

Cover Page for Protocol

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16.1.1 Protocol and protocol amendments

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*Redacted protocol
Includes redaction of personal identifiable information only.*

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Protocol

Trial ID: NN8022-4274

SCALE™ IBT

**Effect and safety of liraglutide 3.0 mg as an adjunct to intensive
behaviour therapy for obesity in a non-specialist setting**

Trial phase: 3b

Protocol originator



1797- TrialOps 2, Obesity.

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Appendix A Monitoring of Calcitonin

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List of abbreviations

| | |
|-------------------|--|
| AD | available drop-out |
| ADA | American Diabetes Association |
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransaminase |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| AT | available on treatment |
| BMI | body mass index |
| CCDS | Company Core Data Sheet |
| CLAE | clinical laboratory adverse event |
| CMS | Centers for Medicare & Medicaid Services |
| COA | clinical outcome assessments |
| CRF | case report form |
| C-SSRS | Columbia suicide severity rating scale |
| CTR | clinical trial report |
| DILI | drug-induced liver injury |
| DUN | dispensing unit number |
| ECG | Electrocardiogram |
| eCRF | electronic case report form |
| EMA | European Medicines Agency |
| FAS | full analysis set |
| FDA | U.S. Food and Drug Administration |
| FFA | free fatty acids |
| FSFV | first subject first visit |
| FPG | fasting plasma glucose |
| GCP | Good clinical practise |
| GLP-1 | glucagon-like peptide-1 |
| GLP-1 RA | glucagon-like peptide-1 receptor agonist |
| HbA _{1c} | glycosylated haemoglobin |
| hCG | human chorionic gonadotrophin |

| | |
|-------------------|---|
| HDL | high-density lipoprotein |
| hs-CRP | High sensitivity C-reactive protein |
| IBT | Intensive behaviour therapy |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | independent ethics committee |
| IMP | investigational medicinal product |
| INR | international normalised ratio |
| IRB | institutional review board |
| ITT | intention- to-treat |
| IWQoL-Lite for CT | Impact of Weight on Quality of Life-Lite for Clinical Trials |
| IWRS | interactive voice/web response system |
| LAO | last available observation |
| LAO-OT | last available observation (of body weight) on randomised treatment |
| LDL | low-density lipoprotein |
| LLOQ | lower limit of quantification |
| LSFV | last subject first visit |
| LSLV | last subject last visit |
| MCS | mental component summary |
| MCID | Minimal Clinically Important Difference |
| MD | missing drop-out |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| MEN2 | multiple endocrine neoplasia type 2 |
| MHP | mental health professional |
| MI | Multiple Imputation |
| MT | missing on treatment |
| MTC | medullary thyroid carcinoma |
| NIH | National Institutes of Health |
| NYHA | New York Heart Association |
| OR | odds ratio |
| PCS | physical component summary |
| PGI-C | Patients' global impression of change |

| | |
|---------|---|
| PGI-S | Patients' global impression of status |
| PHQ-9 | Patient Health Questionnaire-9 |
| PG | plasma glucose |
| PRO | patient reported outcome |
| PYE | patient years of exposure |
| PYO | patient years of observation |
| sBP | systolic blood pressure |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| s.c. | subcutaneous(ly) |
| SD | standard deviations |
| SDV | source data verification |
| SIF | safety information form |
| SF-36 | short form-36 version 2.0 acute |
| SmPC | summary of product characteristics |
| SUSAR | suspected unexpected serious adverse reaction |
| T2DM | type 2 diabetes mellitus |
| T3 | Triiodothyronine |
| T4 | Thyroxine |
| TBL | total bilirubin |
| TC | total cholesterol |
| TG | Triglycerides |
| TMM | trial materials manual |
| TSH | thyroid stimulating hormone |
| UNL | upper normal limit |
| UNR | upper normal range |
| UTN | Universal Trial Number |
| VLDL | very low density lipoprotein |
| wANCOVA | weighted analysis of covariance |
| WC | waist circumference |
| WRSS | Weight related sign and symptom measure |

1 Summary

Objectives and endpoints:

Primary objective

To confirm superiority of liraglutide 3.0 mg vs. placebo, as an adjunct to CMS-IBT*, on weight loss effectiveness in subjects with obesity

*Intensive Behaviour Therapy for obesity in a primary care setting according to Centers for Medicare & Medicaid Services (CMS) visit schedule

Primary endpoints

Primary endpoints addressing the primary objective:

- Change in body weight (%) from baseline to week 56
- Proportion of subjects losing at least 5% of baseline body weight at week 56

Secondary objectives

- To establish the effects of liraglutide 3.0 mg vs. placebo, as an adjunct to CMS-IBT, on cardiometabolic and relevant efficacy endpoints in subjects with obesity
- To establish the safety and tolerability of liraglutide 3.0 mg vs. placebo, as an adjunct to CMS-IBT, in subjects with obesity

Key secondary endpoints

- Proportion of subjects losing more than 10% of baseline body weight at week 56
- Proportion of subjects losing more than 15% of baseline body weight at week 56
- Proportion of subjects losing $\geq 4\%$ of baseline body weight at week 16

Change from baseline to week 56 in:

- Waist circumference (cm)
- Systolic blood pressure (mmHg)
- Six minutes walking distance (m)
- Impact of Weight on Quality of Life-Lite for Clinical Trial Version (IWQoL-Lite for CT), physical functioning score
- IWQoL-Lite for CT, mental/emotional functioning score

Trial design:

This is a 56-week, randomised, double-blind, placebo-controlled, two-armed multi-centre trial in subjects with obesity, who have not been diagnosed with type 1 or 2 diabetes mellitus.

A total of 282 subjects will be randomised in a 1:1 manner to receive either liraglutide 3.0 mg or placebo, as an adjunct to CMS-IBT.

Throughout the 56-week treatment period, subjects will attend site visits to monitor response to treatment and 23 brief (approximately 15-minute) CMS-IBT counselling visits.

A 30-day follow-up period is included after the 56-week treatment period in accordance with FDA guidance.

Trial population:

The planned number of subjects to be randomised on trial product is 282.

Key inclusion criteria

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. BMI ≥ 30 kg/m²
3. Male or female, age ≥ 18 years at the time of signing informed consent

Key exclusion criteria

1. HbA_{1c} $\geq 6.5\%$ (at screening visit), or diagnosis of type 1 or type 2 diabetes mellitus
2. Recent history of cardiovascular disease (myocardial infarction or stroke within the past 6 months), severe congestive heart failure (NYHA class III, IV), or second degree or greater heart block
3. Personal or family history of Medullary Thyroid Carcinoma (MTC), or Multiple Endocrine Neoplasia type 2 (MEN2)
4. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice)
5. Use in past 90 days of medications known to induce significant weight loss (e.g., prescription weight loss medications) or weight gain (e.g., chronic use of oral steroids, second generation antipsychotics)
6. History of pancreatitis (acute or chronic)
7. History of major depressive disorder within the past 2 years
8. Any lifetime history of a suicide attempt
9. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic ≥ 180 mmHg or diastolic ≥ 110 mmHg)
10. History of malignancy (except for non-melanoma skin cancer) within the past 5 years

Assessments:

Efficacy

- Body measurement (weight and waist circumference)
- Blood pressure
- Six minutes walking distance (m)
- Clinical outcome assessments (IWQoL-Lite for CT, Short Form 36 v2.0 acute)

Safety

- Adverse events
- Resting pulse
- ECG
- Biochemistry and haematology

Trial products:

The following products will be delivered by Novo Nordisk A/S Denmark:

- Liraglutide 6 mg/mL, solution for injection, 3.0 ml PDS290 pen-injector
- Liraglutide placebo, solution for injection, 3.0 ml PDS290 pen-injector

¹Counselling is the intensive behaviour therapy (CMS-IBT)

²PGI-S and PGI-C questions are different for the WRSS and 6MWT

³For women of childbearing potential: A negative pregnancy test (s-HCG) is required for inclusion

⁴Breast neoplasm follow up form is to be filled up only for female subjects

⁵A urine pregnancy test must be performed at any time during the trial if there is a suspicion of pregnancy or if a menstrual period is missed, or as required by local law

⁶Estimated Glomerular Filtration Rate (eGFR) is calculated at each visit with biochemistry. hs-CRP is only measured at Visit 2 and Visit 24.

