Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05579249
Sponsor trial ID:	NN9536-4741
Official title of study:	Effectiveness of semaglutide 2.4 mg vs. commercially available medications for chronic weight management in participants with obesity in a multi-employer setting in the US – a pragmatic clinical study
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Protocol

Protocol Title:

Effectiveness of semaglutide 2.4 mg vs. commercially available medications for chronic weight management in participants with obesity in a multi-employer setting in the US – a pragmatic clinical study

Substances: semaglutide 2.4 mg, orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide 3.0 mg

Universal Trial Number: U1111-1263-7301

Study phase: 4

Protocol amendment summary of changes table

Document History		
Document version	Date	Applicable in country(-ies) and/or site(s)
Protocol version 2.0	15 September 2022	Yes
Original protocol version 1.0	01 February 2022	Submitted for IRB review

Protocol version 2.0 (15 September 2022)

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

Overall rationale for preparing protocol, version 2.0:

Section # and name	Description of change	Brief rationale
Section 4.1 Study design Section 6.1.1 Lifestyle management Section 1.1 Synopsis	The “Center for Health Promotion” has been changed to “Nutrition Research Centre”	The Investigator of the study has moved to a new site, the previous site “Center for Health Promotion” has been replaced with “Nutrition Research Centre” throughout the document

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1 Protocol summary

1.1 Synopsis

This is an interventional, randomized, parallel-group, open-label, active comparator-controlled, two-armed, pragmatic study in a multiple employer setting in the US.

Rationale:

The purpose of this post approval pragmatic clinical study is to demonstrate the real-world comparative effectiveness of semaglutide 2.4 mg versus existing commercially available Anti-Obesity Medications, with respect to relative weight reduction, across three US-based employers. These employers represent approximately 28,000 employees of diverse demography and job functions including hospitality, clerical, administrative, housekeeping, maintenance, and specialised employees across a range of socioeconomic and educational backgrounds.

Pragmatic studies can bridge the gap between randomized clinical studies and clinical practice, providing valuable real-world effectiveness data, while maintaining some of the elements of clinical study design such as treatment randomization .[1, 2] This study will generate important evidence to inform health care decision makers such as employers, clinicians, payers, and policy makers about comprehensive approaches to obesity care management for employees. This study also complements the semaglutide development program by generating novel, 'real-world' data on semaglutide 2.4 mg compared with other anti-obesity medications, Xenical®, Qsymia®, Contrave®, and Saxenda® (Other AOMs), within a US-based, multiple employer setting.

Objectives, endpoints and estimand(s):

Primary and secondary confirmatory objectives and endpoints are:

Objectives	**Endpoints**		
Primary	Title	Time frame	Unit
To demonstrate the superiority of semaglutide 2.4 mg s.c. once weekly versus Other AOMs[1], as an adjunct to lifestyle management, with respect to achieving ≥10.0% body weight reduction from baseline, in adults with obesity.	***Primary**:*		
	Body weight reduction ≥10.0% (yes/no)	At week 52	Count of participants
Secondary Confirmatory	Title	Time frame	Unit
To demonstrate the superiority of semaglutide 2.4 mg s.c once weekly versus Other AOMs, as an adjunct to lifestyle management, with respect to the relative change in body weight from baseline, in adults with obesity	***Confirmatory***		
	Change in body weight	Week 0 to week 52	Percent
To demonstrate the superiority of semaglutide 2.4 mg s.c once weekly versus Other AOMs, as an adjunct to lifestyle management, with respect to the change in physical functioning, in adults with obesity	Change in IWQOL-Lite-CT physical function domain	Week 0 to week 52	Score

[1] Other AOMs defined as Xenical®, Qsymia®, Contrave®, and Saxenda®

The primary estimand:

The primary clinical question of interest is: What is the effectiveness of semaglutide 2.4 mg versus Other AOMs, as an adjunct to lifestyle management, in adults employed in the US living with obesity. This will be measured by the number of participants achieving ≥10% body weight loss at week 52, regardless of adherence to randomised treatment, and regardless of initiating other anti-obesity therapies.

The estimand is described by the following attributes (according to International Council for Harmonisation (ICH) E9(R1)[3]):

Attributes for the primary estimand	
Treatment	Semaglutide 2.4 mg versus Other AOMs, as an adjunct to lifestyle management.
Population	Adults employed in the US living with obesity.
Endpoint	Achieving body weight reduction ≥10.0% from baseline to week 52.
Treatment condition	The randomised treatment regardless of discontinuation or dose reduction of randomised study product, and regardless of initiating other anti-obesity therapies.
Remaining intercurrent events	None, all intercurrent events (discontinuation or dose reduction of randomised study product and initiation of other anti-obesity therapies) are captured by the treatment condition attribute and handled by the treatment policy strategy.
Population-level summary	For achieving body weight reduction ≥10.0%, the treatment effect will be quantified by the difference in proportions (calculated from odds) between treatment conditions.
Rationale for estimand	The primary estimand takes into account both safety and efficacy and reflects clinical practice in an employer setting. The primary estimand is thus relevant when evaluating treatment effect in an employer setting.

Overall design:

This is a 52-week, interventional, randomized, open-label, parallel-group, active comparator-controlled, two-armed pragmatic study in a multiple employer setting in the US. See Figure 4-1 for an overview of the study design.

The clinical investigators participating in this study are part of the coordinating healthcare system, Loma Linda University Health, Nutrition Research Center.

The investigators will manage/facilitate the identification and consenting of potential participants who are employees at employers enrolled in this study based on evaluation of participants' meeting eligibility criteria. Throughout the study period the investigators will provide obesity care and treat the participants based on their clinical judgement and routine practice and document decisions and assessment results into the eCRF.

Following the investigators decision to initiate therapy with a commercially available anti-obesity medication for chronic weight management, participants will be randomized 1:1 to receive either semaglutide 2.4 mg (Wegovy®) or one of the Other AOMs.Other than the randomization to study treatment, the investigators will follow their routine care and medical judgement to treat the participants.

To ensure treatment is as close to real world practice as possible, the commercially available anti-obesity medications currently approved for chronic weight management (Xenical®, Qsymia®, Contrave®, and Saxenda®) are allowed as randomized treatment in the Other AOMs treatment group.

Total study duration for the individual participant will be approximately one year. The study consists of the following visits:

- screening and informed consent
- randomization and treatment initiation
- intermediate visits depending on the local clinical practice
- a mid-point visit
- end of IMP treatment/end of study

If deemed appropriate by the investigator, screening and randomization can occur at the same visit. All intermediate visits can be converted to phone/virtual visits at the discretion of the investigator and preference of the patient and in accordance with local clinical practice.

The investigator will be responsible for reporting of safety information within reporting timelines, and for contacting the participant for any required follow-up.

Study intervention groups and duration:

The medications used in this study are:

- Wegovy® used in accordance with US approved prescribing information
- Other AOMs, used in accordance with approved US prescribing information

The investigators may make treatment adjustments according to their clinical judgement, and the prescribing information provided on the labels.

The participants will be randomized equally (1:1) to either Wegovy® or one of the Other AOMs. Participants randomized to Wegovy® are to remain on that treatment throughout the course of the study. For participants randomized to the Other AOMs arm, the choice of treatment, Xenical®, Qsymia®, Contrave®, or Saxenda®, is at the discretion of the investigator in dialogue with the participant and based on prescribing information.

The randomized treatments will be dispensed by a pharmacy. Novo Nordisk A/S will be providing partial payment of the randomized treatment prescription cost via a prescription card to ensure an out-of-pocket maximum for all participants regardless of treatment arm as part of the study for the duration of the study.

The duration of intervention for each participant is 52 weeks.

Number of participants:

Approximately 600 participants will be screened to achieve 500 participants randomized to semaglutide 2.4 mg or Other AOMs.

Participant characteristics:

The participants will be aged ≥18 years at inclusion who meet the following key inclusion criteria, and none of the following key exclusion criteria.

Key inclusion criteria:

- BMI ≥30.0 kg/m^2.
- Employed at randomisation by one of the selected employers and expecting to be so for the duration of the study.

Key exclusion criteria:

- Known or suspected hypersensitivity or contraindications to Wegovy® or related products according to the label.
- Known or suspected hypersensitivity or contraindications to all of the Other AOMs for chronic weight management (Xenical®, Qsymia®, Contrave®, and Saxenda®) or related products according to the labels.
- Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using highly effective contraceptive method, as defined in Appendix 3 (Section 10.3).
- History of type 1 or type 2 diabetes mellitus.
- Any disorder, unwillingness, or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.

