and V18 for Part 2b) and end of trial visit (V17 for Part 1 and V19 for Part 2b) to ensure continued data collection.

If the subject does not wish to attend the scheduled clinic visits efforts should be made to have the visits converted to phone contacts. However, all efforts should be made to have the subject attend at least the 'end of treatment' visit (V15 for Part 1 and V18 for Part 2b) and the 'end of trial' visit (V17 for Part 1 and V19 for Part 2b).

The visit guidance provided in the protocol flowchart must be followed to the extent possible. However, for subjects who have discontinued treatment > 8 weeks prior to the end-of-treatment visit (V15 for Part 1 and V18 for Part 2b) and under no circumstances are willing to show up for the scheduled end-of-trial visit (V17 for Part 1 and V19 for Part 2b) according to the protocol, the site can suggest to combine the two visits.

Subjects who discontinue trial product in Part 2a and where re-initiation and re-escalation to the target dose level of once-weekly semaglutide 2.4 mg before week 28 is not possible at the investigator's discretion should attend the end-of-trial visit approximately 8 weeks after actual last dosing of semaglutide.

If the subject (Part 1 and Part 2) refuses to attend the 'end of treatment' and/or 'end of trial' visit, information about the attempts to follow up with the subject must be documented in the subject's medical record.

7.1.1 Temporary discontinuation of trial treatment

If a subject has discontinued trial product, the subject should follow the guide for missed doses (see Section 6.1) if treatment should be resumed.

If a "treatment status" session previously has been made in IWRS to indicate discontinuation of trial product, a new "treatment status" session must be made to resume trial product.

7.2 Subject discontinuation/withdrawal from the trial

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

If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessment performed according to the end-of-treatment-visit (V15 for Part 1 and V18 for Part 2). See the flowchart for data to be collected.

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

If the subject withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

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

Although a subject 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 subject's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the end of trial form in the CRF.

7.2.1 Replacement of subjects

Subjects who discontinue trial product or withdraw from trial will not be replaced.

7.3 Lost to follow-up

A subject will be considered lost to follow-up if he or 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 subject fails to return to the site for a required visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.
- Should the subject continue to be unreachable at the end-of-trial visit (V15 for Part 1 and V18 for Part 2), he/she will be considered to have withdrawn from the trial with a primary reason of 'lost to follow-up'.

8 Trial assessments and procedures

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

- Informed consent must be obtained before any trial related activity, see Section 10.1.3.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all inclusion criteria and none of the exclusion criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant site staff that can be contacted in case of emergency.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- The investigator must ensure to keep regular contact with each subject throughout the entire trial, and always have updated contact information. Even if a visit is missed and it is not possible to reschedule, every effort must be made to have all subjects followed for the primary endpoint and AEs.
- It is the responsibility of the investigator to schedule the visits and contacts as per the protocol flowchart (see Section 1.2) and to ensure they take place. See Section 6.4 for treatment compliance.
- Assessments should be conducted according to the clinic's standard of practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments. The suggested order of the assessments:
  1. ECG and vital signs
  2. Blood and urine samples
  3. Mental health assessments instruments (see Section 8.2.1)
  4. Other assessments
- Diaries will include the following in relation to the visit they support:
- Reminders:
  - to attend visit fasting (see flowchart in Section 1.2)
  - to return trial product at next site visit
  - to return diary at next site visit
  - to perform 24-hour urine collection
- Instruction on how to use the diary
- Information to be collected:
  - date of all dosing at home (see Section 6.1)
  - weekly evaluation of whether dosing instructions have been followed
  - date and time of last dose prior to PK visit
  - 24-hour urine collection
  - health issues
- Subjects must receive training in how to collect dosing information in the designated paper diary.
- Only the subject can make entries and corrections in the diaries, unless the section is specified for site staff.

- Source data of clinical assessments performed and recorded in the eCRF must be available and will usually be the subject's medical records. Additional recordings to be considered source data include, but are not limited to, laboratory reports, ECG, diary recordings, clinical outcome assessments. Ensure to transcribe into the eCRF:
- Evaluation of ECG
- Information collected in the diary
- Subject's weight history must be recorded in the subject's medical record.
- Review of diaries, ECG, laboratory reports etc. must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the diary is needed, the subject must be questioned, and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.
- 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.
- The investigator or site staff must inform subjects about symptoms of hypoglycaemia.

8.1 Efficacy assessments

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

8.1.1 Body measurements

- Body weight will be measured and recorded as specified in the flowchart (see Section 1.2). Body weight must be measured on a digital scale. The calibration standard should preferably be once yearly or reflect the country requirements. The same scale must be used throughout the trial. Measurement must be performed without shoes, on an empty bladder and only wearing light clothing and recorded in the eCRF in kilogram [kg] or pounds [lb] with the precision of 1/10 unit (e.g. 75.3 kg /166.0 lb).

- Height is measured without shoes in centimetres or inches (one decimal). BMI will be calculated by the CRF from screening data and must be in agreement with inclusion criterion no.3.

- Waist circumference will be measured and recorded as specified in the flowchart (see Section 1.2). The measurement of waist circumference should be performed using the non-stretchable measuring tape provided by Novo Nordisk and recorded in the eCRF to the nearest cm or inch. Waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest. Measurement must be performed in a standing position while the subject is breathing normally. The measuring tape should touch the skin but not compress soft tissue and twists in the tape should be avoided.

8.1.2 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 Safety assessments

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

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 trial procedures performed before exposure to trial product.

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

Only relevant and significant medical history as judged by the investigator must be recorded in the Medical history/Concomitant illness forms in the eCRF according to the flowchart (see Section 1.2). Relevant medical history includes, but is not limited to, COVID-19 and the following pre-specified disease classes:

- Breast neoplasm
- Skin cancer and skin disorder
- Gastrointestinal disorder and neoplasm
- Gallbladder disease and procedure
- Pancreatic disease
- Cardiovascular disorder
- Psychiatric disorder
- Weight disorder

If the field is left blank in the eCRF it will be interpreted as if the subject did not have a history of the pre-specified disease classes at screening.

Weight history and risk factors for pre-specified cancer types must be recorded in the Risk Factors and Weight History eCRF according to the flowchart (see Section 1.2) and includes:

- Weight history (including previous weight, debut time of overweight, previous weight loss attempts, previous use of anti-obesity prescription medication, considerations regarding bariatric surgery, and family history of overweight/obesity)

- Risk factors for breast (for female subjects only), colon and skin cancer (including family history of breast, colon and/or skin cancer and age at time of diagnosis for relevant family members, predisposing factors for breast and skin cancer, menarche/menopause, breast cancer screening, hormone replacement therapy)

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

8.2.1 Mental Health instruments

- PHQ-9[41] is a 9-item depression module of the patient health questionnaire, which is a self-administered diagnostic tool used for assessment of mental disorders. The questionnaire will be available in a linguistically validated translated version.

- C-SSRS[42] is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation. The questionnaire will be administered as an interview by the investigator or a qualified delegate. The questionnaire (C-SSRS Baseline and C-SSRS Since Last Visit) will be available in a linguistically validated translated version.
- Prior to administering the C-SSRS questionnaire, the investigator or qualified delegate must complete sufficient training.

If a subject has a PHQ-9 score of 10-14 both inclusive the subject should be referred to a mental health professional (MHP) if judged relevant by the investigator. If referral is not deemed relevant this, along with the reason why, must be documented in the subject's medical records.

A subject must be referred to a MHP if:
- the subject has a PHQ-9 score ≥15 or
- the subject has any suicidal behaviour or
- the subject has any suicidal ideation of type 4 or type 5 on any C-SSRS assessment or
- in the opinion of the investigator, it is necessary for the safety of the subject

If one or more of the referral criteria are met, the investigator should explain to the subject why the referral and psychiatric evaluation by a MHP is needed. If the subject refuses to be referred to a MHP, the subject's decision should be documented in subject's medical record and the investigator must assess if it is safe for the subject to continue in the trial or if the subject should be discontinued from trial product.

If a subject's psychiatric disorder can be adequately treated with psychotherapy and/or pharmacotherapeutic treatment, then the subject, at the discretion of the investigator (and in agreement with the MHP), may continue in the trial. Otherwise, the subject must be discontinued from trial product due to safety concern as judged by the investigator.

8.2.2 Physical examinations

- A physical examination will include assessments of the breast, head (ears, eyes, nose, throat and neck), respiratory -, cardiovascular -, gastrointestinal (including mouth) -, musculoskeletal - and central and peripheral nervous system, skin, general appearance, lymph node palpation, thyroid gland and abdomen. as specified in the Flowchart (see Section 1.2).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.3 Vital signs

- Pulse rate, respiratory rate, oxygen saturation (SaO2) as well as systolic and diastolic blood pressure will be assessed.
- Vital sign assessment should be preceded by at least 5 minutes of rest for the subject 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 will consist of 3 systolic and diastolic blood pressure measurements with intervals of at least 1-2 minutes. An additional fourth blood pressure measurement must be performed if the first two readings on systolic or diastolic blood pressure differ by >10 mmHg. Systolic blood pressure is to be recorded as the mean of the last 2 systolic blood pressure

readings, and diastolic blood pressure as the mean of the last 2 diastolic blood pressure readings in the eCRF. The eCRF will calculate the mean of the last 2 systolic blood pressure readings and the mean of the last 2 diastolic blood pressure readings.