⁷At screening a paper food diary is dispensed, which the subject should fill in for minimum 5 days before randomisation visit in order to meet the randomisation criterion. At all other visits paper diaries will be provided to the subject, if this is his/her preferred method for recording daily dietary intake

⁸Subject is not allowed to eat or drink at least eight hours overnight before attending a fasting visit (water consumption is allowed)

⁹The follow up visit should be performed 30 days after the end of treatment as a minimum

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP¹ and applicable regulatory requirements, and in accordance with the Declaration of Helsinki².

In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

3.1 Background information

Obesity is common, serious and costly. In the U.S. alone, more than one-third of adults and 17% of youth have obesity³. Obesity is a multifactorial, chronic disease that is associated with major comorbidities, including hypertension, hyperglycemia, T2DM, dyslipidemia, certain types of cancer, obstructive sleep apnea and atherosclerosis^{4,5 6 7} in combination leading to reduced life expectancy^{8,9}. Patients with obesity also suffer from physical symptoms (e.g., joint pain, urinary incontinence), functional limitations (e.g., impaired mobility), and psycho-social problems (e.g., body image disorders and depression)¹⁰⁻¹⁴. In 2010, overweight and obesity were estimated to cause 3.4 million deaths, 4% of years of life lost, and 4% of disability-adjusted life years worldwide¹⁵.

Intensive behaviour therapy for obesity has produced mean weight losses of 8-10% of initial weight across clinical trials¹⁶ and significant reductions in the risk for developing T2DM and cardiovascular disease^{17,18}. Importantly, shorter-term and perhaps more patient-centric benefits of weight loss, such as alleviation of symptoms of obesity (joint pain, urinary incontinence), functional limitations (such as decreased mobility), depression, and improved quality of life has also been observed¹⁹.

Weight losses of this magnitude can be induced by a high intensity program of lifestyle modification consisting of hypo-caloric diet, increased physical activity, and frequent behaviour therapy provided in counselling sessions in 6 months. This is the frequency of group or individual counselling recommended by a recent NIH expert panel²⁰. It is also the frequency of brief (approximately 15-minutes) individual counselling prescribed and reimbursed in primary care for patients with obesity (body mass index (BMI) ≥ 30 kg/m²) by the Centers for Medicare and Medicaid Services (CMS)²¹.

After 6 months, most subjects will equilibrate (caloric intake balancing energy expenditure) and will require adjustment of energy balance if they are to lose additional weight. Continued intervention contact after initial weight loss treatment is associated with better maintenance of lost weight, with more frequent visits associated with greater weight loss²⁰. The CMS schedule specifies monthly visits after 6 months²¹. Remarkably, the efficacy of the specific CMS model of counselling (CMS-IBT) has not been evaluated.

Adding weight loss medication to high intensity lifestyle modification typically results in a mean weight loss equal to the sum of the two separate interventions²²⁻²⁴.

Larger weight losses of 10-15% are associated with greater improvements in risk factors and other patient-relevant outcomes²⁵⁻²⁷.

For an assessment of benefits and risks of the trial, see Section [18.1](#)

3.2 Rationale for the trial

To evaluate the combined effect of CMS-IBT and liraglutide 3.0 mg, this 56-week trial will compare the CMS-recommended schedule of lifestyle counselling (CMS-IBT: 15 sessions in 6 months, 8 sessions in months 7 to 13) to CMS-IBT used in combination with liraglutide 3.0 mg in a primary care (i.e., non-specialist) setting.

It will employ the principal components of an effective high-intensity, on-site comprehensive lifestyle intervention²⁰ by:

1. prescription of a moderately reduced-calorie diet
2. a program of increased physical activity
3. the use of behavioural strategies to facilitate adherence to diet and activity recommendations, as defined by the “5A framework” (Ask, Assess, Advise, Agree, Assist)²⁸⁻³¹.

For an assessment of benefits and risks of the trial, see Section [18.1](#)

4 Objectives and endpoints

4.1 Objectives

Primary objective

To confirm superiority of liraglutide 3.0 mg vs. placebo, as an adjunct to CMS-IBT*, on weight loss effectiveness in subjects with obesity

*Intensive Behaviour Therapy for obesity in a primary care setting according to Centers for Medicare & Medicaid Services (CMS) visit schedule

Secondary objectives

- To establish the effects of liraglutide 3.0 mg vs. placebo, as an adjunct to CMS-IBT, on cardiometabolic and relevant efficacy endpoints in subjects with obesity
- To establish the degree of adherence to randomised trial product, caloric diet and physical activity, and to explore the effect thereof on weight loss in subjects with obesity
- To establish the safety and tolerability of liraglutide 3.0 mg vs. placebo, as an adjunct to CMS-IBT, in subjects with obesity

4.2 Endpoints

4.2.1 Primary endpoints

- Change in body weight (%) from baseline to week 56
- Proportion of subjects losing at least 5% of baseline body weight at week 56

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoints

Confirmatory secondary endpoints addressing the first and second of secondary objectives:

- Proportion of subjects losing more than 10% of baseline body weight at week 56
- Proportion of subjects losing more than 15% of baseline body weight at week 56
- Proportion of subjects losing $\geq 4\%$ of baseline body weight at week 16

Change from baseline to week 56 in:

- Waist circumference (cm)
- Systolic blood pressure (mmHg)
- Six minutes walking distance (m)
- Impact of Weight on Quality of Life-Lite for Clinical Trial Version (IWQoL-Lite for CT), physical functioning score
- IWQoL-Lite for CT, mental/emotional functioning score

Only primary and confirmatory secondary endpoints have been selected for disclosure (e.g. clinicaltrials.gov and EudraCT).

4.2.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

Change from baseline to week 56 in:

- HbA_{1c} (%)
- Fasting plasma glucose (mg/dL)
- Diastolic blood pressure (mmHg)
- Lipids (total cholesterol [TC], low density lipoprotein cholesterol [LDL cholesterol], high density lipoprotein cholesterol [HDL cholesterol], very low density lipoprotein cholesterol [VLDL cholesterol], triglycerides [TG], free fatty acids [FFA])
- Short Form-36 v2.0 acute (SF-36) (physical component summary (PCS), mental component summary (MCS) and subdomains)
- Weight related sign and symptom (WRSS) measure, total score

Proportion of subjects with the following at week 56:

- ≥ 2 T-score points increase from baseline in SF-36 PCS
- ≥ 3 T-score points increase from baseline in SF-36 MCS

Number of weeks (completed calendar weeks) from randomisation to week 56 adherent to:

- Trial product
- Caloric diet
- Physical activity
- Caloric diet and physical activity
- Trial product, caloric diet and physical activity

Supportive secondary safety endpoints

- Adverse events from randomisation until and including the follow-up visit (see Section [17.4.3.2](#))

Change from baseline to week 56 in:

- Physical examination
- Resting pulse
- ECG
- Laboratory measurements

5 Trial design

5.1 Type of trial

This is a 56-week, randomised, double-blind, placebo-controlled, two-armed multi-centre trial in subjects with obesity, who have not been diagnosed with type 1 or type 2 diabetes mellitus.

A total of 282 subjects will be randomised in a 1:1 manner to receive either liraglutide 3.0 mg or placebo, as an adjunct to CMS-IBT.

Throughout the 56-week treatment period, subjects will attend site visits to monitor response to treatment and 23 brief (approximately 15-minute) behavioural counselling visits (see Section 2).

A 30-day follow-up period is included after the 56-week treatment period in accordance with FDA guidance³².

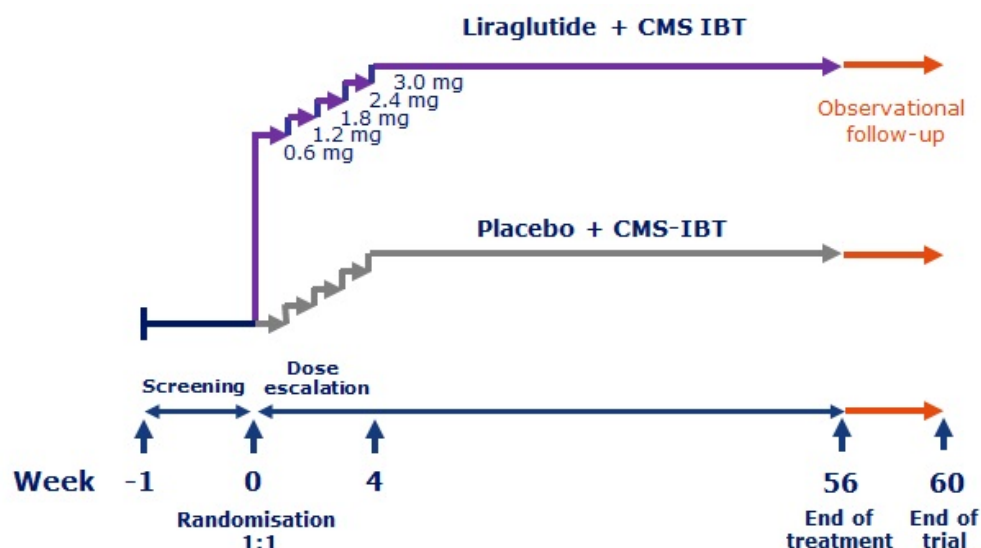


Figure 5-1 Trial Design

5.2 Rationale for trial design

A randomised controlled and double-blinded trial design is used to minimise bias in the assessment of the effect and safety of liraglutide 3.0 mg vs placebo, both as an adjunct to CMS-IBT^{18,23}.