Data monitoring committee: No

1.2 Flowchart

	Screening	Randomization	Intermediate visits	Intermediate visits	Intermediate visits	Required visit	Intermediate visits	End of treatment/End of study
Visit	V1	V2	V3	V4	V5	V6	VX.X	V7
Timing of Visit (Weeks) [a]	0	0	4	8	12	26	1-51	52
Visit Window (Days)	-29 to 0	0	±14	±14	±14	±28	±0	-1/+28
SUBJECT RELATED INFORMATION AND ASSESSMENTS								
Bariatric surgery			X	X	X	X	X	X
Employment and time missed from work		X		X		X		X
Occupational relationship	X							
Informed Consent and Demography	X							
Date of Birth	X							
Ethnicity	X							
Informed Consent Obtained Date	X							
Race[b]	X							
Sex[b]	X							
Eligibility Criteria	X	X						
Inclusion Criteria 5.1	X	X						
Exclusion Criteria 5.2	X	X						
Medical History/Concomitant Illness	X							
Medical History/Concomitant Illness	X							
Concomitant Medication	X	X				X		X
Concomitant Medication 6.8	X	X				X		X
Randomisation		X						
Subject Randomised		X						
EFFICACY								
Body Measurements 8.1.1	X	X	X	X	X	X	X	X
Body Weight	X	X	X	X	X	X	X	X
Height	X							
OTHER ASSESSMENTS								
Clinical Outcome Assessments		X				X		X
WLQ-25 8.1.2.3		X				X		X
IWQOL-lite for Clinical Trials 8.1.2.1		X				X		X
TSQM-9 8.1.2.2								X
SAFETY								
Adverse Event 8.3, 10.2		X	X	X	X	X	X	X
End of Treatment								X
End of Study								X
RTSM Session		X						
REMINDERS								
HbA1c[c]	X							
Handing out Prescription Card		X						

[a] Intermediate visits/contact will follow standard care frequency, data collected will be entered in the eCRF

[b] Self-reported by participant

[c] The value is based on available data at screening or within the last 90 days prior to the day of screening.

2 Introduction

Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA). GLP-1 is an incretin hormone with multiple physiological actions, including stimulation of insulin secretion and inhibition of glucagon secretion in a glucose-dependent manner.[4, 5] GLP-1 RAs induce feelings of satiety and fullness and reduce the feeling of hunger[6-8] via GLP-1 receptors in the brain.[9-11] The effect is reduced energy intake that results in weight loss.

Semaglutide 2.4 mg s.c. once-weekly has been approved by the Food and Drug Administration (FDA) as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one weight-related comorbidity (Wegovy®). Clinical[12-17] and non-clinical data[18] indicate that the body weight-reducing effect of semaglutide is mainly mediated by a reduced energy intake.

The phase 3a clinical development program with semaglutide 2.4 mg enrolled approximately 4,500 adults with overweight or obesity. The program consisted of four phase 3a studies (NN9536-4373, NN9536-4374, NN9536-4375 and NN9536-4376). Analysis of the pooled data from the studies indicates that the safety and tolerability of semaglutide 2.4 mg is similar to that of other approved GLP-1 RAs. No new or unexpected safety findings were identified. Across all four studies, clinically significant weight loss was observed for semaglutide 2.4 mg versus placebo. Additionally, significant improvements in glycaemic status and cardiovascular parameters were observed.

2.1 Study rationale

The prevalence of obesity has been increasing globally.[19] In the United States (US), 42% of adults have obesity, with varying prevalence among the different states.[20, 21] Obesity is associated with serious health risks.[22-25] Severe obesity further increases the risk of obesity-related complications, such as pre-diabetes and cardiovascular disease.[26, 27]

Lifestyle interventions in the form of improving diet and increasing physical activity is first-line treatment for obesity and overweight.[28] However, the majority of people with obesity and overweight struggle to achieve and maintain weight loss.[29] Medications approved for chronic weight management can be useful adjuncts to lifestyle change for patients who have been unsuccessful with diet and exercise alone.[30]

In the US, employers are the ultimate purchasers of health care for the majority (56%) of Americans.[31] The prevalence of obesity in the US is increasing,[32] and employer health care expenditures associated with obesity complications are rising.[33] In addition to increased health risks, and reduced quality of life, employees with obesity are more likely to experience increased absenteeism, premature disability, and reduced productivity. [33]

Results from the pragmatic Cleveland Clinic study, comparing the effectiveness of a single employer-based Weight Management Program (WMP) with anti-obesity medications versus WMP without anti-obesity medications on weight loss, have been recently published.[34] Among 200 participants who were members of the Cleveland Clinic Employee health plan, 62% of those randomized to WMP with anti-obesity medications lost at least 5% of their baseline body weight (mean weight loss of 7.7%) compared to 44.8% of those randomized to the WMP without anti-obesity medications (mean weight loss of 4.2%). In addition, more participants in the WMP with

anti-obesity medications group (34.3%) than in the WMP without anti-obesity medications group (16.7%) lost at least 10% of their baseline body weight.

Currently, in order for anti-obesity medications to be included in the health care offered to employees, employers must "opt-in," or deliberately decide to pay for these medications for employees, even when payers have added them to their formulary. The purpose of this post approval pragmatic clinical study is to demonstrate the real-world comparative effectiveness of semaglutide 2.4 mg versus existing commercially available anti-obesity medications, with respect to relative weight reduction, across three US-based employers. These employers represent approximately 28,000 employees of diverse demography and job functions including hospitality, clerical, administrative, housekeeping, maintenance, and specialised employees across a range of socioeconomic and educational backgrounds.

Pragmatic studies can bridge the gap between clinical studies and clinical practice, providing valuable real-world effectiveness data, while maintaining some of the elements of clinical study design, such as treatment randomization.[1, 2] This study will generate important evidence to inform health care decision makers such as employers, clinicians, payers, and policy makers about comprehensive approaches to obesity care management for employees. This study also complements the semaglutide development program by generating novel, 'real-world' data on semaglutide 2.4 mg compared with Other AOMs, within a US-based, multiple employer setting.

2.2 Background

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 (IB)[35] and any updates hereof, and in the US FDA approved prescribing information.

The study population will consist of employees with obesity (BMI ≥30.0 kg/m^2), a population that is likely to benefit from intervention with weight loss medications and has been shown to be associated with high costs in major US industries. Few eligibility criteria are included to keep the study as close to real-world as possible.

2.3 Benefit-risk assessment

A summary of the known and potential risks and benefits for semaglutide 2.4 mg (Wegovy®) and Other AOMs to which the participant can be randomized are described in the respective prescribing information. For each participant a benefit risk assessment is done according to regular clinical practice and current approved prescribing information by the investigator as part of the inclusion in the study.

Other than mandatory visits, study participation and visits will follow regular clinical practice and include participants deemed appropriate to start on weight management medication by the investigator. Participants randomized to Wegovy® are to remain on the treatment throughout the course of the study. For participants randomized to the Other AOM arm, the choice of treatment, Xenical®, Qsymia®, Contrave®, or Saxenda®, is at the discretion of the investigator in dialogue with the participant and based on prescribing information.

3 Objectives, endpoints and estimands

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	Title	Time frame	Unit
To demonstrate the superiority of semaglutide 2.4 mg s.c once weekly versus Other AOMs[1], as an adjunct to lifestyle management, with respect to achieving ≥10.0% body weight reduction from baseline, in adults with obesity.	***Primary****:*		
	Body weight reduction ≥10.0% (yes/no)	At week 52	Count of participants
Secondary Confirmatory	Title	Time frame	Unit
To demonstrate the superiority of semaglutide 2.4 mg s.c once weekly versus Other AOMs, as an adjunct to lifestyle management, with respect to the relative change in body weight from baseline, in adults with obesity	***Confirmatory***		
	Change in body weight	Week 0 to week 52	Percent
To demonstrate the superiority of semaglutide 2.4 mg s.c once weekly versus Other AOMs, as an adjunct to lifestyle management, with respect to the change in physical functioning, in adults with obesity	Change in IWQOL-Lite-CT physical function domain[2]	Week 0 to week 52	Score
Secondary Supportive	Title	Time frame	Unit
To compare the effect of semaglutide 2.4 mg s.c once weekly versus Other AOMs, as an adjunct to lifestyle management, with respect to additional body weight parameters, in adults with obesity	***Supportive***		
	Body weight reduction ≥15.0% (yes/no)	At week 52	Count of participants
	Body weight reduction ≥20.0% (yes/no)	At week 52	Count of participants
To compare the effect of semaglutide 2.4 mg s.c once weekly versus Other AOMs, as an adjunct to lifestyle management, with respect to achieving responder threshold for physical functioning, in adults with obesity	Change in IWQOL-Lite for CT physical function domain score > 14.6(yes/no)[2,3]	At week 52	Count of participants
To compare the effect of semaglutide 2.4 mg s.c once weekly versus Other AOMs, as an adjunct to lifestyle management, with respect to adherence to medication for chronic weight management and work limitations, in adults with obesity	Proportion of days covered (PDC) by study product	Week 0 to week 52	Percent
	Covered by study product ≥80% of days (yes/no)	At week 52	Count of participants
	Change in Work Limitations Questionnaire 25-item version (WLQ-25), total score[2]	Week 0 to week 52	Score
Exploratory	Title	Time frame	Unit
To compare the effect of semaglutide 2.4 mg s.c once weekly versus Other AOMs, as an adjunct to lifestyle management, with respect to absence from work, in adults with obesity	***Exploratory:***		
	Proportion of days missed from work due to participant illness or not feeling well	Week 0 to week 52	Percent