- Pulse rate will be measured in connection to the blood pressure measurements. Record the pulse rate for the last 2 blood pressure measurements in the eCRF. The eCRF will calculate the mean of the last 2 pulse measurements.

8.2.4 Electrocardiograms

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

Part 1 only:

- At visits where PK samples are collected the ECG recordings must be performed prior to PK sample collection

- At each visit where an ECG assessment is scheduled, three consecutive ECG recordings must be performed after the subject has been placed in a supine position for a least 10 minutes. The ECGs will be stored for potential future research.

- All original ECG recordings, including electronic versions, must be kept at site for the duration of the trial.

Part 2 only:

- At visits where PK samples are collected the ECG recordings must be performed prior to PK sample collection

8.2.5 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.

8.2.5.1 Urine samples

Urinalysis

Urinalysis must be conducted in accordance with the flowchart and as defined in Appendix 2, Section 10.2.

24-hour urine collection

All subjects must receive a container for urine collection, and instructions (verbal and in writing) in how to collect the urine at home. The collection must be conducted in accordance with the flowchart. The collected urine should be stored in a cold place during the collection period. The subjects will be asked to measure and record the fluid intake (mL) in the diary.

Subjects should have an empty bladder (after morning void) when the urine collection time starts and be encouraged to urinate at the end of the collection time (must include morning void).

The urine collected during the 24-hour period will be pooled and the total volume will be determined and assessed by the central laboratory.

Start and stop date of urine collection and time (start-and end time) of the 24-hour period must be reported in the eCRF.

The urinalysis and 24-hour urine collection will be analysed for the following parameters:

Assessment	Urinalysis	24-hour urine
Calcium	X	X
Sodium	X	X
Potassium	X	X
Cortisol, free	X	X
Creatinine	X	X
Albumin	X	X
Cortisol/Creatinine	X	X
Albumin/Creatinine	X	X
Neutrophil gelactinase-associated lipocalin/Creatinine	X	
Volume		X
Creatinine Clearence		X

8.2.6 Injection site reactions

Injection site reactions will be assessed by the investigator as outlined in the flowchart. All injection site reactions will be reported as AEs. All injection site reactions related to the same injection will be reported as one AE with start and stop date covering the first appearance and last disappearance of any local symptoms or local objective signs. Additional information about the injection site reaction, i.e., local symptoms and/or local objective signs, must be provided in the eCRF injection site reaction form.

Additional assessments will be performed until resolution, as judged necessary by the investigator.

8.3 Adverse events and serious adverse events

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

- SAEs
- Following AEs irrespective of seriousness
- AEs leading to discontinuation of trial product
- AEs with additional data collection (please refer to Table 8-1)
- Pregnancies and pregnancy-related AEs
- Technical complaints

The definition of AEs and SAEs can be found in Appendix 3, Section 10.3.1 and 10.3.2, along with a description of AEs requiring additional data collection.

Some AEs require additional data collection on a specific event form. This always includes medication error, misuse and abuse of IMP. The relevant event(s) are listed below in Table 8-1.

Table 8-1 AEs requiring additional data collection (serious and non-serious AEs)

Event type	AE requiring additional data collection
Medication error	X
Misuse and abuse	X
Acute gallbladder disease	X
Hepatic event	X
Malignant neoplasm	X
Acute pancreatitis	X
Acute kidney injury	X
Injection site reactions	X

*Additional data for misuse or abuse of trial product is reported on the medication error event form.

A detailed description of the events mentioned in the above table can be found in Appendix 3, Section 10.3.3.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs must be collected from the randomisation visit and until the end of trial visit at the time points specified in the flowchart.

Medical occurrences that take place or have onset prior to the time point from which AEs are collected will be recorded as concomitant illness/medical history. AE and SAE reporting timelines can be found in Appendix 3, Section 10.3. All SAEs must be recorded and reported to Novo Nordisk or designee within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

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

8.3.2 Method of detecting AEs and SAEs

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 subject is the preferred method to inquire about events.

8.3.3 Follow-up of AEs and SAEs

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

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk or designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial product 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 trial product 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.

8.3.5 Pregnancy

Details of pregnancies in female subjects and if indicated, female partners of male subjects will be collected after first exposure to trial product.

If a female subject becomes pregnant, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 4, Section 10.4.

If a female partner of a male subject becomes pregnant and the outcome of the pregnancy is abnormal, the investigator should inform Novo Nordisk within 14 calendar days of learning of the abnormal outcome and should follow the procedures outlined in Appendix 4, Section 10.4.

8.3.6 Technical complaints

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

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

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

8.4 Treatment of overdose

Any dose of NNC0165-1875 or semaglutide ≥ 1 pen unit of planned trial product dose in trial 4708 will be considered an overdose.

Per the cut-off date there are no reports of overdose of NNC0165-1875[36].

Overdoses with semaglutide of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported AE was nausea. All subjects recovered without complications.

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

There are no specific antidotes for overdose with semaglutide or NNC0165-1875. In the event of an overdose, appropriate supportive treatment should be initiated according to the subject's clinical signs and symptoms.

In the event of an overdose, the investigator should closely monitor the subject for overdose-related AE/SAEs. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-lives of semaglutide and NNC0165-1875 of approximately 1 week.

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

For more information on overdose, consult the current Investigator's Brochures for NNC0165-1875 or semaglutide[36, 38] and any updates hereof and/or contact Novo Nordisk.

8.5 Pharmacokinetics

- Blood samples for measuring plasma concentration of NNC0165-1875 and semaglutide will be drawn for all subjects on visits specified in the flowchart (see Section 1.2) and in Appendix 2, Section 10.2.
- At visits where IMPs are administered, the PK samples must be collected pre-dose.
- The exact timing (date and time) of trial product dose must be recorded in the diary by the subject and transcribed into the eCRF.
- The purpose of measuring plasma NNC0165-1875 and semaglutide levels is to perform pharmacokinetic analyses and to assess potential drug interference with antibody analyses.
- Blood samples will be used to evaluate the pharmacokinetics and safety of co-escalation of NNC0165-1875 and semaglutide. In Part 1, NNC0165-1875 bioanalytical results (PK data) will be analysed and evaluated on an ongoing basis by an internal Novo Nordisk safety oversight group according to 'the internal Novo Nordisk safety oversight group charter'.
- Blood samples for PK assessments must be collected, handled and shipped according to the description in the laboratory manual supplied by the central laboratory. The bioanalysis of NNC0165-1875 and semaglutide plasma concentrations will be performed by special laboratories. Details of the bioanalysis will be outlined in a bioanalytical study plan issued by the special laboratories. Bioanalysis of plasma samples for NNC0165-1875 and semaglutide concentrations will be carried out using validated LC-MS/MS assays.
- Each plasma sample will be divided into 2 aliquots (e.g., one for pharmacokinetics and a backup). Plasma samples may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial. Residual sample material may be used for exploratory investigation of metabolites and bioanalysis assay development and troubleshooting in relation to the pharmacokinetic assay. Potential metabolite analysis will be reported separately from the CTR. Backup samples will be stored at the central laboratory until final Clinical Trial Report (CTR) in case Novo Nordisk requests further analysis of the PK samples.

8.6 Pharmacodynamics

Not applicable in this trial.

8.7 Genetics

Genetic samples may be collected for future analyses. Refer to Section 8.9 for further details and Appendix 8, Section 10.8 for storage.

8.8 Biomarkers

Collection of samples for biomarker research is part of this trial. The following samples are required and will be collected from all subjects in this trial:

- Biomarkers linked to hunger and satiety:
  - Soluble Leptin Receptor
  - Leptin
- Biomarkers linked to safety monitoring:
  - Prostate Specific Antigen (PSA)

The assays used for Soluble Leptin Receptor and Leptin are for research use only, these results will be reported directly to Novo Nordisk.

8.9 Biosamples for future research

Collection of biosamples for future analysis is a component of this trial. The samples will be stored in a biobank and allow for future analyses of biomarkers, both genetic and circulating biomarkers, when new knowledge or improved testing technologies may have become available during or after the trial. Participation is optional, and subjects must sign a separate informed consent to indicate their participation in the biobank components of the trial. Subjects who do not wish to participate in the biobank components may still participate in the trial. For the biobank, blood samples will be collected according to Section 10.8 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 and NNC0165-1875 as well as to understand obesity or other related conditions.

Analyses of circulating biomarkers will measure hormones, metabolites or other non-genetic serum entities with the purpose of understanding and predicting response to semaglutide and NNC0165-1875 as well as understanding obesity or other related conditions.

The samples may be analysed as part of a multi-trial assessment.