To minimise missing data and in line with current clinical recommendations³³, subjects discontinuing randomised treatment prematurely are encouraged to stay in the trial and continue CMS-IBT and the scheduled site visits. This is to mimic the ‘real-world’ situation of an approved weight loss drug. CMS-IBT consists of a frequent structured counselling, reduced calorie diet and increased physical activity is an integrated part of the trial

Weekly dose escalation of the trial drug (see [Table 5–1](#)) is included in accordance with the Saxenda[®] US prescribing information³⁴.

Based on the weight loss time course established in phase 3a trials, trial duration of 56 weeks is considered sufficient to measure the full effect of liraglutide 3.0 mg on the weight loss curve.

5.3 Treatment of subjects

5.3.1 Investigational medicinal product

The investigational medicinal product (IMP) is injected subcutaneously (s.c.) once daily for 56 weeks. Dose escalation of trial product will take place during the first 4 weeks after randomisation (see [Table 5–1](#)).

Table 5–1 Dose Escalation and treatment period

| IMP | Dose | Duration |
|---------------------|--------|----------|
| Liraglutide/placebo | 0.6 mg | 1 week |
| Liraglutide/placebo | 1.2 mg | 1 week |
| Liraglutide/placebo | 1.8 mg | 1 week |
| Liraglutide/placebo | 2.4 mg | 1 week |
| Liraglutide/placebo | 3.0 mg | 52 weeks |
| Follow up period | 0 mg | 4 weeks |

If the subject does not tolerate an increased dose during the dose escalation window, the investigator can delay the dose escalation by maintaining the subject at the current dosage step for one additional week. Such a delay is allowed only once during dose escalation (i.e. maximum allowed time for complete dose escalation to 3.0 mg is 5 weeks). After reaching the maintenance dose (3.0 mg), the dose and dosing frequency should not be changed.

If a single dose is missed, once-daily regimen should be resumed as prescribed at the next scheduled dose. If more than 3 consecutive days have elapsed since the last dose, subject should re-initiate dose escalation, (i.e., restart the dosing at 0.6 mg and follow the dose escalation schedule again). This is done to reduce the occurrence of gastrointestinal symptoms associated with re-initiation of treatment.

NB: Additional or increased dose should not be taken to make up for missed doses.

Trial product can be taken at any time of day, irrespective of timing of meals. Trial product can be injected subcutaneously in the abdomen, thigh, or upper arm. The injection site and timing can be changed without dose adjustment.

NB: Trial product must not be administered intravenously or intramuscularly.

If a subject cannot tolerate the 3.0 mg dose, or if any of the other treatment discontinuation criteria are met, then treatment with trial product must be discontinued. For treatment discontinuation reasons, please refer to Section [6.5](#). In case this happens, it is acceptable to restart trial product (at the discretion of investigator and according to the local clinical practice); the dose must be escalated according to the algorithm above, and date of restart and rationale must be documented in the CRF.

5.3.2 Counselling (intensive behaviour therapy)

The CMS intensive behaviour therapy (CMS-IBT) will consist of counselling on diet, physical activity and other lifestyle modifications. Subjects will attend a total of 23 individual approximate 15-minutes sessions during the 56 weeks.

The CMS-IBT will be delivered by a primary care physician, a nurse practitioner, a clinical nurse specialist, or physician assistant. Registered dietitians are also eligible to provide lifestyle counselling under CMS rules, when supervised by a nurse practitioner or physician³⁵. The individual performing the CMS-IBT is called interventionist in this protocol. Interventionists will be trained in obesity and its behavioural management prior to beginning the trial and provided on-going assistance and share better practice in how to perform CMS-IBT during the trial. The content of the CMS-IBT is based on an abbreviated version of the Diabetes Prevention Program (DPP) employing the 5A counselling framework (Ask, Assess, Advise, Agree, Assist)^{36,37}.

The structure and content of each CMS-IBT session is specified in an IBT guide, consisting of an interventionist part and a subject hand out. Generally each CMS-IBT session will begin with the subject being weighed and informed of the weight change. Then the subject and interventionist will review the subject's completion of food and physical activity records (see Section [8.7.1](#)) and the interventionist assists with solving individual problems.

In addition to the above, each CMS-IBT session will cover a specific topic, for example, advice on diet or physical activity as well as lifestyle modification (e.g., challenging negative thoughts, obtaining social support). Most of the topics will be accompanied by a homework assignment from the IBT guide to be completed before the next session with the interventionist.

CMS-IBT sessions that cannot be completed on-site (because of illness, travel, etc.), may be completed on telephone in few cases.

Calorie targets

Caloric deficit and diet composition are aligned with clinical evidence-based guidelines for management of overweight and obesity in adults²⁰.

Daily caloric target throughout the trial for subjects will be based on body weight at randomisation:

- Subjects weighing less than 200 lbs will be prescribed a diet of 1200 kcal/day
- Subjects weighing between 200 lbs and 300 lbs will be prescribed a diet calculated as:
$$\text{Daily caloric target (kcal)} = \text{body weight (lb)} * 6 \text{ (kcal/lb)}$$
- Subjects weighing more than 300 lbs will be prescribed 1800 kcal/day

The initial caloric target will be kept throughout the trial. If a subject achieves a BMI $\leq 22 \text{ kg/m}^2$, the recommended energy intake will be re-calculated with no caloric deficit for the remainder of the trial.

The diet will consist of conventional foods with approximately 15-20% kcal from protein, 20-35% from fat, and the remainder from carbohydrate. Carbohydrate intake should be monitored by the interventionist. Carbohydrate intake from vegetables, fruits, whole grains, legumes and dairy products should be advised³⁸. Meal plans may be provided.

Subjects will be instructed to record their food and calorie intake daily (see Section [8.7.1](#)).

Physical activity targets

All subjects will initially be prescribed 100 minutes physical activity per week (e.g., walking or similar aerobic activity). Subjects should be physically active in bouts of >10 minutes in duration with moderate intensity (such as brisk walking), and the physical activity should be spread equally across 4-5 days each week. Physical activity should progress gradually by 25 minutes every 4 weeks until 250 minutes/week, consistent with targets required for maintenance of lost weight³⁹.

Subjects will be instructed to record their physical activity daily using a physical activity tracker provided by NN (see Section [8.7.1](#))^{17,37}.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products, the subject should be switched to a suitable marketed product at the discretion of the investigator.

After premature discontinuation of trial product (temporary/permanent), the subject should still remain in the trial and follow the IBT sessions and site visits if possible, see Section [8.1](#). The investigator must note down in the medical record and eCRF if the subject has re-started the trial product, see Section [5.3.1](#).

5.5 Rationale for treatment

Subjects are treated for a period of 56 weeks in order to be able to evaluate the full effect of treatment with liraglutide 3.0 mg on the primary and secondary endpoints. This is based on the

knowledge from previous liraglutide 3.0 mg trials. Also, the regulatory authorities' guidelines for trials in weight management state that the duration of at least 1 year is deemed appropriate to evaluate efficacy, safety and tolerability.

The comparator in the trial is placebo in order to evaluate the absolute safety and efficacy of liraglutide 3.0 mg.

Combining frequent behavioural counselling, highly structured hypo-caloric diets and increased physical activity is an effective tool for achieving and maintaining weight loss. It has been shown to be more effective than less intensive lifestyle modification programs for inducing weight loss¹⁸, and combining IBT and pharmacologic treatment leads to more weight loss than pharmacologic treatment alone²³. Subjects in the trial will receive CMS-IBT irrespective of the treatment arm they belong to.

The CMS-IBT mandates 22 sessions within a span of one year (52 weeks). Since the treatment duration is 56 weeks, an extra CMS-IBT session has been added at week 56.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be randomised: 282

6.2 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered “yes”.