Objectives	Endpoints		
To compare the effect of semaglutide 2.4 mg s.c once weekly versus Other AOMs, as an adjunct to lifestyle management, with respect to treatment satisfaction, in adults with obesity	Treatment satisfaction assessed by Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9), Global Satisfaction, total score[2]	End of treatment at week 52	Score points

[1] Other AOMs are defined as one of the following medications approved for chronic weight management: Xenical®, Qsymia®, Contrave®, and Saxenda®.

[2]Please refer to Section 8.1 for detailed information on scales and scoring of patient reported outcomes forms

[3]Responder threshold is the threshold for meaningful within participant change. The threshold is anchor based using the Patient Global Impression of Status, PGI-S.

Primary estimand

The primary clinical question of interest is: What is the effectiveness of semaglutide 2.4 mg versus Other AOMs, as an adjunct to lifestyle management, in adults employed in the US living with obesity. This will be measured by the number of participants achieving ≥10% body weight loss at week 52, regardless of adherence to randomised treatment, and regardless of initiating other anti-obesity therapies (weight management drugs not included in the randomized treatment arm, see Table 6-1, or bariatric surgery).

The estimand is described by the following attributes (according to International Council for Harmonisation (ICH) E9(R1)[3]):

- **Population**: Adults employed in the US living with obesity
- **Endpoint**: Body weight reduction ≥10.0% (yes/no) from baseline to week 52
- **Treatment condition**: The randomised treatment regardless of discontinuation or dose reduction of randomised study product, and regardless of initiating other anti-obesity therapies (as defined above).
- **Remaining intercurrent events**: None, all intercurrent events (discontinuation or dose reduction of randomised study product and initiation of other anti-obesity therapies) are captured by the treatment condition attribute and handled by the treatment policy strategy.
- **Population-level summary**: The treatment effect will be quantified by the difference in proportions (calculated from odds) between treatment conditions.
- **Rationale for estimand**: The primary estimand takes into account both safety and efficacy and reflect clinical practice in an employer setting. The primary estimand is thus relevant when evaluating treatment effect in an employer setting.

Secondary estimand

For secondary objectives assessed by binary endpoints, the estimands are similar to the primary estimand except for the endpoint attribute. For secondary objectives assessed by continuous endpoints, the estimands are similar to the primary estimand except for the endpoint and the population level summary, which is the difference between treatment conditions for means in change from baseline to week 52.

Additional estimand

An additional clinical question of interest for the primary objective is: What is the effectiveness of semaglutide 2.4 mg, as an adjunct to usual employer-offered lifestyle management, in adults employed in the US living with obesity had they remained on their randomised treatment (possibly on reduced dose) for the entire planned duration of the study, and not initiated other anti-obesity therapies (weight management drugs not included in the randomized treatment arm, see Table 6-1, or bariatric surgery). This will be measured by the number of participants achieving ≥10% body weight loss at week 52

The estimand is described by the following attributes (according to ICH E9(R1)[3]):

- **Population**: Adults employed in the US living with obesity
- **Endpoint**: Body weight reduction ≥10.0% (yes/no) from baseline to week 52
- **Treatment condition**: randomised treatment if participants had remained on randomized treatment (regardless of dose reductions) for the entire duration of the study and not initiated any other anti-obesity therapies (as defined above).
- **Remaining intercurrent events**: None, all intercurrent events (discontinuation or initiation of other anti-obesity therapies and dose reduction) are captured by the treatment condition attribute. Discontinuation or initiation of other anti-obesity therapies are handled by the hypothetical strategy. Dose reduction of randomised study product is captured by the treatment policy strategy.
- **Population-level summary**: The treatment effect will be quantified by the difference in proportions (calculated from odds) between treatment conditions.
- **Rationale for estimand**: The additional estimand aims at reflecting the treatment effect without the confounding effects of other anti-obesity therapies or treatment discontinuation.

Similar additional estimands apply to secondary objectives assessed by binary endpoints, except for the endpoint attribute. For secondary objectives assessed by continuous endpoints, the estimands are similar except for the endpoint attribute and the population level summary, which is the difference between treatment conditions for means in change from baseline to week 52.

4 Study design

4.1 Overall design

This is a 52-week, interventional, randomized, open-label, parallel-group, active comparator-controlled, two-armed pragmatic study in a multiple employer setting in the US. See Figure 4-1 for an overview of the study design.

The conduct and operations of the study will be managed by the investigators within the coordinating healthcare system, Loma Linda University Health, Nutrition Research Center. The investigators will manage/facilitate the identification and consenting of potential participants who are employees at employers enrolled in this study based on evaluation of participants' meeting eligibility criteria defined in Section 5.1 and 5.2. Throughout the study period the investigators will provide obesity care and treat the participants based on their clinical judgement and routine practice and document decisions and assessment results into the eCRF.

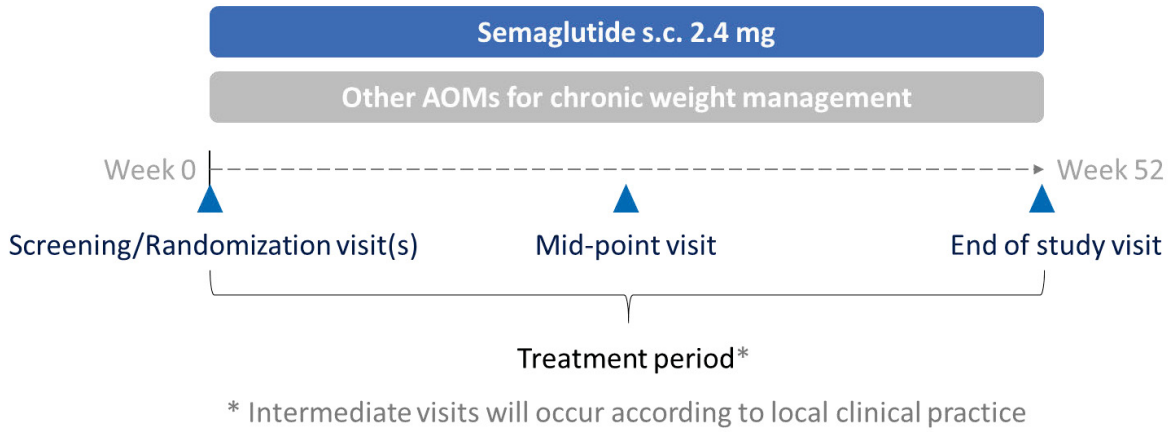
Following the investigators' decision to initiate therapy with a commercially available anti-obesity medication for chronic weight management, participants will be randomized 1:1 to receive either semaglutide 2.4 mg (Wegovy®) or Other AOMs.To ensure treatment practice is as close to real world as possible, the commercially available anti-obesity medications currently approved for chronic weight management (Xenical®, Qsymia®, Contrave®, and Saxenda®) are allowed as randomized treatment in the Other AOMs treatment group. Total study duration for the individual participant will be approximately one year. The study consists of the following visits:

- screening and informed consent
- randomization and treatment initiation
- intermediate visits depending on the local clinical practice
- a mid-point visit
- end of treatment/end of study

If deemed appropriate, screening and randomization can occur at the same visit. All intermediate visits can be converted to virtual visits at the discretion of the investigator and preference of the participant and in accordance with local clinical practice. Participants who terminate employment with participating employers during the study will be permitted to continue in the study.

The investigator will be responsible for reporting of safety information within reporting timelines, and for contacting the participant for any required follow-up.