Results will not be part of the CTR. The primary objective of the analyses 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 pseudo-anonymised data. Therefore no results from analysis performed on these samples will be reported to sites or trial subjects. Moreover, no data analysis or publications will be performed on patient identifiable data.

The biobank samples will be stored up to 15 years after the trial has reported at an appropriate long term storage facility (see Appendix 8, Section 10.8).

8.10 Immunogenicity assessments

Blood samples to be analysed for antibodies against NNC0165-1875 will be drawn at pre-specified time points according to the flow chart (see Section 1.2). For details on blood sampling, serum preparation and storage, please refer to the laboratory manual.

The investigator will not be able to review the results of antibody measurements in relation to AEs as these are analysed after end of trial.

Assessment of antibodies against NNC0165-1875 will be performed by Novo Nordisk using validated assays developed by Novo Nordisk to specifically determine antibody levels against NNC0165-1875 and to further characterise the antibodies with respect to cross-reactivity and neutralising effect.

- All samples will be screened for anti-NNC0165-1875 antibodies.
- Samples confirmed positive for antibodies against NNC0165-1875 will be further characterised for cross reactivity to PYY_{3-36}.
- Samples confirmed cross-reactive to PYY_{3-36} at the End of Trial visit (V17 for Part 1 and V19 for Part 2) will be further characterised for neutralising effect against PYY_{3-36}.
- The neutralising effect of anti-NNC0165-1875 antibodies will also be evaluated by correlation to PK/PD.

A detailed description of the assay method will be included in an analytical report. Antibody assays will be validated according to international guidelines and recommendations.

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

- Anti-NNC0165-1875 binding antibodies (pos/neg and titre)
- Anti-NNC0165-1875 binding antibodies cross-reacting with PYY_{3-36} (pos/neg)
- Anti- PYY_{3-36} neutralising antibodies (pos/neg)

Residual antibody samples will be retained (please refer to Appendix 8, Section 10.8).

Severe hypersensitivity

In the event of a severe local and/or systemic hypersensitivity reaction possibly or probably related to trial product, blood sampling for assessment of the following should be conducted within 3 hours of the reaction, 1-2 weeks after the reaction, 3-4 weeks after the reaction and if possible, 3 months after the reaction. Analysis will be performed by Novo Nordisk.

- anti-NNC0165-1875 IgE antibodies
- anti-NNC0165-1875 binding antibodies (additional to scheduled time points)

In addition to above, blood sampling for assessment of tryptase (total and/or mature tryptase) should be conducted within 3 hours of the reaction and 1-2 weeks after the reaction (to be used as baseline concentration).

9 Statistical considerations

9.1 Statistical hypotheses

Part 1

There is no formal hypothesis testing for Part 1.

Part 2

For the primary endpoint percentage weight change from randomisation (week 32) to end-of-treatment (week 48), the superiority test for NNC0165-1875 1.0 mg and semaglutide s.c. 2.4 mg versus placebo 1.0 mg and semaglutide s.c. 2.4 mg will be carried out as follows. As all subjects will receive semaglutide s.c. 2.4 mg and to ease notation, semaglutide s.c. 2.4 mg is ignored in the notation. Let $\mu_{\text{NNC0165-1875 ,1.0 mg}}$ and $\mu_{\text{placebo, 1.0 mg}}$ denote the true mean of percentage weight change for dose level NNC0165-1875 1.0 mg and the placebo 1.0 mg group, respectively.

The null and alternative hypotheses tested are

$$H_0: \mu_{\text{NNC0165-1875 ,}x} \geq \mu_{placebo} \text{ vs. } H_A: \mu_{\text{NNC0165-1875 ,}x} < \mu_{placebo}$$

The null hypothesis will be rejected if the upper limit of the estimated two-sided 95% CI for the treatment difference is below 0.

9.2 Sample size determination

Part 1

Part 1 is exploratory in nature, as the primary objective is to assess safety and tolerability following multiple s.c. once-weekly doses of NNC0165-1875 and semaglutide. Therefore, the sample size is not based on a formal statistical assessment but is considered to be sufficient to evaluate the safety and tolerability based on summaries of results. Specifically, in Part 1, 24 subjects will be randomised 2:1:2:1 to receive NNC0165-1875 1.0 mg, NNC0165-1875 1.0 mg placebo, NNC0165-1875 2.0 mg or NNC0165-1875 2.0 mg placebo. All subjects will receive semaglutide.

Approximately 75 subjects will be screened to achieve 24 subjects randomly assigned to trial product.

Part 2

Taxonomy of week 48 assessments

For each subject, a given assessment at week 48 may be available or missing and the subject may be on randomised treatment or not. Table 9-1 describes the taxonomy for this. Note that this is done per assessment and per subject; subjects may be a different type for different assessments (a subject may have 'available on randomised treatment (AT)' for body weight but 'missing on randomised treatment (MT)' for waist circumference).

Table 9-1 Taxonomy for subjects based on week 48 assessments

Assessment at week 48	Subjects on randomised treatment at week 48	Type description	Type Abbreviation
Available	Yes	Available on randomised treatment: Subjects who complete the trial on randomised treatment with an assessment at week 48. This includes those that stop and restart trial product.	AT
	No	Available but discontinued Subjects who discontinue randomised treatment prematurely but return to have an assessment at week 48. These are also called retrieved subjects.	AD
Missing	Yes	Missing on randomised treatment: Subjects who complete the trial on randomised treatment without an assessment at week 48. This includes those that stop and restart trial product.	MT
	No	Missing and discontinued: Subjects who discontinue randomised treatment prematurely and do not return to have an assessment at week 48. These are also called non-retrieved subjects.	MD

Sample size assumptions

The assumptions for the sample size calculations are:

- The two-sided significance level is 5%
- 50 subjects are randomised to the NNC0165-1875 added on to semaglutide arms
- 25 subjects are randomised to the NNC0165-1875 placebo added on to semaglutide arms

Assumptions corresponding to the primary estimand:

- Non-retrieved subjects (MD) in any of the active arms are assumed to have a 11% body weight gain compared to subject completing treatment with placebo added on to semaglutide s.c. 2.4 mg
- Retrieved subjects (AD) in any of the active arms are assumed to have an effect corresponding to half the treatment difference between non-retrieved subjects and subjects who complete the trial in that arm (AT)
- The groups of non-retrieved subjects, retrieved subjects and completers are assumed to have a standard deviation for body weight change of 4.8%
- 10% of subjects are assumed to discontinue randomised treatment permanently and 60% of these are retrieved (AD) at week 48 (Based on data from trial NN9536-4153)
- Standard deviation after adjustment for treatment discontinuation and missing data is 5.9%
- The treatment differences are analysed by two-sided t-tests which is a simplification of the main analyses including explanatory variables.

Given the assumptions above, a treatment difference of NNC0165-1875 added on to semaglutide s.c. 2.4 mg compared to placebo added on to semaglutide s.c. 2.4 mg for completers of 4.5% corresponds to a treatment difference of 4.2% for targeting the treatment policy estimand. Standard deviation after adjustment for treatment discontinuation and missing data is 5.9%.

Furthermore, 50 subjects randomised to NNC0165-1875 1.0 mg added on to semaglutide arm and 25 randomised to the NNC0165-1875 placebo added on to semaglutide arms, gives a power of 81% for the test of difference between high dose of NNC0165-1875 combined with semaglutide and placebo group under the assumption of a 4.5%-point difference in weight loss for completers.

Based on NN9536-4376, it is expected that 11% subjects will drop out by week 32. To account for this, it is planned to enrol 90 subjects. Further, approximately 106 subjects will be screened to ensure 90 subjects for enrolment.

The probabilities and power calculations beneath are based on assumptions for the primary estimand. However, both the primary and secondary estimands will be covered, since the probabilities and power for the secondary estimand are higher compared to the primary estimand.

In protocol version 4.0, the additional run-in visits (V9.1 and V9.2) have been activated, this means that the subjects will be 8 weeks longer on semaglutide 2.4 mg before randomisation. However, this does not affect the power.

Table 9-2 lists the power for different choices of sample size and assumed treatment difference for completers.

Table 9-2 Power when comparing NNC0165-1875 1.0 mg added on to semaglutide s.c. 2.4 mg versus placebo added on to semaglutide s.c. 2.4 mg

N subjects randomised 2:1	Treatment difference	Power
60	4.0	63%
75	4.0	73%
90	4.0	80%
60	4.5	72%
75	4.5	81%
90	4.5	88%
60	5.0	80%
75	5.0	88%
90	5.0	93%

9.3 Populations for analyses

The following populations are defined:

Population	Description
Full analysis set	Full analysis set (FAS): All subjects randomised. Exclusion of data from analyses should be used restrictively, and normally no data should be excluded from the FAS. Subjects will be analysed according to the randomised treatment
Safety analysis set	Safety analysis set (SAS): All subjects randomly assigned to trial treatment and who take at least one dose of trial product. Subjects are analysed according to the treatment they actually received.

The subjects or observations to be excluded, and the reasons for their exclusion must be documented before unblinding. The subjects and observations excluded from analysis sets, and the reason for this, will be documented in the CTR.