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. BMI ≥ 30 kg/m²
3. Maximum 5 kg self-reported weight change within the past 90 days since screening
4. Age ≥ 18 years at the time of signing informed consent
5. Increased physical activity is considered to be safe as judged by the investigator

6.3 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered “no”.

1. HbA_{1c} $\geq 6.5\%$ (at screening visit), or diagnosis of type 1 or type 2 diabetes mellitus
2. Recent history of cardiovascular disease (myocardial infarction or stroke within the past 6 months), severe congestive heart failure (NYHA class III, IV), or second degree or greater heart block
3. Hypersensitivity to liraglutide or any product components
4. Personal or family history of Medullary Thyroid Carcinoma (MTC), or Multiple Endocrine Neoplasia type 2 (MEN2)
5. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice)
6. Uncontrolled thyroid disease, defined as TSH > 6 mIU/L or < 0.4 mIU/L (at screening visit)
7. Use in past 90 days since screening of medications known to induce significant weight loss (e.g., prescription weight loss medications) or weight gain (e.g., chronic use of oral steroids, second generation antipsychotics)
8. History of (or plans for) weight loss surgery (e.g. bariatric, intra-gastric balloons, maestro system) or implant of weight loss device (e.g., Reshape, vBloc). However, liposuction and/or abdominoplasty performed > 1 year before screening is allowed
9. History of pancreatitis (acute or chronic)
10. History of major depressive disorder within the past 2 years since screening
11. Diagnosis of other severe psychiatric disorder (e.g., schizophrenia, bipolar disorder)

12. A Patient Health Questionnaire-9 (PHQ-9) score of ≥ 15 at screening or randomisation
13. Any lifetime history of a suicide attempt
14. Any suicidal behaviour within the past 30 days since screening
15. Any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the past 30 days at screening or randomisation
16. Inadequately treated blood pressure defined as Grade 3 hypertension or higher (Systolic ≥ 180 mmHg or diastolic ≥ 110 mmHg)
17. History of malignancy (except for non-melanoma skin cancer) within the past 5 years
18. Any disorder, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the subject's safety or compliance with the protocol
19. Known or suspected abuse of alcohol or narcotics
20. Language barrier, mental incapacity, unwillingness or inability to adequately understand or comply with study procedures
21. Subjects from the same household participating in the trial
22. Participation in any clinical trial with or without an investigational medicinal product within the past 90 days before screening
23. Previous participation in this trial. Participation is defined as signed informed consent

6.4 Randomisation criterion

1. Have kept a food diary for at least 5 days (minimum one entry per day) in the period between screening and randomisation

To be randomised, the above randomisation criterion must be answered "yes".

6.5 Criteria for premature discontinuation of trial product

Efforts must be made so that subjects attend and complete all scheduled visit procedures. Subjects should stay in the trial regardless of adherence to randomised treatment, visit schedule or missing assessments. Only subjects who decline any further contact with the site in relation to the trial or withdraw consent are considered as withdrawn from the trial (see Section [6.6](#)).

The subject may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

The subject must be prematurely discontinued from trial product if the following applies:

1. Included in the trial in violation of any of the inclusion and/or exclusion criteria and/or randomisation criteria
2. Safety concern (not covered by any of below criteria) or unacceptable intolerability to trial product, as judged by the investigator

3. Hypersensitivity to trial product(s). If a hypersensitivity reaction occurs, discontinue trial product and other suspect medications and promptly seek medical advice
4. Pregnancy
5. Intention of becoming pregnant
6. Suspicion of pancreatitis (see Section [8.4.2.2](#) and [8.8.1](#))
7. Suspicion of acute gallstone disease (see Section [8.4.2.2](#) and [8.8.2](#))
8. Suspicion of drug-induced liver injury (DILI) (see Section [8.4.2.2](#) and [8.8.4](#))
9. Calcitonin ≥ 100 ng/L
10. Psychiatric disorder(s) that cannot be adequately treated with psycho- and/or pharmacotherapy (see Section [8.4.2.2](#), [8.8.5](#) and [8.6.4](#)).
11. Initiation of anti-obesity medication and/or (plans for) weight loss surgery
12. Initiation of treatment with glucagon-like peptide-1 receptor agonist (GLP-1 RA)
13. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product

See Section [8.1](#) for procedures to be performed for subjects discontinuing trial product prematurely.

It is allowed for subjects meeting the premature discontinuation criteria or who have wished to discontinue prematurely to be restarted on the trial product should the suspicion not be confirmed or if the condition has been resolved at the investigator's discretion. Trial product may be restarted for subjects meeting discontinuation criteria 7 should the gallbladder be removed.

6.6 Withdrawal from trial

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected. See Section [8.1](#) for procedures to be performed for subjects withdrawing consent. The trial drug cannot be re-initiated if the consent has been withdrawn.

6.7 Subject replacement

Subjects who discontinue trial product prematurely will not be replaced.

6.8 Rationale for trial population

The trial will be conducted in subjects with obesity without T2DM. Subjects with obesity represent a clinically relevant population to treat for weight loss as they are likely to benefit from weight reduction. Subjects with T2DM have been excluded from the trial, as there may be a confounding effect of improvements in glycaemic control on weight loss and as subjects with T2DM may have different safety concerns.

7 Milestones

Planned duration of recruitment period: 10 weeks.

End of trial is defined as last subject last visit (LSLV). End of treatment is defined as visit 24 for each subject.

Recruitment:

The screening and randomisation rate will be followed closely via the interactive voice/web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects screened during the recruitment period and found eligible for randomisation can be randomised within the timelines specified in the flow chart (see Section [2](#)).

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure⁴⁰, it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)⁴¹, the Food and Drug Administration Amendment Act⁴², European Commission Requirements^{43,44} and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

8.1 Visit procedures

The following sections describe the assessments and procedures. These are also included in the flow chart (see Section [2](#)).

Informed consent must be obtained before any trial-related activity; see Section [18.2](#).

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. Only subjects who have signed the informed consent form should be included on the logs. The subject screening log and subject enrolment log may be combined in one log.

At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff. Subjects should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

Fasting requirements

The subjects should be fasting when attending some visits, please see flow chart (Section [2](#)). Fasting is defined as at least 8 hours without food and drink intake, except water and other prescribed medication. Trial product and other glucose lowering agents should be withheld on the day of the visit until blood sampling have been performed. If the subject attends a fasting visit in a non-fasting state, the blood sampling should be re-scheduled within the visit window.

Screening failures

For screening failures, the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial. Serious adverse events (SAEs) from screening failures must be transcribed by the investigator into the eCRF. Follow-up on SAEs must be carried out according to Section [12](#). A screening failure session must be made in the IWRS. The case book must be signed.

Re-screening is NOT allowed if the subject has failed one of the inclusion, exclusion, or randomisation criteria, this includes re-sampling if the subject has failed one of the inclusion or exclusion criterion related to laboratory parameters.

Premature discontinuation of trial product

The subject may discontinue trial product for several different reasons and after different treatment durations.

If a subject meets a discontinuation criterion, the trial product must be immediately discontinued and the date should be noted in the medical records and eCRF. Discontinuation can be either temporary or permanent. The last paragraph of Section [6.5](#) outlines which discontinuation can be considered temporary. The investigator must note down the date in the medical record and the eCRF once there is resolution and the subject has re-started the trial product.

The subject may also wish to discontinue trial product temporarily or permanently, irrespective meeting any criteria. Discontinuation of treatment with trial product, whether temporary or permanent, must not prompt the investigator to withdraw the subject from the trial. Instead, the subject should maintain adherence to trial visits (including CMS-IBT) and procedures to the extent possible.

In cases where the subject is not willing to attend all scheduled visits after discontinuation of trial product, efforts must be made to collect as much of the scheduled data as possible. Especially important is collection of the data points (primarily body weight) at visit 24 (week 56). Statistical considerations emphasizing the importance can be found in Section [17](#).

Premature trial product discontinuation should be registered in the eCRF and in IWRS. The trial product can be interrupted by performing a 'treatment status' session in IWRS, to indicate subject should no longer receive trial product. The primary reason for discontinuation of trial product must be specified when recording the treatment discontinuation in the eCRF. If the discontinuation of trial product is judged permanent or of a longer period, drug accountability until discontinuation must be performed in IWRS.