Figure 4-1 Study design



4.2 Scientific rationale for study design

Based on the clinical development program of semaglutide 2.4 mg, and the clinical data provided in the Other AOMs labels, the study treatment duration of 52 weeks is considered sufficient to evaluate the weight loss potential of the interventions.

Randomization is included to reduce selection bias and ensure comparable patient populations in the two treatment arms (semaglutide 2.4 mg versus the Other AOMs).

The study population will consist of employees with obesity (BMI ≥30.0 kg/m^2), a population likely to benefit from intervention with weight loss medications.[36-39]

There are three mandatory visits to ensure adequate data collection: the randomization visit; a study mid-point visit; and an end of study visit.

4.2.1 Patient input into design

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

4.3 Justification for dose

All the medications included in this study are approved by the FDA as adjuncts to a reduced-calorie diet and increased physical activity for chronic weight management. The investigators will prescribe the randomized treatment, and instruct the participant on dosing, based on the US prescribing information and their clinical judgment.

4.4 End of study definition

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

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

The primary completion date (PCD) is defined as the date of visit 7 (week 52) on which the last participant in the clinical study has an assessment for the primary endpoint. If the last participant is

withdrawn early, the PCD is considered the date when the last participant would have completed visit 7.

5 Study population

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

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

5.1 Inclusion criteria

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

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Age ≥18 years at the time of signing informed consent.
3. BMI ≥30.0 kg/m^2.
4. Employed at randomization by one of the selected employers and expecting to be so for the duration of the study.

5.2 Exclusion criteria

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

1. Known or suspected hypersensitivity or contraindications to Wegovy® or related products according to the label.
2. Known or suspected hypersensitivity or contraindications to all of the Other AOMs for chronic weight management (Xenical®, Qsymia®, Contrave®, and Saxenda®) or related products according to the labels.
3. Previous randomization in this study
4. More than one rescreening for this study
5. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using highly effective contraceptive method, as defined in Appendix 3 (Section 10.3).
6. Participation (i.e., signed informed consent) in any interventional, clinical study within 30 days before screening.
7. Treatment with any medication prescribed for the indication of obesity or weight management within 90 days before screening.
8. A self-reported change in body weight >5 kg (11 lbs) within 90 days before screening irrespective of medical records.
9. History of type 1 or type 2 diabetes mellitus[a].
10. HbA_{1c} ≥6.5% (48 mmol/mol) at screening or within the last 90 days prior to the day of screening.
11. Previous or planned (during the study 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) adjustable gastric 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 liner (e.g., Endobarrier), if the sleeve has been removed >1 year before screening.

12. Any disorder, unwillingness, or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.

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

5.3 Lifestyle considerations

Lifestyle considerations will follow standard of care (see Section 6.1.1).

5.4 Screen failures

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

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

Individuals who do not meet the criteria for participation in this study may be rescreened once.

Individuals who are rescreened are required to sign a new informed consent form and provided with a new patient ID. A new screening session must be made in the RTSM.

5.5 Run-in criteria and/or randomisation criteria and/or dosing day criteria

Not applicable.

6 Study interventions and concomitant therapy

Study intervention is defined as any investigational interventions, marketed products, placebo, or medical devices intended to be administered to a study participant according to the study protocol.

Study product comprises the approved medicinal products prescribed in the study.

6.1 Investigational medicinal products (IMP)

Table 6-1 provides an overview of the study products.

Table 6-1 Study products

Study group	API (route of administration)	Brand name
Semaglutide	Semaglutide 2.4 mg (s.c.)	Wegovy®
Other AOMs	Orlistat (p.o.)	Xenical®
	Phentermine/Topiramate extended release (p.o.)	Qsymia®
	Naltrexone/Bupropion extended release (p.o.)	Contrave®
	Liraglutide 3.0 mg (s.c.)	Saxenda®

Abbreviation: API: active pharmaceutical ingredient; p.o.: per os (by mouth); s.c.: subcutaneous.

All study products should be used in accordance with clinical practice and prescribing information. The participant will be provided instructions per routine practice.

For participants randomized to the Other AOMs group, switch of treatment between the Other AOMs listed in Table 6-1 can be done at the discretion of the investigator. Participants must only be treated with one anti-obesity medication at a time, in accordance with labels. For participants randomized to the semaglutide group, switch of treatment to Other AOMs during the study must not be done.

6.1.1 Lifestyle management

All participants should be instructed in how to follow recommended lifestyle management as per standard local clinical practice and in accordance with label instructions, at the discretion of the investigator.

The standard of care for obesity diagnosis and management at Loma Linda University Nutrition Research Center follow the AACE/ACE obesity guidelines[40] and may involve laboratory testing. Blood samples may be taken as part of routine procedures.

6.2 Co-pay assistance

The randomized treatment will be handled and dispensed by a pharmacy to remain as close to real world as possible. Novo Nordisk A/S will ensure partial reimbursement by providing an out-of-pocket maximum for all randomized treatments. Co-pay assistance will only apply to the randomized treatment as defined above (i.e., not to any subsequent add-on treatment or treatment changes outside the randomized treatment definition). Prescription cards will be issued to participant to ensure co-pay assistance . Data regarding study product use registered on the card will be provided to Novo Nordisk A/S by an external vendor.

6.3 Measures to minimise bias: Randomisation and blinding

This is an open-label study. Randomization will be included to reduce selection bias and ensure comparable patient populations in the two treatment groups.

All participants will be screened and centrally randomized using an RTSM system and assigned to treatment according to the randomization schedule.

Participants randomized to Wegovy® are expected to remain on that treatment throughout the course of the study.

For participants randomized to the Other AOMs arm, the choice of treatment (Xenical®, Qsymia®, Contrave®, or Saxenda) is at the discretion of the investigator in dialogue with the participant and based on prescribing information.

The amount of co-payment required by the participant will be the same for all of the prescribing options, to remove cost bias in treatment selection.

6.4 Study intervention compliance

Participants' adherence to randomized treatment will be captured via the participant's prescription card. The investigator should support compliance to randomized treatment as for all other treatments as part of regular clinical practice.

6.5 Dose modification

See section 4.3 on dose justification.

6.6 Continued access to study intervention after end of study

At the end of the study participants can continue their randomized treatments at the discretion of the investigator but co-pay assistance will be discontinued.

6.7 Treatment of overdose

In the event of overdose, appropriate supportive treatment should be initiated according to the participants' clinical signs and symptoms and the investigator should closely monitor the participant for overdose-related AEs/SAEs.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.3 and Appendix 2 (Section 10.2) for further details.

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

For more information on overdose, also consult the current version of the prescribing information provided in the labels of all the anti-obesity medications included in the study.

6.8 Concomitant therapy

Any medication related to the treatment of diabetes (developed during the study), hypercholesterolemia, hypertension, and obesity (that are not included as randomized treatments) that the participant is receiving at the time of the first visit, or receives until end of study, must be recorded along with:

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

Collection of specific concomitant medication reflects the pragmatic approach of this study by focusing on the co-morbidities associated with obesity that directly impact cardiovascular status, as this presents the greatest risk of morbidity and mortality in the target population.[41, 42]

Initiating anti-obesity medications that are not part of the randomized treatments in the study is not permitted. If such treatment is initiated, the participant should be instructed to discontinue the additional therapy immediately, and the information on the medication must be recorded in the eCRF.

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

7 Discontinuation of study intervention and participant discontinuation/withdrawal

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

7.1 Discontinuation of study intervention

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

Efforts must be made to have the participants who discontinue study intervention attend visit V7 (end of study/end of treatment visit) to collect the required data for the analysis of the primary and confirmatory secondary estimands/endpoint. Only participants who withdraw consent will be considered as withdrawn from the study. Participants must be informed about the continued scientific importance of their data, even if they discontinue study intervention.

The study intervention must be discontinued if any of the following applies for the participant:
1. Pregnancy
2. Intention of becoming pregnant
3. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study
4. Other reasons according to prescribing information

The primary reason for discontinuation of study intervention must be specified in the CRF. A discontinuation session must be made in the RTSM system.

Participants should be reminded that use of a highly effective method of contraception is needed for two months after end of study treatment.

7.1.1 Temporary discontinuation of study intervention

If a participant has discontinued study intervention due to temporary safety concern not related to the study intervention and is allowed to resume, or if a participant discontinues study intervention on their own initiative, he/she should be encouraged to resume the study intervention.

7.2 Participant discontinuation/withdrawal from the study

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

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

If a participant withdraws consent or is withdrawn by the investigator after receipt of study intervention, the investigator must ask the participant if he/she is willing, as soon as possible, to have assessments performed according to V7. See the flowchart for data to be collected.