Treatment periods

Three observation periods are defined for each subject in Part 2:

- In-trial: The in-trial period is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site.
- On-treatment: A time-point is considered as 'on-treatment' if any dose of trial products has been administered within the prior 8 weeks. The on-treatment period is defined as all times which are considered on-treatment. The on-treatment period will therefore be from the date of first trial product administration to date of last trial product administration excluding potential off-treatment time intervals.
- Treatment-adherent: A time-point is considered as 'treatment-adherent' if trial product has been administered within the prior 2 weeks with NNC0165-1875 and semaglutide and only before the first event of 'treatment non-adherence'. The derived date of the missed or lowered dose causing treatment non-adherence (second consecutive with NNC0165-1875 or semaglutide) will be used as the latest date for including assessments in this observation period. For subjects who initiate any other weight loss intervention before this date, the date of starting other weight management drugs or undergoing bariatric surgery will be used as latest date for using assessments in this observation period. Thus, the assessment closest in time and before the date of starting any weight loss intervention will be used as last assessment on randomised treatment. For subjects not reaching target dose according to the escalation regimen no post-baseline assessments will be included.

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

9.4 Statistical analyses

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

9.4.1 General considerations

Handling of missing baseline data

The last available and eligible observation at or before randomisation is used as the baseline value. If no assessments are available, the mean value at randomisation across all eligible subjects is used as the baseline value.

9.4.2 Primary endpoint

Definition of primary endpoint: % weight change

Change from randomisation at week 32 to week 48 in body weight (%) is defined as:

$$\%\ \text{weight change} = \frac{(\text{body weight at week 48} - \text{body weight at week 32})}{\text{body weight at week 32}} \times 100\%$$

Analyses addressing the primary estimand

The following statistical analyses and imputation methods are designed to address the primary estimand, i.e., to assess the effectiveness of NNC0165-1875 1.0 mg.

The analysis model for % weight change is an ANCOVA with randomised treatment as factor and baseline body weight (kg) as a covariate.

Primary imputation approach for the primary estimand (RS-MI)

The primary analysis of the primary estimand is a retrieved subjects-based multiple imputation approach (RS-MI) which is simplified but similar to the one described by McEvoy[43]. Missing body weight measurement at week 48 for non-retrieved subjects (MD) are imputed using assessments from retrieved subjects (AD). Missing body weight measurements at week 48 for subjects on randomised treatment (MT) are imputed using available measurements at week 48 from subjects on randomised treatment (AT).

The multiple imputation approach is done in three steps:

1. **Imputation**: An imputation model is defined using retrieved subjects (AD) from the FAS. The model will be a linear regression of body weight (kg) at week 48 with treatment as factor and baseline body weight (kg), last available treatment-adherent observation of body weight (kg) and number of days in the treatment-adherent observation period as covariates. No interactions will be included. If any subjects are MT, an imputation model for missing body weight measurements at week 48 for MT subjects will also be defined using AT subjects in a similar way. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 48 body weight values. This will be done 1000 times, resulting in 1000 complete data sets.

2. **Analysis**: Analysis of each of the 1000 complete data sets using the ANCOVA with treatment as factor and baseline body weight as covariate, resulting in 1000 estimates for each treatment comparison.

3. **Pooling**: The 1000 estimation results are integrated into a final result using Rubin's formula.

The estimated treatment difference between NNC0165-1875 1.0 mg dose as add on to semaglutide s.c. 2.4 mg and placebo group will be reported together with the associated two-sided 95% CI and corresponding two-sided p-value.

Sensitivity analyses

The sensitivity analyses investigate how assumptions on body weight development after discontinuation of randomised treatment impact the estimated treatment contrasts between active doses and placebo. This will be done using a multiple imputation approach using retrieved subjects. The details of the sensitivity analyses will be given in the SAP.

Tipping-point multiple imputation analysis (TP-MI): First, missing data are imputed according to the primary RS-MI analysis. Second, for the active treatment arm, a penalty will be added to the imputed values at week 48. The approach is to gradually increase this penalty until all conclusions from the primary analysis are reversed. For superiority hypothesis testing an NNC0165-1875 dose plus semaglutide vs. placebo the specific value of the penalty that reverses the conclusion will be used to evaluate the robustness of the assumption that subjects with missing data have the same effect as placebo.

9.4.3 Secondary endpoint

9.4.3.1 Confirmatory secondary endpoints

Not applicable for this trial.

9.4.3.2 Supportive secondary endpoints

Supportive secondary endpoints are listed in Section 3.

Efficacy endpoints

Change from randomisation at week 32 to week 48 in:

- Body weight (kg)
- Waist circumference (cm)
- $HbA1_c$ (%-point)
- Fasting Plasma Glucose (mmol/l)
- Fasting insulin (pmol/l)

These continuous supportive secondary efficacy endpoints will be analysed using the same analysis model as the primary analysis for the primary endpoint addressing the primary estimand described in Section 9.4.2. The outcome variable % weight change and the covariate baseline body weight will be replaced by the corresponding outcome and baseline assessments of the endpoint to be analysed. The estimated treatment difference between individual NNC0165-1875 1.0 mg doses as add on to semaglutide s.c. 2.4 mg and placebo group will be reported together with the associated two-sided 95% CI.

Relative change from randomisation at week 32 to week 48 in following lipids:

- Total cholesterol
- HDL cholesterol
- LDL cholesterol
- VLDL cholesterol
- Triglycerides
- Free Fatty acids

For lipids, a multiplicative model will be used, i.e., the ratio between post-randomisation measurements and baseline will be analysed as the outcome variable instead of differences, and both the outcome variable and the baseline assessment will be log-transformed prior to analysis.

These endpoints will be summarised by descriptive statistics using the FAS.

The analysis model for % weight change will be analysed using MMRM with the same factor and covariate as for the primary analysis all nested within visit. In the analysis all the data from the subjects who remain on their randomised treatment for the entire planned duration of the treatment period or until before the start of rescue intervention (anti-obesity drugs or bariatric surgery) or until first discontinuing of randomised treatment. The estimated treatment difference between individual NNC0165-1875 1.0 mg doses as add on to semaglutide s.c. 2.4 mg and placebo group will be reported together with the associated two-sided 95% CI and corresponding two-sided p-value.

Safety Endpoints

Part 1

A TEAE is defined as an event that either:

- Has onset after administration of trial product and no later than the follow-up visit
- Is present before trial product administration and increases in after the first dose of trial product and no later than the follow-up visit.
- No formal statistical inference will be carried out based on the number of TEAEs and SAEs. TEAEs and treatment-emergent SAEs will be summarised by descriptive statistics.

Part 2

Adverse events will be defined as 'treatment-emergent' (TEAE), if the onset of the event occurs in the on-treatment period, see definition in Section 9.2. No formal statistical inference will be carried out based on the number of TEAEs and SAEs. TEAEs and treatment emergent SAEs will be summarised by descriptive statistics for both 1.0 mg NNC0165-1875/placebo and 2.0 mg NNC0165-1875/placebo.

9.4.4 Exploratory endpoint

Not applicable in this trial.

9.4.5 Other safety analyses

All safety analyses will be made on the safety analysis set. The standard safety assessments (AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively.

9.4.6 Other analyses

9.4.6.1 Pharmacokinetic and/or pharmacodynamic modelling

Population PK and exposure-response analyses will be used as supportive evidence for the evaluation of efficacy and safety as well as to support the dose selection of s.c. NNC0165-1875 for future clinical development in subjects with obesity. Firstly, plasma NNC0165-1875 concentrations will be analysed using a population PK model, quantifying covariate (such as baseline body weight, age, sex, race, ethnicity) effects on NNC0165-1875 exposure. Secondly, model-based estimates of steady-state average concentrations will be derived for each subject, 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.

A modelling analysis plan will be prepared before last patient last treatment, outlining details of the analyses. The modelling will be performed by Quantitative Clinical Pharmacology at Novo Nordisk and will be reported separately from the CTR.

9.5 Database lock

Part 1:

DBL 1 of part 1 will be performed after LPLV (week 16). The data in scope are pharmacokinetic and safety lab data until week 16, which will be used for the initial safety committee decision. After DBL 1, data will be unblinded for part 1. Unblinding after DBL 1 is not of any concern for continuing part 2, as sites and subjects are dissimilar for part 1 and part 2 of the trial.

DBL 2 of part 1 will be performed after the rest of the data has been collected. The data in scope are pharmacokinetic and safety lab data (until week 24) and antibody data.

Part 2:

DBL of part 2 will be performed after LPLV. After the DBL has been completed, the data will be unblinded for part 2.

9.6 Interim analyses

Not applicable in this trial.

9.7 Data monitoring committee

Not applicable in this trial.

9.8 Reporting of the main part of the trial

Not applicable in this trial.