If the subject has previously discontinued trial product, it is possible, at the discretion of the investigator and at the wish of the subject, to re-initiate treatment with trial product. This will only apply, if it can be confirmed that the subject has not withdrawn consent, and does not fulfil any of the criteria leading to permanent discontinuation or if a criterion leading to temporary discontinuation has been resolved. A 'treatment status' session is performed in the IWRS, to indicate that the subject should again receive trial product. See Section [10](#) for registration in IWRS. This should be further noted in the medical records and eCRF.

Withdrawal from trial

A subject who wishes to withdraw their consent must be withdrawn from the trial. If a subject wants to withdraw consent, the investigator must aim to undertake procedures similar to those for end-of-

treatment visit, as soon as possible. If the subject agrees, the follow-up visit must be performed at least 30 days after discontinuation of trial product.

The end-of-trial form in the eCRF must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. The investigator must perform a 'treatment status' session in IWRS and discontinue trial product for this subject. The case book must be signed.

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

Lost to follow-up

If a subject loses contact with the study staff or does not come for visit 24 or visit 25, attempts must be made to locate the subject and obtain relevant safety information. A subject cannot be deemed lost to follow-up until at least substantial contacts with family/relatives/family physician have been attempted. Subject information may be retrieved from other health care professionals, medical records or publicly available records. A subject will only be considered lost to follow-up in case vital status cannot be determined at the time of visit 25 for that subject.

8.2 Subject-related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.2.2 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e., at the screening visit) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Medical history is a medical event that the subject has experienced in the past. Only relevant and significant medical history as judged by the investigator should be recorded. Findings of specific medical history described below should be entered on the specific forms.

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

Any change to a concomitant illness should be recorded during the trial. Any clinically significant worsening of a concomitant illness must be reported as an AE.

It must be possible to verify the subject's medical history in source documents such as subject's medical record. If a subject is not from the investigator's own practice; the investigator must make reasonable effort to obtain a copy of subject's medical record from relevant party (e.g., primary physician). The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

Findings of specific medical history described below should also be entered on the specific forms in the eCRF:

History of gallstone disease

Information related to gallstone disease (i.e., gallstone disease and cholecystectomy) must be recorded.

History of breast neoplasms

Information related to history of breast neoplasms must be recorded for all female subjects. Information regarding menopausal status, previous mammograms and outcome, first degree relatives with breast cancer and predisposing factors (alcohol intake above recommended local guidelines, hormone replacement therapy, age of menarche, number of births, maternal age at first birth, and if the subject ever breastfed) should be recorded.

History of colon neoplasms

Information related to history of colon neoplasms, previous endoscopic examination(s) of the colon, history of inflammatory bowel disease, and first degree relatives with colon neoplasms must be recorded.

History of psychiatric disorders

Information related to psychiatric disorders (specifically history of depression, substance and alcohol abuse, suicidal ideation/behaviour, anxiety, mood disorders, insomnia, or sleep disorders) must be recorded.

8.2.3 Concomitant medication

A **concomitant medication** is any medication, other than the trial product, which is taken during the trial, including the screening and follow-up periods.

Details of any concomitant medication must be recorded at visit 1. Changes in concomitant medication must be recorded at each visit as they occur. The investigator must assess the concomitant medication at every visit for any changes.

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation.

If a change in concomitant medication is due to an AE, then this must be reported according to Section [12](#). If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.2.4 Childbearing potential

It must be recorded in the eCRF whether female subjects are of childbearing potential.

Pregnancy testing must be performed on female subjects of childbearing potential as described in Section [8.5.2](#). Female subjects of childbearing potential must be instructed to use adequate contraceptive methods throughout the trial and until 1 week after end of treatment.

Female of non-childbearing potential is defined as:

- Female who has undergone a hysterectomy, bilateral oophorectomy or bilateral tubal ligation
- Postmenopausal defined as no menses for 12 months without an alternative medical cause
- Other medical reasons preventing childbearing potential

8.2.5 Tobacco use

Details of tobacco use must be recorded at visit 1. Smoking is defined as smoking at least one cigarette or equivalent daily.

Smoking status:

- Never smoked
- Previous smoker
- Current smoker

8.2.6 Amount of alcohol consumed

Details of alcohol use must be recorded at visit 1. Alcohol consumption should be collected. Alcohol use is defined as consumption of minimum one unit of alcohol per week on average.

8.2.7 Weight history, including weight-related comorbidities

Information regarding maximum lifetime weight, progression of weight pattern, family history of weight and previous weight loss attempts (e.g., maximum weight loss) must be recorded for all subjects.

8.2.8 Barriers and motivation interview

The barriers and motivation interview identifies barriers to lifestyle change and compliance with the protocol. The interview guide will ensure that these are addressed during CMS-IBT sessions. The interview guide will be available in local language.

8.2.9 7-day food diary in screening period

A food diary will be dispensed to the subjects at the screening visit to ensure that randomised subjects are able to comply with the protocol requirements for daily recording of food intake.

8.3 Efficacy assessments

All assessments and samples collected at randomisation will be considered as baseline for efficacy, unless otherwise specified.

8.3.1 Body weight

The body weight should be measured at all visits without shoes, on an empty bladder and only wearing light clothing. It should be measured on a digital scale to the nearest 0.1 kg or lb using the same scale throughout the trial. The scale must be calibrated yearly as a minimum.

BMI will be calculated by the eCRF from visit 1 data and must be in accordance with inclusion criterion 2. BMI will be calculated as follows:

$$\text{BMI} = \text{weight (kg)} / \text{height}^2 \text{ (m}^2\text{)} \text{ or}$$

$$\text{BMI} = (\text{weight (lb)} / \text{height}^2 \text{ (inch}^2\text{)}) * 703$$

8.3.2 Height

Height is measured at screening without shoes to the nearest cm or inch with one decimal.

8.3.3 Waist circumference

The waist circumference will be measured at the specified visits (see Section [2](#)) and is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest.

Waist circumference is measured in the horizontal plane and rounded to the nearest cm or inch using a non-stretchable measuring tape. The same measuring tape should be used throughout the trial.

The subject should be measured in a standing position and wearing light clothing. The subject should be standing, feet together with arms at the side and waist accessible. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally.

8.3.4 HbA_{1c}

Blood samples will be drawn at the specified visits (see Section [2](#)) for measurement of HbA_{1c}.

8.3.5 Fasting plasma glucose

FPG is measured in order to evaluate metabolic control. The subject must attend these visits fasting. For definition of fasting, see Section [8.1](#).

A FPG result ≤ 3.9 mmol/L (70 mg/dL) should not be reported as a hypoglycaemic episode but as a clinical laboratory adverse event (CLAE) at the discretion of the investigator (see Section [12.1.1](#)).

8.3.6 Vital signs (blood pressure)

For blood pressure, measurement with a precision of minimum 2 mmHg must be performed. The value must be used to evaluate eligibility of the subject in relation to exclusion criterion.

The method for measuring systolic and diastolic blood pressure needs to follow the standard clinical practice at site, but as a minimum, the following guideline must be adhered to:

Avoid caffeine, smoking and exercise at least 30 minutes prior to measuring the blood pressure. Blood pressure should be measured in a sitting position, with the legs uncrossed, the back and arms supported. The subject should be sitting for five minutes before the measurement is taken. The same arm and an appropriate cuff size should be used for blood pressure measurements at all visits.

8.3.7 Clinical outcome assessments

Clinical outcome assessments (COA) are used to collect clinical data for all subjects enrolled in the trial at the visits specified in Section [2](#). The questionnaires are linguistically validated to fluent language of all subjects participating.

The questionnaires must be completed by the subject and should preferably be completed after conclusion of all fasting-related activities, but before any other visit-related activities. Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. Each of the questionnaires takes approximately 10 minutes to complete.

The questionnaires are:

Impact of Weight on Quality of Life-Lite for Clinical Trials Version

The IWQoL-Lite for CT questionnaire is a 22-item modified version of an instrument designed to assess weight-related quality of life⁴⁵.

Alongside this trial in another project, Novo Nordisk is adapting the IWQoL-Lite for CT by conducting additional concept elicitation with patients, cognitive interviewing, consultation with expert clinicians, translatability assessment, and psychometric validation. Development and validation process is aligned with the FDA PRO guidance (2009)⁴⁶.

Short Form 36 v2.0 acute

Short Form 36 v2.0 acute (SF-36)⁴⁷ is a 36-item, patient-reported survey of patient health. SF-36 measures the subject's overall HRQoL (Health related quality of life) on 8 domains: physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health.

In addition SF-36 is included to validate the outcome of IWQoL-Lite for CT and WRSS questionnaires.