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

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

7.2.1 Replacement of participants

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

7.3 Lost to follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's source document.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.

8 Study assessments and procedures

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

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

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

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

At randomisation, participants will be provided with a prescription card they will use to buy the prescribed medication at the pharmacy.

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

8.1 Efficacy assessments

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

8.1.1 Body measurements

Body weight should be measured without shoes, on an empty bladder and only wearing light clothing. It should be measured on a digital scale and recorded in the eCRF in pounds (lb.) (with one decimal point) using the same scale throughout the study.

Height is measured without shoes in inches (with one decimal point).

Initial BMI will be calculated by the site from screening data and must be in agreement with inclusion criterion no. 3.

8.1.2 Patient reported outcomes and treatment satisfaction questionnaires

All questionnaires will be administered electronically directly to the participant or by the investigators. Investigators will ensure all questionnaires are completed for the mandatory assessments noted in the flowchart.

8.1.2.1 Impact of Weight on Quality of Life-Lite for Clinical Trials (IWQOL-Lite for CT)

IWQOL-Lite-CT is a 20-item patient reported outcome instrument used to assess the impact of body weight changes on patients' physical and psychosocial functioning in three composite scores (physical function, physical and psychosocial) and a total score. The possible score range for each composite score and for the total score is 0 to 100. Higher values on composite scores as well as total score of the IWQOL-Lite-CT indicate improved patient functioning.

8.1.2.2 Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The TSQM-9 (version 9) is a generic questionnaire to measure patients' satisfaction with medication using yes/no answers, and 5- or 7-point Likert scale response options. It is a self-administered patient reported outcome instrument designed for adults aged 18 years or older with a recall period of two to three weeks, or since the last medication use. Version TSQM-9 includes three domains: effectiveness (three items), convenience (three items), and global satisfaction scale (three items). It takes approximately five minutes to complete. Scores range from 0 to 100. Higher scores indicate better treatment satisfaction.

8.1.2.3 Work Limitations Questionnaire (WLQ-25)

The Work Limitations Questionnaire (WLQ-25), version 2.1, is a 25-item questionnaire that measures the degree to which health problems interfere with specific aspects of job performance and the productivity impact of these work limitations during the past 2 weeks using a 5-point Likert scale response option. It is a self-administrated questionnaire consisting of 4 domains of work limitation: Time Management (5), Physical Demands (6), Mental/Interpersonal (9), Output Demands (5). The responses are used to calculate a total WLQ index score. Lower scores indicate less work limitation.

8.2 Safety assessments

There are no safety assessments in this study.

Medical history is a medical event that the participant experienced prior to the time point from which AEs are collected. Only relevant and significant medical history, as judged by the investigator, on comorbidities related to obesity should be recorded, specifically a history of:

- Cardiovascular disorder and procedure
- Heart failure
- Dyslipidaemia
- Gallbladder disease and procedure
- Gastrointestinal disorder
- Genitourinary tract disorder
- Kidney disease
- Liver disease
- Musculoskeletal system disorder
- Psychiatric disorder
- Respiratory disorder
- Glucose metabolism disorder

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

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

8.2.1 Pregnancy testing

Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.

8.3 Adverse events and other safety reporting

The investigator is responsible for detecting, documenting, recording, and following up on the events listed below:

- Serious adverse events (SAEs)
- Adverse events (AEs) leading to discontinuation of randomized treatment
- AEs of COVID-19, irrespective of seriousness. Note: Suspected COVID-19 should be reported if the clinical presentation is suggestive of COVID-19, even in the absence of a COVID-19 test or without a positive COVID-19 test result. In the absence of clinical symptoms, a positive COVID-19 test (antigen or antibody) should be reported, if available.
- Medication errors, misuse, and abuse
- Pregnancies in female participants and pregnancy outcome [until age 1 month] and AEs in the fetus or newborn infant

The definition of AEs and SAEs can be found in Appendix 2 (Section 10.2), along with a description of AEs requiring additional data collection. Table 8-1 lists the events that require additional data collection for both serious and non-serious AEs.

Table 8-1 Events requiring additional data collection

Event type	Additional data collection
Medication error	X
Misuse and abuse	X

Definitions and reporting timelines for the events mentioned in the above table can be found in Appendix 2 (Section 10.2)

8.3.1 Time period and frequency for collecting AE information

All AEs and SAEs specified in Section 8.3 must be collected and reported. The events must be collected from the first administration of study intervention under clinical investigation to (and including) the end of study visit, in accordance with the flowchart (1.2).

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

AE and SAE reporting timelines can be found in Appendix 2 (Section 10.2). All SAEs must be recorded and reported to Novo Nordisk within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has

been discontinued from/completed the study, and the investigator considers the event to be related to the IMPs or related to study participation, the investigator must promptly notify Novo Nordisk.

8.3.2 Method of detecting AEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 2 (Section 10.2)

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

8.3.3 Follow-up of AEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs should be followed until final outcome of the event or until the participant is lost to follow-up as described in Section 7.3. Further information on follow-up and final outcome of events is given in Appendix 2 (Section 10.2).

8.3.4 Regulatory reporting requirements for SAEs

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

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR).

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

8.3.5 Pregnancy

Details of pregnancies in female participants will be collected after first exposure to IMP and until end of study visit. For details regarding collection and reporting of pregnancy information, please refer to Appendix 3 (Section 10.3).

Participants should be reminded that use of a highly effective method of contraception is needed for two months after end of study treatment.

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 4 (Section 10.4).

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

8.4 Pharmacokinetics and pharmacodynamics

Not applicable for this study.

8.5 Genetics

Not applicable for this study.

8.6 Biomarkers

Not applicable for this study.

8.7 Immunogenicity assessments

Not applicable for this study.

9 Statistical considerations

The statistical analysis plan (SAP) will be finalized prior to first participant first visit (FPFV) 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 key secondary endpoints.

9.1 Statistical hypotheses

The tests of superiority of semaglutide 2.4 mg to the group of other commercially available medication for chronic weight management (Other AOMs) for the primary and confirmatory secondary endpoints will be based only on analyses addressing the primary and secondary estimands.

For the primary estimand, the following confirmatory 1-sided hypothesis is planned to be tested for semaglutide 2.4 mg versus Other AOMs. Let the odds ratio be defined as OR = (odds[semaglutide 2.4 mg] divided by odds[Other AOMs]):

$$\underline{\text{Superiority:}}\ H0_1 : OR \leq 1 \text{ against } Ha_1 : OR > 1$$

For the two confirmatory secondary estimands, the following confirmatory 1-sided hypotheses are planned to be tested for semaglutide 2.4 mg versus Other AOMs. Let the mean difference be defined as μ = ([semaglutide 2.4 mg] minus [Other AOMs]):

$$\underline{\text{Superiority for change in body weight:}}\ H0_2 : \mu \geq 0.0 \text{ against } Ha_2 : \mu < 0.0$$

$$\underline{\text{Superiority for change in IWQOL-Lite-CT phys. func. domain:}}\ H0_2 : \mu \leq 0.0 \text{ against } Ha_2 : \mu > 0.0$$

Operationally, the hypotheses will be evaluated by 2-sided tests.

9.1.1 Multiplicity adjustment

The type I error will be controlled in the strong sense using a hierarchical (fixed sequence) testing procedure. This is based on priority ordering of the null hypotheses and testing them in this order using the 2-sided 95% confidence interval approach until an insignificant result appears. For example, the second null hypothesis will only be tested if the first null hypothesis has been rejected in favour of semaglutide 2.4 mg.

The steps in the hierarchical testing procedure are as follows:

- Step 1: ≥10% body weight reduction (yes/no) from baseline (week 0) to end of treatment (week 52) superiority of semaglutide 2.4 mg versus Other AOMs.
- Step 2: Change in body weight (%) from baseline (week 0) to end of treatment (week 52) superiority of semaglutide 2.4 mg versus Other AOMs.
- Step 3: change in IWQOL-Lite-CT physical function domain from baseline (week 0) to end of treatment (week 52) superiority of semaglutide 2.4 mg versus Other AOMs

9.2 Analysis sets

The following analysis sets and data point sets are defined:

Table 9-1 Analysis sets

Participant Analysis Set	Description
Full analysis set (FAS)	Consists of all randomized participants. Participants will be included in the analyses according to the planned intervention.
Safety analysis set (SAS)	All participants who are exposed to study intervention. Participants will be included in the analyses according to the intervention they actually received.