10 Supporting documentation and operational considerations

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

10.1.1 Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[44] and applicable ICH Good Clinical Practice (GCP) Guideline[45]
- Applicable laws and regulations
- The protocol, informed consent form, Investigator's Brochure (as applicable) and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial subjects.
- Before a site is allowed to start screening subjects, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
- Providing written summaries of the status of the trial 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 trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- Ensuring submission of the CTR 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 trial and one year after completion of the trial.

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 trial to the subject and answer all questions regarding the trial.

- The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial, if applicable.
- Subjects must be informed that their participation is voluntary.
- Subjects must be informed about their privacy rights.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[45], Declaration of Helsinki[44] and the IRB/IEC or site.
- The medical record must include a statement that written informed consent was obtained before any trial-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 trial 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.
- Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the trial.

10.1.4 Information to subjects during trial

The site will be offered a communication package for the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the subjects. The written information will be translated and adjusted to local requirements and distributed to the subject at the discretion of the investigator. The subject may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further, the subject may receive other written information during the trial.

All written information to subjects 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

- Subjects will be assigned a 6-digit unique identifier, a subject number. Any subject records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the subject are transferred to Novo Nordisk.
- The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.
- The subject must be informed about his/her privacy rights, including that his/her personal trial 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 subject.
- The subject 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.

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 trial independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

10.1.6.2 Internal Novo Nordisk safety oversight group

For Part 1, Novo Nordisk will constitute an internal Novo Nordisk safety oversight group to evaluate safety and NNC0165-1875 PK data on an ongoing basis. The internal Novo Nordisk safety oversight group will work under pre-defined conditions according to 'the internal Novo Nordisk safety oversight group charter'. If a safety concern emerges, the internal Novo Nordisk safety oversight group will inform the Novo Nordisk safety committee. The Novo Nordisk safety committee will decide on potential actions to be taken.

10.1.6.3 Data monitoring committee

Not applicable in this trial.

10.1.6.4 Event adjudication committee

Not applicable in this trial.

10.1.7 Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements, such as those of the International Committee of Medical Journal Editors (ICMJE)[46], the Food and Drug Administration Amendment Act (FDAAA)[47], European Commission Requirements[48-50] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The primary completion date (PCD) is the last assessment of the primary endpoint and is for this trial last subject first visit (LSFV) in Part 2a + 48 weeks corresponding to visit 18. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 18. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All subject data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g., laboratory and diary data). The investigator is

responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The following will be provided as paper CRFs:
- Pregnancy forms
- The following will be provided as paper CRFs to be used when access to the eCRF is revoked or the eCRF is temporarily unavailable:
- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints on trial product not yet allocated to a subject)
- Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.
- The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk A/S for data verification and validation purposes.

10.1.8.2 Monitoring

- The investigator must permit trial-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 trial. If the electronic medical record 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).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents, that the safety and rights of subjects are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- 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.
- Monitors will review the subject's medical records and other source data, e.g., the diaries to ensure consistency and/or identify omissions compared to the CRF.

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 actions taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the CRF or via listings from the trial database.

10.1.9 Source documents

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 trial staff making the entry.

- For eCRFs: All data entered in the eCRF must be verifiable in source documentation other than the CRF, except for the following data that has been recorded directly into the eCRFs and will be considered source data:
- For paper diaries the original of the completed diaries must not be removed from the site, unless they form part of the CRF and a copy is kept at the site.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data reported on the paper CRF or entered in the eCRF that are transcribed 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 subject's medical history in source documents, such as subject's medical record.
- The investigator must document any attempt to obtain external medical information by noting the dates 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 trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial 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 trial documents without involving Novo Nordisk in any way. If applicable, eCRF and other subject data will be provided in an electronic readable format to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. Site-specific CRFs and other subject 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.
- Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

10.1.11 Trial and site closure

Novo Nordisk reserves the right to close the site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or terminated, the investigator must

inform the subjects 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 trial completion. A site is considered closed when all required documents and trial 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 subjects by the investigator
- Discontinuation of further trial product development.

10.1.12 Responsibilities

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

A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-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 trial and the quality of the data produced) in the investigator trial master file. The documents, including the subject 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 subjects to a specific qualified physician who will be readily available to subjects 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 tasks.

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 trials 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 trial 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 trial 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 trial product. All information supplied by Novo Nordisk in connection with this trial 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 trial.

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

Novo Nordisk may publish on its clinical trials website a redacted CTR for this trial.

One investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon criteria defined by the International Committee of Medical Journal Editors for research publication[51].

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of trials 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 trial 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 CTR 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 trial.

At the end of the trial, 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 trial 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, the opinions of both the investigators and Novo Nordisk will be fairly and sufficiently represented in the publication.

10.1.14.2 Authorship

Novo Nordisk will work with one or more investigators and other experts who have contributed to the trial 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[51,52].

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 multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, 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 trial.

10.1.14.4 Investigator access to data and review of results

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

Individual investigators will have their own research subjects' data and will be provided with the randomisation code after results are available.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10-1 and Table 10-2 will be performed by the central laboratory, except for the following which will be performed at a specialised laboratory:
  - NNC0165-1875 plasma concentration
  - Semaglutide plasma concentration
  - NNC0165-1875 antibodies (cross reactivity and neutralising effect)
  - Leptin
  - Soluble leptin receptor
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g., to follow up on AEs, this must be done at a local laboratory.
- The central laboratory will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their lab SOPs. These data will not be transferred to the trial 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.
- Laboratory samples will be destroyed no later than at finalisation of the CTR, except biosamples for future analysis and samples for measurements of NNC0165-1875 plasma concentration, semaglutide plasma concentration and NNC0165-1875 antibodies.
- 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.
- Human biosamples for retention will be stored as described in Appendix 8, Section 10.8.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Glucose metabolism	• Fasting plasma glucose (FPG) • HbA_{1c} • Glucagon[1] • HOMA B • HOMA A insulin resistance • Fasting insulin
Lipids	• Total Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Very low-density lipoprotein (VLDL) cholesterol • Triglyceride • Free Fatty Acids (FFA)s
Notes: [1] Results obtained using assays for research use only will be reported directly to Novo Nordisk.	

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters

Haematology	• Haemoglobin
	• Leukocytes
	• Thrombocytes
	• Erythrocytes
	• Differential count (absolute):
	  • Eosinophils
	  • Neutrophils
	  • Basophils
	  • Lymphocytes
	  • Monocytes

Biochemistry[1]	• Alanine Aminotransferase (ALT)[1] • Albumin • Alkaline phosphatase • Aspartate Aminotransferase (AST)[1] • Creatinine • Potassium • Phosphate • Sodium • Total Bilirubin[1] • Total Calcium • GGT • Amylase • Lipase • HsCRP • Magnesium • Serum total protein • Blood urea nitrogen (BUN) test
Hormones	• Thyroid stimulating hormone (TSH) • Antidiuretic Hormone (ADH) • Parathyroid hormone, intact (PTH) • Cortisol • Calcitriol 1,25 Dihydroxy (Vitamin D) • Estradiol • Prolactin • Follicle-stimulating hormone (FSH) • Luteinizing hormone • Testosterone total • 25-hydroxy-vitamin D • IGF-1
Biomarkers	• Soluble Leptin Receptor[2] • Leptin[2] • Prostate Specific Antigen (PSA)
Antibodies	• Anti-NNC0165-1875 antibody (titre) • Anti-NNC0165-1875 antibody (pos/neg) • Anti-NNC0165-1875 binding antibodies cross-reacting with PYY_{3-36} (pos/neg) • Anti PYY_{3-36} Neutralising Antibodies
Coagulation Parameter	• PT and INR • Fibrinogen • APTT

Pregnancy testing Measured at all clinic visits	• Highly sensitive urine pregnancy test (as needed for women of childbearing potential)
Urinalysis	• Calcium • Sodium • Potassium • Cortisol, free • Creatinine • Albumin • Cortisol/creatinine • Albumin/creatinine • Neutrophil gelatinase-associated lipocalin/creatinine[3]
24-hour urine	• Time of collection • Calcium • Sodium • Potassium • Cortisol, free • Creatinine • Albumin • Cortisol/creatinine • Albumin/creatinine • Volume • Creatinine clearence

Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation
	• NNC0165-1875 plasma concentration
	• Semaglutide plasma concentration
	• Biosamples for future analysis
	  • serum (part1 : V2, V10) ; (part2 : V2, V8, V12, V16)
	  • plasma (Part 1 :V2, V10) ; (Part 2 :V2, V8, V12, V16)
	  • DNA (V2 for both Part 1 and Part 2)

Notes: [1] Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Section 10.3 (Hy's Law) and Section 7.1. [2] Results from biomarker assays related to hunger and satiety, for research use only, will be reported directly to Novo Nordisk. [3] Results obtained using assay for research use only will be reported directly to Novo Nordisk.	

Laboratory/analyte results that could unblind the trial (NNC0165-1875 plasma concentration, semaglutide plasma concentration and NNC0165-1875 antibodies) will not be reported to the sites. Furthermore, the assays used for glucagon, neutrophil gelatinase-associated lipocalin/creatinine, soluble leptin receptor and leptin are for research use only, hence these results will not be reported to the sites, but will be reported directly to Novo Nordisk.