Patients' global impression of change

The PGI-C assesses subjects' impressions of change during the clinical trial. It is used to establish the Minimal Clinically Important Difference (MCID) as part of the psychometric properties of the Weight related sign and symptom measure (WRSS) questionnaire and support the 6 minute walk test.

Patients' global impression of status

The PGI-S assesses subjects' impressions of status at the time in the clinical trial. It is used to establish the MCID as part of the psychometric properties of the WRSS questionnaire and support the 6 minute walk test.

Weight related sign and symptom measure

The WRSS measures the presence and bothersome associated with weight-related symptoms. It is a tool to assess the multifaceted aspects of obesity on symptom experience in subjects with obesity.

In this trial, Novo Nordisk is validating the WRSS. Development and validation process is aligned with the FDA PRO guidance (2009)⁴⁶.

8.3.8 Six-minute walking distance test

The six-minute walking distance test (6MWT) is a common test of functional exercise capacity that assesses the distance a subject can walk in 6 minutes. A direct and timed measure of walking ability, the 6MWT is technically simple, reproducible, and when administrators are well trained, readily standardised. The goal is for the subject to walk as far as possible in six minutes without running. The subject is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway of 66 feet (20 m) (see [Figure 8–1](#)). The primary outcome is the distance covered in feet over 6 minutes^{48, 49}.

To ensure adequate 6MWT standardisation across clinical sites and test administrators, training materials will be developed and provided to all clinical sites prior to subject recruitment. Specifically, all principal investigators and 6MWT clinical site administrators will receive an instruction manual, providing detailed instructions for administration of the 6MWT. In addition to the instruction manual, each 6MWT administrator will have a checklist that must be completed prior to initiating each test administration to confirm and document that specific test administration criteria are met (e.g., the test is assessed along a flat, straight, enclosed corridor that is at least 6 feet wide; proper footwear as judged by the investigator is worn by the subject or otherwise noted)⁵⁰. The clinical outcome assessments (PGI-S and PGI-C) will support the test and help establish the MCID of the test.

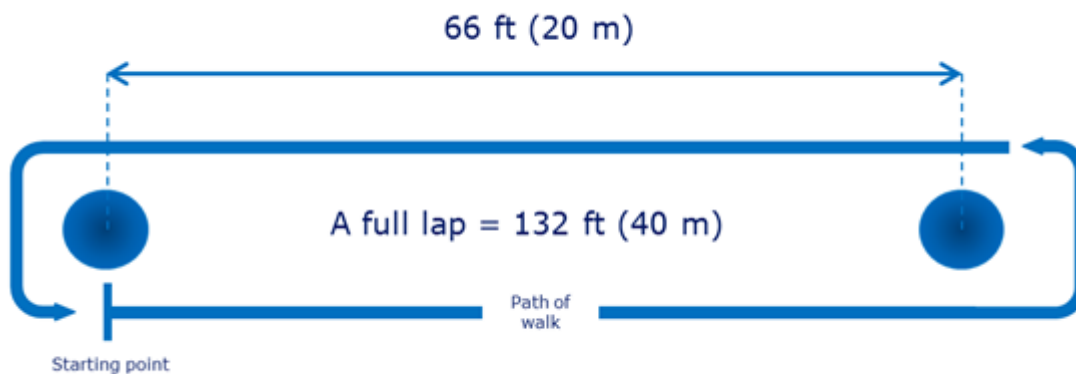


Figure 8–1 Hallway marking for the six minute walking distance test

8.4 Safety assessments

All assessments and samples collected at randomisation will be considered as baseline for safety, unless otherwise specified.

8.4.1 Physical examination

Physical examination will be performed at the specified visits (Section [2](#)) according to local procedure. Physical examination should include general appearance, thyroid gland, respiratory system, cardiovascular system, gastrointestinal system including mouth, abdomen, musculoskeletal system, central and peripheral nervous system, skin, lymphoid node palpation, and head, ears, eyes, nose, throat and neck, and must be recorded in the subject's medical record and eCRF. Any abnormal, clinically significant findings at screening (visit 1) must be recorded as a concomitant illness (see Section [8.2.2](#)).

Physical examination performed at screening will be considered as baseline.

8.4.2 Adverse events

Adverse events (AEs) must be reported at each visit in accordance with the procedures outlined in Section [12](#).

8.4.2.1 Medication error

If a medication error is observed during the trial, the following information is required and a specific event form for medication error must be completed in the eCRF in addition to the AE form:

- Trial product(s) involved
- Classification of medication error
- Whether the subject experienced any adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see Section [12.1.4](#).

8.4.2.2 Adverse events requiring additional data collection

For the following AEs, additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form:

- Acute gallstone disease
- Neoplasm
- Pancreatitis
- Depression, suicidal ideation/behaviour
- Hepatic event (Suspicion of DILI)

In case any of these events fulfil the criteria for a SAE, please report accordingly, see Section [12](#).

Acute gallstone disease

If an event of acute gallstone disease or clinical suspicion of this is observed during the trial, the following additional information should be reported if available on the acute gallstone disease form:

- Signs and symptoms of acute gallstone disease
- Specific laboratory test supporting a diagnosis of gallstone disease (see Section [8.8.2](#))
- Imaging performed and consistency with gallstone disease
- Treatment given for the event
- Relevant risk factors associated with the event

Neoplasm

All events of benign, pre-malignant/carcinoma in-situ and malignant neoplasms must be reported during the trial and the following additional information should be obtained if available as part of standard of care on the neoplasm form:

- Type of neoplasm
- Signs and symptoms leading to identification of event
- Diagnostic imaging
- Pathological examination results
- Treatment given for the event
- Participation in screening programs
- Relevant risk factors associated with the event

Pancreatitis

If an event of pancreatitis, acute or chronic is observed during the trial, the following information must be reported, if available on the pancreatitis form:

- Signs and symptoms of pancreatitis
- Specific laboratory test supporting a diagnosis of pancreatitis (see Section [8.8.1](#))
- Imaging performed and consistency with pancreatic disease
- Treatment given for the event
- Relevant risk factors associated with the event

Depression, suicidal ideation/behaviour

If an event of depression, suicidal ideation or behaviour or clinical suspicion of this is observed during the trial the following additional information should be reported if available on the Depression, suicidal ideation/behaviour form:

- Signs and symptoms of depression, suicidal ideation or behaviour
- Relevant risk factors associated with the event
- Treatment given for the event

Hepatic event (suspicion of drug induced liver injury)

In case of suspicion of DILI, following additional information should be reported if available on the drug induced liver injury form:

- Signs and symptoms of drug induced liver injury
- Specific laboratory test supporting a diagnosis of drug induced liver injury (see Section [8.8.3](#))
- Treatment given for the event
- Relevant risk factors associated with the event

Prompt testing (at central laboratory) including alanine aminotransaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), international normalised ratio (INR) and total bilirubin (TBL) should be done and trial product should be discontinued until the abnormalities return to normal or baseline state.

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

The event should be reported as an AE requiring additional data collection (see Section [12.1.5](#)).

8.4.3 Vital signs (pulse)

Pulse (beats/minutes) will be recorded in a sitting position after resting for five minutes at the specified visits (Section [2](#)).

8.4.4 Electrocardiogram

An electrocardiogram (ECG) will be performed at the visits specified in the flow chart (Section [2](#)). The investigator or delegate must sign, date and interpret the ECG by using the following categories:

- Normal
- Abnormal: Was the result clinically significant? (Yes/No)

Clinically significant is an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example, change of medicine dose or more frequent follow-up due to the abnormality.

If the result is clinically significant, the investigator must report such an abnormal finding as an AE or SAE (see Section [12.2](#)).

ECG performed at screening will be considered as baseline.

8.4.5 Hypoglycaemic episodes

Liraglutide increases insulin secretion and reduces glucagon secretion in a glucose dependent manner. Thus, the stimulation of insulin release and inhibition of glucagon release subsides as the blood glucose decreases and approach euglycemia. Therefore, the risk of hypoglycaemia in subjects without T2DM is considered to be low.

A hypoglycaemic episode during the trial should be recorded as an AE according to standard AE reporting (see Section [12](#)).

Subjects should be instructed in potential symptoms of hypoglycaemia: sweating, trembling, hunger or palpitations (rapid or irregular heart beat), confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement).

According to ADA classification, a severe episode of hypoglycaemia is defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by low plasma glucose concentration⁵¹. Such a severe episode of hypoglycaemia must be reported as a SAE (see Section [12.2](#)).

Blood glucose meters will not be handed out to subjects in this trial.