Table 9-2 Defined data point sets

Defined data point sets (DPS)	Description
In-study (DPS1)	The time period where the participant is assessed in the study. The in-study observation period for a participant begins on the date of randomization and ends at the first of the following dates (both inclusive): • End of study visit • Withdrawal of consent • Last contact with participant (for participants lost to follow-up) • Death
Adherent (DPS2)	The consecutive time period where the participant is adherent to treatment (possibly on a lower than intended dose) and has not initiated other anti-obesity therapies (weight management drugs not included in randomised treatment arm (see Table 6-1) or bariatric surgery). End of the adherent period is defined as: • End of study visit • Treatment discontinuation[1] • Initiation of other anti-obesity therapies[2]

[1] Treatment discontinuation is defined as when the period with no coverage of prescription claims exceeds 20%.
[2] Other anti-obesity therapies are defined as weight management drugs not included in the randomized treatment arm, see Table 6-1, or bariatric surgery.

FAS and DPS1 are used to estimate the primary estimand and the secondary estimands.

FAS and DPS2 are used to estimate the additional estimands.

SAS and DPS1 are used to present safety data.

9.3 Statistical analyses

9.3.1 General considerations

This section is a summary of the planned statistical analyses of the most important estimands including primary and confirmatory secondary estimands.

The last available observation at or before randomization is used as the baseline value. If no assessments are available, the mean value at randomization across all participants is used as the baseline value.

All tests are tests of superiority of semaglutide s.c. 2.4 mg once weekly to Other AOMs. All estimated treatment contrasts between semaglutide 2.4 mg and Other AOMs will be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

9.3.2 Primary estimand analysis

The primary estimand will be estimated by logistic regression (LR) with randomised treatment as factor and baseline body weight (kg) as covariate.

All available weight measurements (kg) at week 52 are used, and missing values at week 52 will be imputed. The imputation method for the primary analysis is a multiple imputation approach similar to the one described by McEvoy et al.[43] Imputation is done separately for each treatment group and also separately for participants being on and off treatment at week 52. The imputation model will include sex, baseline BMI-group, baseline body weight, last available observation on treatment (LAO-OT) and timing (as covariate) of last available observation on treatment. Details of the multiple imputation approach are provided in the SAP.

Sensitivity analyses

A tipping point multiple imputation analysis (TP-MI) will be performed as sensitivity analysis. First, missing weight measurements (kg) at week 52 will be imputed as described for the primary estimand. Second, for the semaglutide 2.4 mg arm, a penalty (a weight change) is added to the imputed values and then the logistic regression described for the primary estimand will be performed. The penalty will be increased until the conclusion from the primary estimand analysis is reversed. A max penalty of 30 kg will be added. This maximum is imposed since it may not be possible to reverse the conclusion for a binary endpoint and since systematic weight gains greater than 30 kg on top of the imputed values are highly unrealistic.

Supplementary analyses

The statistical model used to estimate the additional estimand is the same as the one used for the primary estimand.

All available weight measurements (kg) at week 52 for participants that are adherent (see Section 9.2) until and including the week 52 assessment will be used. Measurements for participants that are not adherent at week 52 will be predicted. Prediction of missing values will be done by modelling all available body weight (kg) data from the adherent period for all participants using a mixed model for repeated measurements (MMRM) approach. The MMRM will be fitted using the same factors and covariate as for the primary analysis all nested within visit. An unstructured covariance matrix for measurements within the same participant will be employed, assuming that measurements for different participants are independent.

9.3.3 Secondary estimands analysis

9.3.3.1 Confirmatory secondary estimands

The primary estimand will be analysed by a linear regression model (ANCOVA) with randomised treatment as factor and baseline body weight (kg) as covariate.

All available weight measurements (kg) at week 52 are used and missing values at week 52 will be imputed. The imputation method is identical to the imputation method for the primary estimand.

The analysis model for change in physical function assessed using IWQOL-Lite-CT is identical to the linear regression model for the estimation of the secondary estimand related to change in body

weight (%) except that baseline physical function score is included as covariate instead of baseline body weight. Imputation of missing values will be done using the same approach as for the primary estimand.

Sensitivity analyses

A tipping point multiple imputation analysis (TP-MI) will be performed as sensitivity analysis for each of the two endpoints. This will be done as for the sensitivity analysis for the primary estimand analysis, except that

1. The penalty for physical function will be in score points and with a maximum penalty of 100. A maximum penalty of 100 is set since this corresponds to the range of the score scale.
2. The statistical model used for analysis of change since baseline will be as described for the confirmatory secondary estimands analyses.

Supplementary analyses

The additional estimand for change in body weight (%) will be estimated using an MMRM approach. The MMRM will use the adherent data point set for all participants. The MMRM will be fitted using change in body weight (%) and the same factor and covariate as for the primary analysis all nested within visit. An unstructured covariance matrix for measurements within the same participant will be employed, assuming that measurements for different participants are independent.

Change in physical function assessed using IWQOL-Lite-CT is estimated as for change in body weight (%) except that baseline physical function score is included as covariate instead of baseline body weight.

9.3.3.2 Supportive secondary endpoints

Supportive secondary endpoints are described in Section 3, and the statistical analyses are detailed in the SAP.

9.3.4 Exploratory endpoints/estimand analysis

Exploratory endpoints are described in Section 3, and the statistical analyses are detailed in the SAP.

9.3.5 Other safety analyses

No formal safety analyses are planned.

The reported safety assessments (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and descriptively summarised by System Organ Class (SOC) and preferred term. No AE-rates will be calculated.

9.3.6 Other analyses

For other analyse(s), please refer to the SAP.

9.4 Interim analysis

There is no interim analysis planned for this study.

9.5 Sample size determination

The study is designed with an effective power of >80% to demonstrate superiority of semaglutide 2.4 mg to the group of Other AOMs with respect to all three endpoints in the test hierarchy. The calculated powers are for the primary and confirmatory secondary estimands. The effective power is calculated under the assumption of independence of hypotheses by multiplying the respective marginal powers successively which is a conservative approach. The power calculations for continuous endpoints are based on a t-test on the mean difference assuming equal variances, whereas the power calculation for the categorical endpoint is based on the Pearson chi-square test for two independent proportions.

Assumptions used for the power calculations are presented in Table 9-3. Assumptions for the power calculations are based on study NN8022-4432 (Cleveland Clinic obesity pragmatic study) and study NN9536-4373 (STEP 1). Additional important assumptions and assumptions with effect on assumed treatment effects and SDs in Table 9-3 are:

- 1:1 randomization
- 25% of the participants are expected to permanently stop study product in each treatment arm prior to the end of study.
- 50% of the participants that stop study product administration prior to week 52 are expected to have the end of study assessments performed.
- Participants that do not have end of study assessments performed are assumed to have a treatment effect corresponding to other participants in the respective treatment arm and according to treatment status (i.e., on/off allowed obesity medication in relevant treatment arm) at week 52.
- Dose reductions are assumed to have negligible impact on treatment effect in each arm, since dose reductions happening in this study are not likely to differ significantly from dose reductions happening in NN8022-4432 and NN9536-4373 wherefrom effect estimates originate.
- Based on NN8022-4432 and NN9536-4373, the number of participants undergoing bariatric surgery is expected to be low and the impact on treatment effect in each arm is expected to be negligible.

Table 9-3 Assumptions, marginal power, and effective power for each endpoint in the hierarchical testing procedure given an anticipated number of 500 randomised participants

Order	Endpoint	Assumed mean (±SD) or proportion for completers		Expected mean (±SD) or proportion (treatment policy)		Expected difference or proportion ratio (treatment policy)	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Other AOMs	Semaglutide 2.4 mg	Other AOMs			
1	Achieving body weight reduction ≥10.0	-	-	73.7%	43.7%	1.69	>99	>99
2	% body weight change	14.4 (±10)	5.04 (±10)	12.6 (±10.5)	4.41 (±10.5)	8.2%-points	>99	>99
3	IWQOL-Lite-CT Physical Function change	-	-	16.9 (±21.5)	11.3 (±21.5)	5.6	83	83

A total of approximately 500 participants will be randomized to treatment.

When considering realistic deviations from assumptions done in the sample size calculation, then the power in the test hierarchy is primarily sensitive to assumptions for IWQOL-Lite-CT Physical Function change. For IWQOL-Lite-CT Physical Function change, test power as function of sample size is plotted for the assumptions used in Table 9-3 and for two selected deviations from assumed treatment difference in Figure 9-1 and two selected deviations from assumed SD in Figure 9-2.