10.3 Appendix 3: Adverse events: Definitions and procedures for recording, evaluation, follow-up, and reporting

10.3.1 Definition of AE

AE definition

An AE is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

An AE can therefore be any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of an IMP.

Events meeting the AE definition

- 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 meeting the AE definition

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

10.3.2 Definition of an SAE

An SAE is an AE that fulfils at least one of the following criteria:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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.

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

- Hospitalisation signifies that the subject has been detained 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, trial 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 trial inclusion, are not considered AEs or SAEs.

d. 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), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Important medical event:

- Medical or scientific judgment should be exercised 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 subject 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 adverse events must always be reported as SAEs using the important medical event criterion if no other seriousness criteria are applicable:
- Suspicion of transmission of infectious agents via the IMP
- Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL where no alternative aetiology exists (Hy's law).

10.3.3 Description of AEs requiring additional data collection

Description of AEs requiring additional data collection (on specific event form)

Adverse events requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the safety of the trial products (see Table 8-1). The selection of these events is based on the non-clinical and clinical data with NNC0165-1875 and semaglutide, knowledge from the GLP-1 RA drug class as well as regulatory requirements.

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 subject, such as:

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

Missed doses or drug pauses are not to be reported as a medication error.

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)

Medication error, misuse and abuse must always be reported as an AE (e.g., accidental overdose, intentional overdose or other) on a separate AE form, and a medication error, misuse and abuse form must be completed. In case of a medication error and/or misuse and abuse resulting in a clinical consequence (e.g., hypoglycaemia or other), this must be reported on an additional AE form.

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

Hepatic event
Hepatic event defined as:
- Disorders of the liver including cholestatic conditions and liver-related signs and symptoms
- ALT or AST > 3x UNL and total bilirubin > 2x UNL or INR >1.5*
- ALT or AST > 3x UNL with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

*Please note that in case of a hepatic event defined as ALT or AST >3x UNL and total bilirubin >2x UNL, where no alternative aetiology exists (Hy's law), this must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable.

Malignant neoplasm
Malignant neoplasm by histopathology or other substantial clinical evidence.

Acute pancreatitis
Diagnosis of pancreatitis requires two of the following three features:
1. abdominal pain consistent with pancreatitis (onset of a persistent, severe, epigastric pain often radiating to the back)
2. serum lipase activity (and/or amylase activity) at least three times greater than the UNL of normal
3. characteristic findings of pancreatitis on imaging.

Acute kidney injury
Events of abrupt or rapid decline in renal filtration rate. This condition is usually characterised by a rise in serum creatinine concentration or by azetomia (a rise in blood urea nitrogen (BUN) concentration).

Acute kidney injury defined as:
1. Increase in serum creatinine ≥ 0.3 mg/dL within 48 hours
2. Increase in serum creatinine to ≥ 1.5 times baseline within 7 days
3. Urine volume < 0.5 mL/kg/h for 6 hours
4. Other

Injection site reactions
Please refer to Section 8.2.6 for more details on injection site reactions.

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

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the CRF.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event.
- There may be instances when copies of source documents (e.g., medical records) for certain cases are requested by Novo Nordisk. In such cases, all subject identifiers, with the exception of the subject number, will 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 trial 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: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, 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.

Assessment of severity

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

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

Assessment of causality

- The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE.

- Relationship between an AE/SAE and the relevant IMP(s) 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, will 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 CRF.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved:** The subject 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 subject is expected to recover from the event. 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).
- Note: For SAEs, this term is only applicable if the subject has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae:** The subject 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 subject has not improved, and the symptoms are unchanged, or the outcome is not known.
  Note: This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject 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 subject is lost to follow-up.

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). This may include additional laboratory tests (e.g., skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject die during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology or certificate of death.

New or updated information will be recorded in the CRF.

10.3.5 Reporting of SAEs

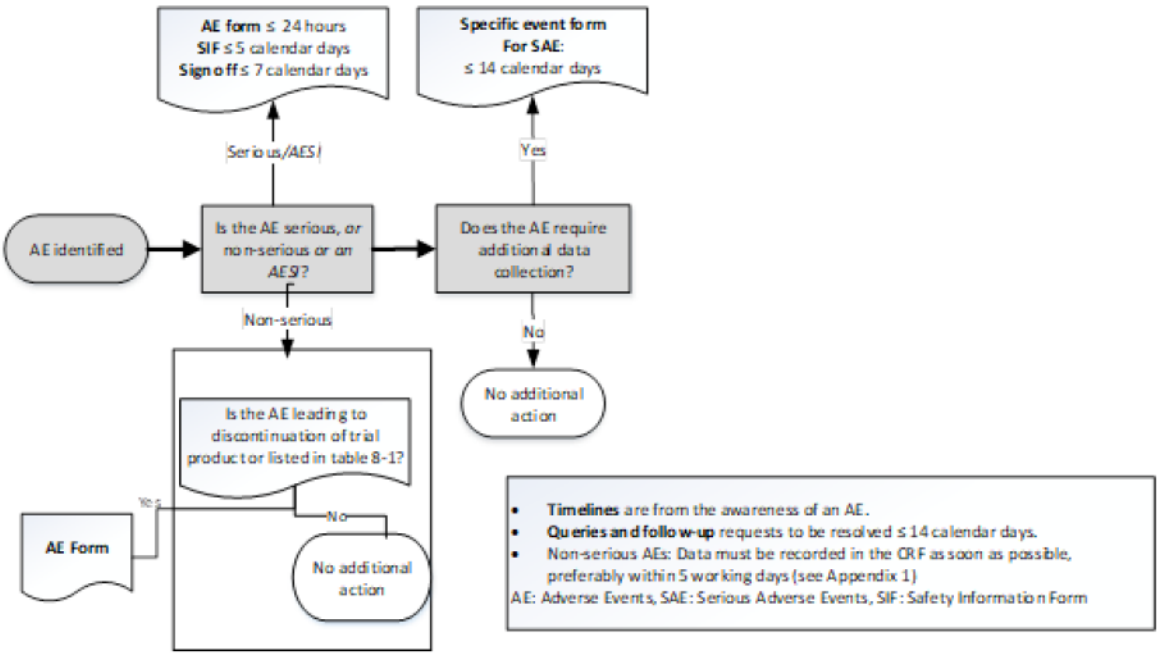
SAE reporting via electronic CRF

- Relevant forms (AE and safety information form) must be completed in the CRF.
- For reporting and sign-off timelines, see Figure 10-1 below.
- If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the CRF is unavailable for more than 5 calendar days, then the site will use the safety information form (see box below).
- The site will enter the SAE data into the CRF as soon as it becomes available.
- After the trial is completed, the trial database will be locked, and the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after CRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

AE and SAE reporting via paper CRF

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk in accordance with Section 10.1.5.
- 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 form within the designated reporting timelines (as illustrated in the figure below):
- 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.
- The specific event form for AEs requiring additional data collection within 14 calendar days

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



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

Definitions

Woman of childbearing potential (WOCBP)

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

Females in the following categories are not considered WOCBP

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

    Females with permanent infertility due to an alternate medical cause other than the above (e.g., Müllerian agenesis, androgen insensitivity).
3. Postmenopausal female:
    - A postmenopausal state is defined as amenorrhoea for 12 months without an alternative medical cause.
    - Females ≥ 50 years of age can be considered postmenopausal (irrespective of treatment with a hormonal contraception or hormone replacement therapy (HRT)) if they have both:
        - Amenorrhoea and
        - Documentation of 2 high FSH measurements in the postmenopausal range and one of these was observed ≥1 year prior to screening.
    - Females ≥ 60 years of age can be considered postmenopausal.

Females on HRT and whose menopausal status is in doubt are considered of childbearing potential and will be required to use one of the highly effective contraception methods.

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

Contraception guidance

Male subjects
The IMP category is "non-genotoxic" and there are no data to support embryo-foetal categorisation (CTFG guideline). For biologics, including protein/peptides, transfer of drug via semen to a non-treated female partner is generally considered to be insignificant[53]. Biologics containing unnatural amino acids and/or chemical linkers can be considered as proteins/peptides. Therefore, the are no measures for male subjects.

Female subjects
Female subjects of childbearing potential are eligible to participate if they agree to use highly effective contraceptive methods, preferably with low user dependency as described in the table below:

Table 10-3 Highly effective and acceptable contraceptive methods

CONTRACEPTIVES[a,g] ALLOWED DURING THE TRIAL INCLUDE:
• **Highly effective methods[b] that have low user dependency** (Failure rate of <1% per year when used consistently and correctly): • Implantable progestogen-only hormone contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomised partner[c] (The two vas deferens are tied and severed. The ends may be cauterized) • **Highly effective methods[b] that are user dependent** (Failure rate of <1% per year when used consistently and correctly): • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal • injectable • Sexual abstinence • Progestogen only hormonal contraception associated with inhibition of ovulation[d] • oral • injectable.
NOTES a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical trials. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Vasectomised partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. d) Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method. e) Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject f) Contraception should be utilised during the treatment period and for at least 60 days (corresponding to time needed to eliminate trial product) after the last dose of trial product.