8.4.6 Patient Health Questionnaire-9

The patient health questionnaire-9 (PHQ-9) is a 9-item depression module of the patient health questionnaire, which is a self-administered diagnostic tool used for assessment of mental disorders⁵². The questionnaire will be available in a linguistically validated version in subject's fluent language. Subjects should be given the opportunity to complete the questionnaires by themselves without interruption. It takes approximately 10 minutes to complete.

A PHQ-9 \geq 15 excludes the subject from participation in the trial.

8.4.7 Columbia Suicidal Severity Rating Scale

The Columbia suicidal severity rating scale (C-SSRS)⁵³ is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation. The questionnaire will be administered as an interview by the investigator or a qualified delegate. The questionnaire will be available in a linguistically validated version in the subject's fluent language. It takes approximately 10 minutes to complete.

Prior to administering the C-SSRS questionnaire, the investigator or qualified delegate must complete sufficient training. Any suicidal ideation of type 4 or 5 within the past 30 days at screening or randomisation excludes the subject from participation in the trial.

8.4.8 Breast and colon neoplasms follow up

These forms must be completed at the end-of-treatment and follow-up visit, even if a subject prematurely discontinues treatment with trial product. The breast neoplasm follow up form should be filled in only for female subjects.

If a subject withdraws consent, the subject must be encouraged to provide this information.

8.5 Laboratory assessments

The laboratory analyses will be performed by a central laboratory. The central laboratory may utilise subcontractors.

Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling, transportation and storage of samples and information regarding who will perform the assessments, will be described in a trial specific laboratory manual, provided by the central laboratory (for central laboratory details, see [Attachment 1](#)).

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to Section [8.2.2](#) and Section [12](#).

Laboratory samples may be drawn on another day than the day of the actual visit, as long as it is within the visit window outlined in the flow chart (see Section [2](#)). For some of the samples drawn during the trial, it is required that the subject is fasting. If a subject is not fasting at these visits, the fasting blood sampling must, as a minimum, be re-scheduled within the visit window.

Laboratory results will be sent by the central laboratory to the investigator on an on-going basis.

Samples will be destroyed no later than at finalisation of the clinical trial report (CTR).

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

Only laboratory samples specified in the protocol must be sent to the central laboratory for analysis; if additional laboratory sampling is needed (e.g., to follow up on AEs) this must be done at a local laboratory.

For laboratory report values outside the reference range, the investigator must specify whether the value is clinically significant or not. If clinically significant, the investigator must report these as clinical laboratory adverse events (CLAE) according to Section [12.1.1](#).

All laboratory report printouts must be reviewed, signed and dated by the investigator or delegate. The evaluation of screening results must be dated and signed prior to visit 2 (randomisation), for the subsequent visits preferably on the day of evaluation.

8.5.1 Laboratory assessments for efficacy

Blood samples must be collected at the specified visits (Section [2](#)).

- HbA_{1c}
- Fasting plasma glucose (FPG)
- Lipids (TC, LDL cholesterol, HDL cholesterol, VLDL cholesterol, TG, FFA)

A FPG result ≤ 3.9 mmol/L (70 mg/dL) should not be reported as a hypoglycaemic episode but as a CLAE at the discretion of the investigator (see Section [12.1.1](#)).

8.5.2 Laboratory assessments for safety

Pregnancy test

Females of childbearing potential will have a human chorionic gonadotropin (hCG) serum pregnancy test performed at the visits specified in the flow chart (see Section [2](#)).

Urine pregnancy tests will be performed for females of childbearing potential if there is suspicion of pregnancy or if she misses a menstrual period, at the visits specified in the flow chart (Section [2](#)). She should contact the site to come in for a urine pregnancy test. Urine pregnancy kits will be supplied by the central laboratory.

Pregnancy testing will not be required for women not of childbearing potential (see Section [8.2.4](#))

Biochemistry

Blood samples for biochemistry must be collected at the specified visits (Section [2](#)).

- Creatinine
- Urea (blood urea nitrogen)
- Uric acid
- Alanine aminotransaminase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase (ALP)
- Albumin
- Amylase
- Lipase
- Sodium
- Potassium
- Calcium, total
- Calcitonin (please refer to [Appendix A](#) for actions to be taken if calcitonin is ≥ 10 ng/L)
- TSH*
- Bilirubin, total (TBL)
- hs-CRP**
- GFR, estimated

*If TSH levels are out of normal range, the investigator must perform additional testing:

- Total and free T3 and T4 and Free Thyroid Index
- Thyroid peroxidase antibodies

** hs-CRP is only measured at Visit 2 and Visit 24.

Haematology

Blood samples for haematology must be collected at the specified visits (Section [2](#)).

- Haemoglobin
- Haematocrit
- Thrombocytes
- Erythrocytes
- Leucocytes

8.6 Other assessments

8.6.1 Trial product usage

Information on premature discontinuation, and permanent discontinuation of trial product will be collected and recorded in the eCRF. If the trial product is re-started, the investigator must note this in the medical record.

8.6.2 Food diary and tracking of physical activity

The subjects will be requested to fill in a food diary daily, where all meals and their caloric content are recorded. The interventionist can provide a paper food diary or the subject can use another tracker, tool or app to register food intake, as preferred by the subject.

Daily minutes of physical activity will be captured using a device provided by Novo Nordisk. The subject's adherence with diet and physical activity must be reviewed at all CMS-IBT visits by the interventionist (see Section [8.7.1](#)). The adherence will be further recorded in the eCRF.

8.6.3 Training in the PDS290 pen-injector

The subjects must be trained in how to handle the PDS290 pen-injector when handed out the first time. Training must be repeated during the trial at each visit if needed, in order to ensure correct use of the device. The following should be emphasised:

- Always use a new needle for each injection as this will prevent contamination and blocked needles
- When using the first time, priming the pen to ensure product flow
- The needle should be kept in the skin while counting slowly to 6 (or as described in the direction for use) after the dose counter has returned to zero after injection. If the needle is removed too early then the full dose may not have been delivered.

8.6.4 Inquire about mood

The subject should be asked about the mood as per flow chart (see Section [2](#)), for example – ‘How has your mood been since the last contact?’

In case the subject reports any adverse events, these should be collected and reported as an AE. Depression and suicidal ideation/behaviour should be reported as AEs requiring additional data collection (see Section [8.4.2.2](#) and Section [12](#)).

8.7 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

Compliance with trial product: At each visit, the investigator should ask the subject whether the subject has continuously been using the trial product since last visit. If the subject has stopped using

trial product, the investigator should fill in the date for the last dose in the eCRF. If the subject has had a pause using trial product longer than one week since last visit, but has started using trial product again, the investigator should fill in the dates corresponding to the last day on trial product and the first day on trial product in the eCRF.

8.7.1 Adherence to dietary and physical activity

Adherence to the dietary and physical activity will be assessed by the interventionist performing the CMS-IBT at all visits. At each CMS-IBT session, the interventionist must, for each calendar week since the last visit, assess and record the number of days per calendar week, where the subject has entered information in the food diary (see Section [5.3.2](#)). In addition, how physically active the subject has been per week for each calendar week since the last visit will be recorded. The result must be noted in the subjects' record in eCRF.

If a subject is found to be non-adherent, the interventionist should remind the subject of the importance of following the advice given. The interventionist will help the subjects solve issues with non-adherence as part of the counselling (see Section [5.3.2](#)).

8.8 Additional safety assessments

8.8.1 Suspicion of acute pancreatitis

If pancreatitis is suspected, trial product should promptly be discontinued (no 'treatment status' session should be made in IWRS before diagnosis of acute pancreatitis is confirmed) and appropriate management should be initiated. Appropriate additional examinations must be performed, including local measurement of amylase and lipase.

The event should be reported as an AE requiring additional data collection (see Section [8.4.2.2](#) and Section [12](#)).

The diagnosis of acute pancreatitis requires two of the following three features:

- Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
- Serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal
- Characteristic findings of acute pancreatitis on imaging (CT/MRI).

Abdominal pain

Most patients with acute pancreatitis experience abdominal pain that is located generally in the epigastrium and radiates to the back. The onset of the pain may be swift reaching maximum intensity within 30 minutes; it is frequently unbearable and characteristically persists for more than

24 hours without relief. The pain is often associated with nausea and vomiting. Physical examination usually reveals severe upper abdominal tenderness at times associated with guarding.