Figure 9-1 Marginal power curves for IWQOL-Lite-CT Physical Function change where two treatment effects differing from 5.6 are included to evaluate robustness of sample size calculations.

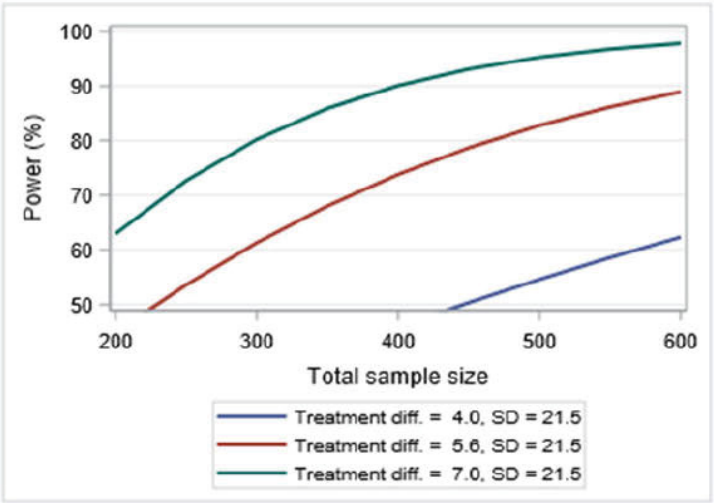
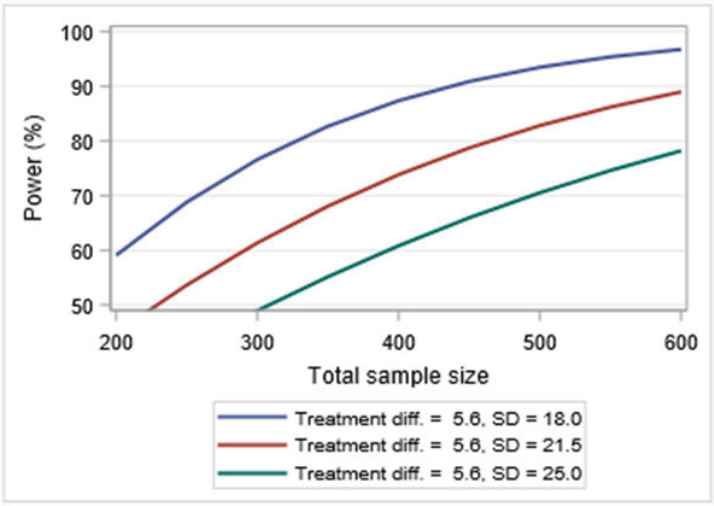


Figure 9-2 Marginal power curves for IWQOL-Lite-CT Physical Function change where two standard deviations differing from 21.5 are included to evaluate robustness of sample size calculations



10 Supporting documentation and operational considerations

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

10.1.1 Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[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 study is initiated.

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

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

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

The investigator will be responsible for:

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

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

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

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

Participants must be informed that their participation is voluntary. Participants will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH GCP[45] guidelines, Declaration of Helsinki,[44] privacy and data protection requirements, where applicable, and the IRB/IEC or site.

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

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

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

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

10.1.4 Information to participants during the study

All written information to participants must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

10.1.5 Data protection

Participants will be assigned a 6-digit unique identifier, a subject ID. Any participant records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the participant are transferred to Novo Nordisk.

The participant and any biological material obtained from the participant will be identified by subject ID, visit number and study ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of participants as required by local, regional, and national requirements.

The participant must be informed about his/her privacy rights, including that his/her personal study-related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Personal data may be collected from participants due to process requirements from Novo Nordisk's suppliers. This data is needed to ensure that the relevant data analysis for the study can be performed but will not be part of the data transferred to Novo Nordisk, the assessment of the study endpoints or the clinical study report. A list of any such data values must be kept as part of the study documentation along with an explanation of why it was required.

10.1.6 Committee's structure

10.1.6.1 Novo Nordisk safety committee

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

10.1.7 Dissemination of clinical study data

Study information will be disclosed at clinicaltrials.gov and novonordisk-trials.com and, if applicable, also on other national or regional study registries. It will be disclosed according to applicable requirements, relevant recommendations or regulations, such as the Declaration of Helsinki,[44] the International Committee of Medical Journal Editors (ICMJE),[46] the Food and Drug Administration Amendment Act (FDAAA),[47] European Commission Requirements[48-50] and in accordance with Novo Nordisk commitment to clinical transparency. If a participant requests to be included in the study via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the participant. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA, see Section 4.4 for definition of PCD.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

Novo Nordisk or designee is responsible for the data management of this study including quality checking of the data.

To demonstrate his/her oversight of the collected data, the investigator should sign the CRF on a regular basis during the conduct of the study as well as at the end of the study.

All participant data relating to the study will be recorded on CRFs unless transmitted electronically to Novo Nordisk or designee (e.g., patient reported outcome, prescription card 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
- Technical complaint forms

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

- AE forms
- Safety information forms

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

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

10.1.8.2 Monitoring

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

Study monitors will perform ongoing source data verification of critical data points to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents. Study monitors will perform ongoing source data review to ensure that the study is being conducted in accordance with the current approved protocol and any other study agreements, ICH GCP[45] and all applicable regulatory requirements, evaluating the adequacy of critical processes at site for the execution of the protocol, collection of study data, to ensure that the safety and rights of participants are being protected.

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

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

10.1.8.3 Protocol compliance

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

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken.

10.1.9 Source documents

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

For ePROs, data in the service providers database is considered source data.

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

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

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

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

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

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

10.1.10 Retention of clinical study documentation

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

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

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

10.1.11 Study and site closure

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

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

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

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

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

10.1.12 Responsibilities

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

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

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

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

otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

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

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

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

10.1.13 Indemnity statement

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

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

10.1.14 Publication policy

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

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

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

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

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

10.1.14.1 Communication of results

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

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

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

In all cases, the study results will be reported in an objective, accurate, balanced, and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk's opinions will be fairly and sufficiently represented in the publication.

10.1.14.2 Authorship

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

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[51]

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

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

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

For a multicentre clinical study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or participants, and therefore may not be supported by Novo Nordisk. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the study.

10.1.14.4 Investigator access to data and review of results

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

10.2 Appendix 2: Adverse Events and Serious Adverse Events: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.2.1 Definition of AE

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

Events to be reported as AEs:

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

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

Events NOT to be reported as AEs:

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

10.2.2 Definition of an SAE

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

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

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

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

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

10.2.3 Description of AEs requiring additional data collection

Adverse events requiring additional data collection

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

Medication error:

- A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the participant, such as:
  - administration of wrong drug
  - wrong route of administration, such as intramuscular instead of subcutaneous
  - accidental administration of a higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the study

participant were likely to happen as judged by the investigator, although they did not necessarily occur.

Misuse and abuse:

- Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g., overdose to maximize effect)
- Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g., overdose with the intention to cause harm)

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

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

10.2.4.1 AE and SAE recording

SAEs and AEs listed in Section 8.3 and AEs/SAEs in connection with pregnancies, must be recorded by the investigator in the CRF. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

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

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

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

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

10.2.4.2 Assessment of severity

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

- **Mild**: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.

- **Severe**: An event that prevents normal everyday activities.
  Note: An AE that is assessed as severe should not be confused with an SAE. Both AEs and SAEs can be assessed as severe.

10.2.4.3 Assessment of causality

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

Relationship between an AE/SAE and the relevant IMP should be assessed as:
- **Probable** - Good reason and sufficient documentation to assume a causal relationship.
- **Possible** - A causal relationship is conceivable and cannot be dismissed.
- **Unlikely** - The event is most likely related to etiology other than the IMP.

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

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

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

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

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

10.2.4.4 Final outcome

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

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

10.2.4.5 Follow-up of AE and SAE

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

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

New or updated information should be recorded in the CRF.

10.2.5 Reporting of SAEs

AE and SAE reporting via CRF

Relevant forms must be completed in the CRF.

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

- AE form within 24 hours
- Safety information form within 5 calendar days
- Both forms must be signed within 7 calendar days after first knowledge by the investigator.
- Specific event form within 14 calendar days.