Pregnancy testing

- Women/WOCBP should only be included after a negative highly sensitive urine pregnancy test (refer to Appendix 2, Section 10.2).
- Additional highly sensitive urine pregnancy testing for WOCBP only should be performed every second week / fourth week during the treatment period, and at end of trial end of relevant systemic exposure; please refer to the flow chart.
- Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.

Collection of pregnancy information

Female subjects who become pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate which will be forwarded to Novo Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding 'gestational', 'pregnancy related' or a similar term when reporting the AE/SAE.
- Pregnancy outcome should be documented in the subject's medical record. Abnormal pregnancy outcome (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the IMP by the investigator will be reported to Novo Nordisk as described in Appendix 3, Section 10.3. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the trial will discontinue IMP.

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

10.5.1 Definition of technical complaint

Technical complaint definition
• 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 trial products (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
Contact details for Customer Complaint Center, please refer to Attachment I. Technical complaints must be reported on a separate technical complaint form: 1. One technical complaint form must be completed for each affected DUN. 2. If DUN is not available, a technical complaint form for each batch, code or lot number must be completed.

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within: • 24 hours if related to an SAE • 5 calendar days for all other technical complaints If the CRF is unavailable, or when reporting a technical complaint on a trial product that is not yet allocated to subject, the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

Follow-up of technical complaints
The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

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

10.5.3 Reporting of technical complaints

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

10.6 Appendix 6: Genetics

Not applicable in this trial.

10.7 Appendix 7: Medical device adverse events, adverse device effects, serious adverse events and device deficiencies: Definition and procedures for recording, evaluating, follow-up, and reporting

10.7.1 Definition of AE and adverse device effects (ADE)

AE and ADE definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in trial subjects, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved, except for events in users or other persons which only include events related to investigational medical devices. • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2 Definition of SAE, serious adverse device effect (SADE) and unexcepted serious adverse device effect (USADE)

An SAE is an AE that:
a. Led to death
b. Led to serious deterioration in the health of the subject that either resulted in: 1. A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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. 2. A permanent impairment of a body structure or a body function. 3. Inpatient or prolonged hospitalisation planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. 4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to foetal distress, foetal death or a congenital abnormality or birth defect
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a SAE.
USADE definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment analysis report (see Section 2.3). • Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

10.7.3 Definition of device deficiency

Device deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling. Device deficiency is part of technical complaint definition, please refer to Appendix 5, Section 10.5.

10.7.4 Recording and follow-up of AE and/or SAE and device deficiencies

AE, SAE and device deficiency recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the subject's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF. • For device deficiencies, it is very important that the investigator describes any corrective actions taken to prevent recurrence of the event.
Assessment of intensity
The investigator will make an assessment of intensity for each AE/SAE reported during the trial and assign it to one of the following categories: • Mild: An event that is easily tolerated by the subject, 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. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality
• The investigator is obligated to assess the relationship between trial product and each occurrence of each AE/SAE • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial product administration, will be considered and investigated. • The investigator will also consult the Investigator's Brochure and, for marketed products, in his/her 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 for AE or SAE.
- There may be situations in which an AE/SAE has occurred, and the investigator has minimal information to include in the initial report to Novo Nordisk. However, it is very 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 send an AE/SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device deficiency

- 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/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to Novo Nordisk within 24 hours of receipt of the information.

10.7.5 Reporting of SAEs

SAE reporting to Novo Nordisk via paper CRF

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk in accordance with Section 10.1.5.
- Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting time frames:
- 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.

10.7.6 Reporting of device deficiencies

Reporting to Novo Nordisk

NOTE: There are additional reporting obligations to notify appropriate regulatory authorities and other entities about certain safety information for device deficiencies that could have led to SAEs. The investigator must therefore indicate in the technical complaint form if a technical complaint (device deficiency) could have led to an SAE. For reporting timelines, please refer to Appendix 5, Section 10.5.

10.8 Appendix 8: Retention of human biosamples

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 (e.g., whole blood, urine, saliva, synovial fluid)
- Cell-free fluids of primary human origin (e.g., serum and plasma)
- Extracts or derivatives of the above, when derived by purification (e.g., DNA, RNA, proteins, membranes, microsomes and other cellular substructures). In countries where applicable, the trial will involve collection of human biosamples for future exploratory analyses during or after the trial, to be stored in a central laboratory facility.

The material to be collected for Part 1

at baseline (V2)

- Whole blood (for genetic analysis)
- Serum and plasma (for analysis of circulating biomarkers)

at V15

- Serum and plasma (for analysis of circulating biomarkers)

The material to be collected for Part 2

at baseline (V2)

- whole blood (for genetic analysis)
- Serum and plasma (for analysis of circulating biomarkers)

at V10, V14, V14c and V18

- Serum and plasma (for analyses of circulating biomarkers)

For serum samples collected (8 mL whole blood per samples) 5 aliquots will be stored
For plasma samples collected (8 mL whole blood per samples) 5 aliquots will be stored
For DNA samples collected (8.5 mL whole blood per sample) 1 aliquot will be stored.

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

Potential further analyses of the samples will not have any consequences for subject and their relatives.

The biosamples will be stored at a central laboratory, at a central storage facility or an analysing laboratory contracted by Novo Nordisk for up to 15 years after the trial has reported. Only relevant Novo Nordisk, consultants, auditors, research organisations or laboratories working for 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 the trial has reported.

The analyses of the biosamples for future research are not intended to identify subject specific findings, but to understand and predict response to semaglutide and NNC0165-1875 or obesity and related conditions on a population level.

Analyses 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 to regulations on data protection

The subject may request the stored biosamples for future research to be destroyed by withdrawing the designated informed consent at any timepoint during or after the trial.

Antibody samples

Residual antibody samples may be retained for later analyses for further characterisation of antibody responses towards drug, if required by health authorities or for safety reasons. Residual antibody samples may also be used for assay development or validation purposes, if needed. Selected samples would be pooled, and not be traceable to any individual. Pooling would not be done if it prevented retention of sufficient sample material for possible further characterisation of antibody responses in this trial.

For samples that have already been analysed the results will not be removed from the datafile.

10.9 Appendix 9: Mitigations to ensure subject safety and data integrity during epidemics/pandemics (e.g. COVID-19)

In case local restrictions due to an epidemic/pandemic leads to lock-down of a site, the site must contact the Sponsor (Novo Nordisk) to allow for implementation of the mitigations mentioned in this Appendix 9, Section 10.9 based on mutual agreement.

- The assessments listed in Table 10-4 indicates the minimum requirements that should be performed during a lock-down, but sites should always make an effort to perform all the assessments as outlined in Section 1.2. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.
- If local regulations, requirements and/or guidelines have been issued, these must be complied with.

10.9.1 Visits

- Screening (Visit 1) and randomisation (Visit 2 in Part 1 and Visit 10 in Part 2) should always be performed as physical on-site visits. If a site is unable to perform these visits on-site, screening and randomisation of new subjects at that site should be on hold until on-site visits are possible.
- For Part 1 all visits should be performed as physical on-site visits, if in any way possible
- For Part 2 Visit 12, 14, 14c, 16, 18 and 19 should be performed as physical on-site visits, if in any way possible.
    - If clinic on-site visits are not possible, visits can be replaced by phone calls and assessments can be conducted remotely (please refer to Section 10.9.2)
- If due to travel restrictions or lock down it is not possible for the subject to come to the on-site visits at the clinic to have blood samples drawn, processes will be implemented to allow for blood sample collection off-site e.g. at the general practitioner or at the subjects home, if at all possible.
- If a site is closed or if the site staff is not allowed at site
    - site must ensure that subjects can still report AEs
    - site must ensure to limit the back-log in EDC completion for completed visits
- It is important that sites stay in close contact with the subjects to keep on motivating them

10.9.2 Assessments

- Local laboratories or diagnostic facilities can be used for haematology, biochemistry and ECG at the investigator's discretion if on-site visits are not possible or in case of temporary lockdown of the central laboratory. Only findings meeting the definition for an AE (please refer to Appendix 3, Section 10.3) should be reported in the eCRF.
- Home measurements of body weight (using the subjects own scale) and vital signs can be performed if on-site visits are not possible and if deemed feasible for the subject. Only findings meeting the definition for an AE (please refer to Appendix 3, Section 10.3) should be reported in the eCRF.
- Alternative ways of collecting body weight e.g. at lobby area or outside the clinic using a 'mobile' calibrated scales approach can be introduced
- CSSRS interview and PHQ-9 questionnaire can be completed on the phone to ensure subject safety

- Sites must ensure that pregnancy testing is performed according to protocol also for phone visits, if possible

If the assessments indicated in Table 10-4 cannot be performed as on-site visits, using remote assessments or at GP/a local laboratory or diagnostic facility, they should be performed at the first possible timepoint following the originally scheduled visit.

10.9.3 Trial product

10.9.3.1 Alternative dispensing methods

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

10.9.4 Minimum assessments for Part 2 to be performed during lockdown

Table 10-4 Minimum assessments for Part 2 to be performed during lockdown

	Protocol section	Randomi-sation	PYY dose escalation	PYY maintenance			End of Treat-ment	End of Trial
Visit		V10	V12	V14	V14c	V16	V18	V19
Timing of Visit Weeks (W)		32	36	42	44	46	48	56
Visit Window (Days)		±3	±3	±3	±3	±3	±3	0/5
Attend Visit Fasting	5.3.1	X		X	X		X	X
Randomisation Criteria and Randomisation	7.1	X						
Discontinuation Criteria	7.1	X	X	X	X	X		
Concomitant Medication	6.5	X	X	X	X	X	X	X
Highly sensitive urine pregnancy Test[b]	10.4	X	X	X	X	X	X	X
Body Measurements	8.1.1	X	X	X	X	X	X	X
Physical Examination	8.2.2	X					X	
Adverse Event	8.3,10.3	X	X	X	X	X	X	X
AE Requiring Additional Data	10.3.3							
Acute Kidney Injury	10.3.3	X	X	X	X	X	X	X
Acute Gallbladder Disease	10.3.3	X	X	X	X	X	X	X
Acute Pancreatitis	10.3.3	X	X	X	X	X	X	X
Hepatic Event	10.3.3	X	X	X	X	X	X	X
Malignant Neoplasm	10.3.3	X	X	X	X	X	X	X
Medication Error, Misuse and Abuse	10.3.3	X	X	X	X	X	X	X
Injection Site Reaction	10.3.3	X	X	X	X	X	X	X
Technical Complaint	10.5	X	X	X	X	X	X	X
Laboratory Assessments	10.2							
Biochemistry	10.2	X	X	X	X	X	X	X
Antibodies[d]	10.2	X	X	X	X	X	X	X
Biomarkers	10.2	X[fg]		X[fg]	X[fg]		X[fg]	X[fg]
Coagulation Parameter	10.2	X	X	X	X	X	X	X
Glucose Metabolism	10.2	X		X	X		X	X
Haematology	10.2	X	X	X	X	X	X	X
Hormones	10.2	X	X	X	X		X	X
Lipids	10.2	X		X	X		X	X
Urinalysis	10.2	X	X	X	X	X	X	X
24-hour urine	10.2	X					X	
PK	8.5,8.6							
Semaglutide plasma		X		X	X		X	X
NNC0165-1875 plasma			X	X	X	X	X	X

	Protocol section	Randomi-sation	PYY dose escalation	PYY maintenance			End of Treat-ment	End of Trial
Visit		V10	V12	V14	V14c	V16	V18	V19
Timing of Visit Weeks (W)		32	36	42	44	46	48	56
Visit Window (Days)		±3	±3	±3	±3	±3	±3	0/5
ECG	8.2.4	X		X	X		X	
Vital Signs	8.2.3	X	X	X	X	X	X	X
Clinical Outcome Assessments	8.2.1							
C-SSRS Since Last Visit	8.2.1	X		X	X		X	
Patient Health Questionnaire – 9 (PHQ-9)	8.2.1	X		X	X		X	
Biosamples for Future Analysis[h]	8.2.1	X		X	X		X	
IWRS Session	6	X	X	X	X			X
Treatment Compliance	6.4	X	X	X	X	X		
Drug Dispensing		X	X	X	X	X	X	
Hand Out Dose Reminder Card	8	X	X	X	X			
Hand Out and Instruct in Diary	8	X	X	X	X			
Collect, Review and Transcribe Diaries		X	X	X	X		X	
Information about Urine collection and dispensing of urine container	8.2.5.1					X		
Training in Devices	6.1.1.1	X	X	X	X	X		

[b] For female subjects of childbearing potential

[d] Antibody samples must be taken pre-dose.

[f] Prostate Specific Antigen in serum - only male subjects

[g] Leptin and Soluble Leptin Receptor

[h] Serum and plasma samples will be collected at all the marked visits

10.10 Appendix 10: Abbreviations

ADE	adverse device effect
AE	adverse event
ALT	alanine aminotransferase
ASADE	anticipated serious adverse device effect
AST	aspartate aminotransferase
BMI	Body mass index
CRF	case report form
CRO	contract research organisation
CTR	clinical trial report
DFU	directions for use
DNA	deoxyribonucleic acid
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated Glomerular Filtration Rate
FAS	full analysis set
FDAAA	FDA Amendments Act
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	glycated haemoglobin
HRT	hormone replacement therapy
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IWRS	interactive web response system
LPLV	last patient last visit
LDL	low-density lipoprotein
PCD	primary completion date
PG	plasma glucose
PHQ-9	Patient Health Questionnaire-9
PLB	Placebo
PYY	peptide YY

PSA	Prostate specific antigen
RNA	ribonucleic acid
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TMM	trial materials manual
UNL	Upper normal limit
USADE	Unanticipated serious adverse device effect
WOCBP	woman of child bearing potential

10.11 Appendix 11: Protocol amendment history

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

Protocol version 3.0 (03 November 2021), USA

Overall rationale for preparing protocol, version 3.0:

The overall rationale for the changes implemented in the amended protocol is due to an ambiguity in the text outlined in the protocol regarding use of serum or highly sensitive urine pregnancy test. Since the trial will only use highly sensitive urine pregnancy tests and the sensitivity between the two tests is considered equally good, the text regarding use of serum pregnancy test has been removed from the protocol.

In addition, physical examination of the genito-urinary system is not regarded as indicated for both female and male subjects. For male subjects in particular, the examination is considered unnecessary since it is not expected to add any clinical value beyond what is already covered by the measurements of testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prostate specific antigen (PSA), 24-hour urine collection and urinalysis. The physical examination of the genito-urinary system will therefore be removed in the current protocol update (version 3.0).

Section # and name	Description of change	Brief rationale
1 Protocol summary 1.1 Synopsis, page 10	**Part 2** The total trial duration for the individual subject will be approximately 58 weeks. Part 2 consists of **a screening period of approximately 2 weeks followed by** two **treatment** parts	Specify the screening period in Part 2 of the trial
1.2 Flowchart Part 1 & Part 2	**Highly sensitive urine** ~~P~~pregnancy test	Clarification that only highly sensitive urine pregnancy tests will be used
10.2 Appendix 2	Table 10.2 (page 76): Highly sensitive ~~serum human chorionic gonadotropin (hCG)~~ **urine** pregnancy test (as needed for women of childbearing potential)	
10.4 Appendix 4	**Pregnancy testing** • Women/WOCBP should only be included after a negative highly sensitive urine ~~or serum~~ pregnancy test • Additional ~~serum~~ **highly sensitive urine** pregnancy testing for WOCBP only should be performed every second week / fourth week during the treatment period, and at end of trial end of	
10.9 Appendix 9	Table 10-4	

Section # and name	Description of change	Brief rationale
10.9.4 Minimum assessments for Part 2 to be performed during lockdown	**Highly sensitive urine p~~P~~regnancy test**	
1.2 Flowchart	Biosamples for Future Analysis[h] **~~8.2.1~~ 10.8**	Wrong link
Section 8.2.2 Physical Examination	A physical examination will include assessments of the breast, head (ears, eyes, nose, throat and neck), respiratory -, cardiovascular -, gastrointestinal (including mouth) -, ~~genito-urinary~~ -, musculoskeletal - and central and peripheral nervous system, skin, general appearance, lymph node palpation, thyroid gland and abdomen. as specified in the Flowchart	Physical examination of the genito-urinary system is not regarded as indicated for both female and male subjects. For male subjects in particular, the examination is not expected to add any clinical value beyond what is already covered by the measurements of PSA, LH, FSH, testosterone, 24-hour urine collection and urinalysis.
Table 10-2 Protocol-required safety laboratory assessments	Biochemistry: • Alanine Aminotransferase (ALT) • Albumin • Alkaline phosphatase • Aspartate Aminotransferase (AST) • Creatinine • Potassium • Phosphate • Sodium • Total Bilirubin • Total Calcium • GGT • Amylase • Lipase • HsCRP • Magnesium • ~~Plasma~~ **Serum** total protein • Blood urea nitrogen (BUN) test	Correction from plasma to serum. Serum total protein is analysed instead of plasma total protein
Section10.8 Appendix 8 Retention of human biosamples and Section 8.9 Biosamples for future research	Appendix 8 ~~Subjects can contact the investigator if they wish to be informed about results derived from stored biosamples obtained from their own body.~~ Section 8.9 Biosamples for future research ~~Therefore, any outcome of the analyses will not be reported directly to subjects or sites. The results may be reported in publications, at scientific conferences or to authorities.~~ **Therefore no results from analysis performed on these samples will be reported to sites or trial subjects. Moreover, no data analysis or publications will be performed on patient identifiable data.**	Clarification that no results from analysis performed on biosamples will be reported to sites or trial subjects. Moreover, no data analysis or publications will be performed on patient identifiable data.

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