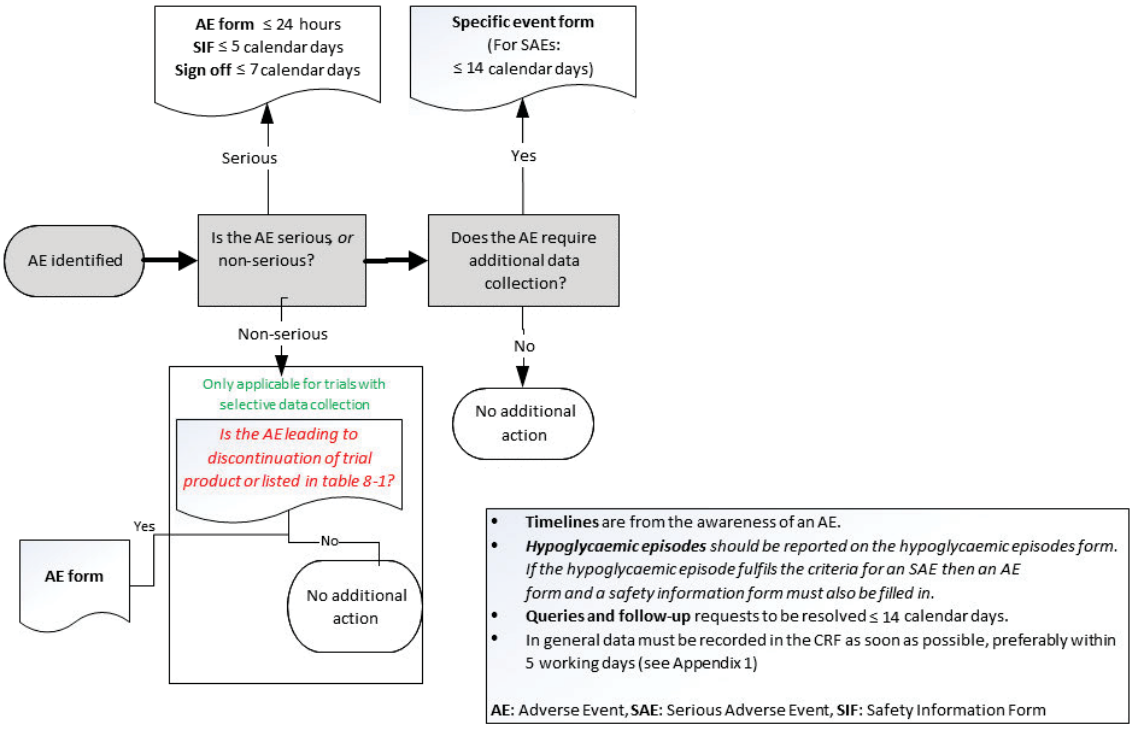
If the eCRF is unavailable for more than 24 hours, then the sites will use the paper AE form, and if the eCRF is unavailable for more than 5 calendar days, then the site will use the paper safety information form. The site should enter the SAE data in the eCRF as soon as it becomes available.

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

After the study is completed, the study database will be locked, and the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a participant or receives updated information on a previously reported

SAE after CRF decommission, the site can report this information on a paper AE and safety information form (see below) or to Novo Nordisk by telephone.

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



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

10.3 Appendix 3: Contraceptive guidance and collection of pregnancy information

10.3.1 Definitions

Woman of childbearing potential (WOCBP)

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Females in the following categories are not considered WOCBP

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

For females with permanent infertility due to an alternate medical cause other than the above (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining study enrolment.

3. Postmenopausal female:
   - A postmenopausal state is defined as amenorrhoea for at least 12 months without an alternative medical cause in a female > 45 years of age. Alternative medical causes for amenorrhoea include, but are not limited to, hormonal contraception or hormonal replacement therapy.
   - Females ≥ 60 years of age can be considered postmenopausal.

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

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

10.3.2 Contraceptive guidance

Male participants

No contraception measures are needed for male participants.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly. Table 10-1 lists the highly effective methods of contraception allowed.

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

Table 10-1 Highly effective contraceptive methods allowed[52]

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

NOTES a. Contraceptive use by men or women should comply with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. c. Male condom and female condom should not be used together (due to risk of failure from friction).

The following methods are not acceptable methods of contraception: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).

10.3.3 Collection of pregnancy information

Female participants who become pregnant

Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.

Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate which will be forwarded to Novo Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.

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

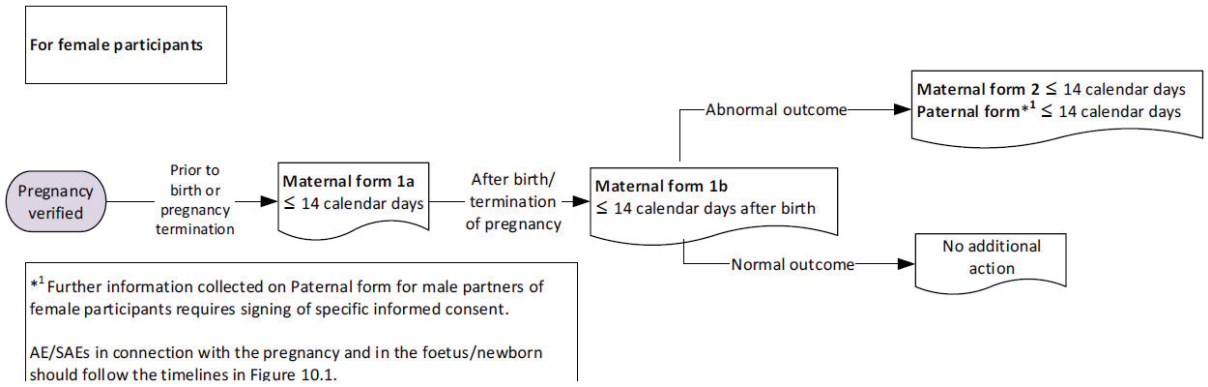
While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or

SAE. If relevant, consider adding 'gestational', 'pregnancy-related' or a similar term when reporting the AE/SAE.

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

If the investigator learns of an SAE occurring as a result of a post-study pregnancy which is considered related to the IMP by the investigator, the SAE should be reported to Novo Nordisk as described in Appendix 2(Section 10.2.)

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



Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.4 Appendix 4: Technical complaints: Definition and reporting

Technical complaints on Wegovy® and Saxenda® which occur from the first time of usage of the product until the last time of usage of the product and which is considered related to:

- - an adverse event leading to product discontinuation
- - an SAE

must be reported to Novo Nordisk via study specific technical complaint form and according to the instructions found in Appendix 4 (Section 10.4.2).

In order for Novo Nordisk to perform a complete investigation of a reported SAE which is not linked to a technical complaint, Novo Nordisk might ask the investigator to complete a technical complaint form for Wegovy® and Saxenda®.

Technical complaints on Wegovy® and Saxenda® NOT related to an adverse event, or related to an adverse event which is not systematically collected according to protocol, may be reported to Novo Nordisk affiliate via the spontaneous reporting system.

Technical complaint on non Novo Nordisk products may be reported to the manufacturing authorization holder of the given product. Still any adverse events or SAEs for the non-Novo Nordisk product must be reported according to Appendix 3 (Section 10.3.2).

10.4.1 Definition of technical complaint

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

Examples of technical complaints:

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

10.4.2 Technical complaint reporting

Recording and follow-up of technical complaints to Novo Nordisk

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

- 24 hours if related to an SAE
- 5 calendar days if related to an adverse event leading to product discontinuation

For contact details for Customer Complaint Center, please refer to instruction page for technical complaint form.

Follow-up of technical complaints

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

10.4.3 Collection, storage, and shipment of technical complaint samples

Technical complaints on Wegovy® and Saxenda® reported on the study specific technical complaint form:

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

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

Other technical complaints:

Instructions will be provided by Novo Nordisk affiliate or the relevant manufacturing authorization holder.

10.5 Appendix 5: Abbreviations

AE	adverse event
ALT	Alanine aminotransferase
AOM	anti-obesity medication
API	active pharmaceutical ingredient
AST	Aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
eCRF	electronic case report form
DPS	data point set
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPFV	first patient first visit
GCP	Good Clinical Practice
GLP-1 (RA)	glucagon-like peptide 1 (receptor agonist)
$HbA1_c$	glycated haemoglobin
IB	investigator's brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IWQOL	Impact of Weight on Quality of Life (questionnaire)
LR	logistic regression
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
Other AOMs	Xenical®, Qsymia®, Contrave®, and Saxenda®
PCD	primary completion date
PDC	proportion of days covered (by medication)
p.o.	per os (by mouth)
RTSM	Randomisation and trial supply management (system)
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	sub-cutaneous

SD	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TP-MI	tipping point, multiple imputation analysis
TSQM	Treatment Satisfaction for Medication (questionnaire)
UNL	upper normal limit
WLQ	Work Limitations Questionnaire
WMP	weight management program
WOCBP	woman of childbearing potential

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