Lipase and amylase

In general, both amylase and lipase are elevated during the course of acute pancreatitis. The serum lipase may remain elevated slightly longer than amylase. The level of the serum amylase and/or lipase does not correlate with the severity of acute pancreatitis. In general, serum lipase is thought to be more sensitive and specific than serum amylase in the diagnosis of acute pancreatitis.

If acute pancreatitis is confirmed, the subject must be permanently discontinued from trial product and appropriate treatment and careful monitoring of the subject should be initiated. Furthermore, the subject should still remain in the trial (see Section [8.1](#)).

If acute pancreatitis is ruled out, trial product should be re-initiated at the investigator's discretion.

8.8.2 Suspicion of acute gallstone disease

In case of suspicion of acute gallstone disease or cholelithiasis, the trial product should promptly be discontinued (no 'treatment status' session should be made in IWRS before a diagnosis of acute gallstone disease is confirmed). Appropriate treatment and careful monitoring should be initiated. Furthermore, the subject should remain in the trial (see Section [8.1](#)).

The event should be reported as an AE requiring additional data collection (see Section [8.4.2.2](#) and Section [12](#)).

If acute gallstone disease is confirmed, the trial product must be permanently discontinued. Appropriate treatment and careful monitoring of the subject should be initiated. Furthermore, the subject should remain in the trial (see Section [8.1](#)).

Trial product can be restarted at the investigator's discretion if cholelithiasis is ruled out or the gallbladder has been removed.

8.8.3 Neoplasm

In case of neoplasm, please consider if the trial drug should be discontinued (no 'treatment status' session should be made in IWRS before a diagnosis is confirmed). The event must be reported as an AE requiring additional data collection (see Section [8.4.2.2](#) and Section [12](#)).

Appropriate treatment and careful monitoring of the subject should be initiated as per local clinical practice. Furthermore, the subject should be encouraged to remain in the trial (see Section [8.1](#)).

Trial product can be re-initiated at the investigator's discretion if diagnosis is not supported.

8.8.4 Hepatic event (suspicion of drug-induced liver injury)

Please consider discontinuing trial product if :

- 1) ALT or AST >5xUNL, or
- 2) ALT or AST > 3x UNL and (total bilirubin >2xUNL or INR >1.5), or
- 3) ALT or AST >3xUNL with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

For the above events, prompt repeat testing at central laboratory, of ALT, AST, ALP, INR and total bilirubin should be done. Thereafter, repeat testing (at central laboratory) of ALT, AST, ALP, INR and total bilirubin should be done regularly until the abnormalities return to normal or baseline state. Additional clinical information such as related symptoms, risk factors and contributing conditions (e.g. viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, hepatobiliary or pancreatic disorders) should be gathered to seek a possible cause of the observed laboratory test abnormalities. Although the trial product is discontinued, no ‘treatment status’ session should be made in IWRS and the subject should remain in the trial.

The event should be reported as an AE requiring additional data collection (see Section [8.4.2.2](#) and Section [12](#)).

If DILI is confirmed, the subject should permanently discontinue the trial product. Appropriate treatment and careful monitoring of the subject should be initiated. However, the subject should remain in the trial (see Section [8.1](#)).

Trial product can be re-initiated at the investigator’s discretion, if diagnosis of DILI is not supported.

8.8.5 Depression, suicidal ideation/behaviour

In case of depression or suicidal ideation/behaviour (see Section [8.6.4](#)), please consider if the trial drug should be discontinued (no ‘treatment status’ session should be made in IWRS before a diagnosis is confirmed). The event must be reported as an AE requiring additional data collection (see Section [8.4.2.2](#) and Section [12](#)).

Appropriate treatment and careful monitoring of the subject should be initiated. A subject should be referred to a MHP if he/she has:

- symptoms of moderate or more severe depression,
- or any suicidal behaviour,
- or any suicidal thoughts with some intent to act, irrespective of whether accompanied by a specific plan.

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In case the subject refuses to consult the MHP, the investigator must state in the medical records whether it is considered safe for the subject to stay in the trial. Trial product can be re-initiated at the investigator's discretion, if a diagnosis is not supported.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the trial materials manual (TMM).

Trial products must not be dispensed to any person not included in the trial.

Trial product comprises investigational medicinal products (IMP); both active and placebo.

Trial product must not be used, if it does not appear clear and colourless or almost colourless.

9.1 Trial products

The following trial products will be provided by Novo Nordisk A/S, Denmark:

Table 9–1 Trial products

| Trial product | Strength | Dosage form | Route of administration | Container/delivery device |
|---------------------------|----------|------------------------|-------------------------------|---------------------------|
| Liraglutide 6 mg/mL (IMP) | 6 mg/mL | Solution for injection | Subcutaneous injection (s.c.) | 3 mL PDS290 pen-injector |
| Placebo (IMP) | NA | | | |

Liraglutide and placebo are visually identical, to ensure double-blinding in the trial.

9.2 Labelling and directions for use

The trial products will be labelled in accordance with Annex 13⁵⁴, local regulations and trial requirements.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to enrolment and randomisation.

The investigator must document that direction for use is given to the subject orally and in writing at the first dispensing visit (visit 2). At the following visits, the investigator will confirm with the subject that the direction for use is still available and that the subject is using the trial product correctly.

9.3 Storage

Table 9–2 Storage conditions

| Trial product | Storage conditions (not-in-use) | In-use conditions | In-use time ^a |
|---------------------|--|--|--------------------------|
| Liraglutide 6 mg/mL | Store in a refrigerator (36°F-46°F) Do not freeze Protect from light | Store at room temperature (59°F-86°F), or in refrigerator (36°F-46°F) Do not freeze Protect from light | Use within 30 days |
| Placebo | | | |

^a *In-use time starts when the product is taken out of the subject's refrigerator.*

The investigator must ensure that trial product is kept under proper storage conditions and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g., outside temperature range). Additional details regarding handling of temperature deviations can be found in the TMM.

Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

Drug accountability of all trial products received at site is the responsibility of the investigator.

The trial products will be dispensed to each subject as required according to treatment group. The IWRS will allocate trial product to the subject at randomisation and each dispensing visit. The correct dispensing unit number(s) (DUN[s]) must be dispensed to the subject.

The investigator or delegated person is responsible for ensuring that:

- Drug accountability is performed using the IWRS drug accountability module
- Subjects are instructed to return all used, partly used and unused trial product including empty packaging material at each dispensing visit and at end-of-treatment visit

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.

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

Dispensed trial product must be accounted for at pen level; either recorded as used/partly used, unused or lost. Distributed and returned pens are subject to be sent for destruction, thus may not be re-allocated to new subjects.

Destruction of trial products can be performed on an on-going basis and will be done according to local procedures after accountability is finalised and reconciled by the monitor. Destruction of products must be documented in the IWRS.

9.5 Auxiliary supplies

Auxiliary supplies comprise supplies other than trial products. The following auxiliary supplies will be provided by Novo Nordisk in accordance with the TMM:

- Needles for pre-filled pen (maximum length to be used is 8 mm)
- Directions for use for pre-filled pen

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

10 Interactive voice/web response system

A trial-specific interactive web response system (IWRS) will be set up which can be accessed at any time via the internet or telephone. Access to the IWRS must be restricted to and controlled by authorised persons.

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Treatment status
- Code break
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

Premature treatment discontinuation and re-initiation

If the investigator or the subject has decided to discontinue treatment, but the subject has not withdrawn consent, it is possible to re-initiate treatment, if no discontinuation criteria are met (see Section [8.1](#)). The subject will remain in the same treatment arm, and a new dose escalation period will be started, if the subject resumes treatment. The investigator must make a note and record dates of any discontinuation and re-initiation in the medical records and eCRF.

To register discontinuation of trial product (temporary or permanent), a 'treatment status' session is performed in the IWRS, to indicate subject should no longer receive trial product. Similarly, if the treatment should later be re-initiated, a 'treatment status' session is performed in the IWRS, to indicate subject should again receive trial product.

Withdrawal

In the case subject has withdrawn consent, a 'treatment status' session must be performed in IWRS, to indicate that subject should no longer receive trial product. If possible after confirmation by the monitor, the subject will be registered as 'withdrawal', to ensure that subject is not allowed to re-initiate trial product.

If the subject is temporarily lost to follow up during the trial, the IWRS session should not be completed until the scheduled Visit 24 at week 56 to confirm the final status.

11 Randomisation procedure and breaking of blinded codes

A randomisation session will be carried out for eligible subjects using the IWRS. The eligible subjects will be randomised centrally 1:1 to either liraglutide 3.0 mg or placebo.

11.1 Breaking of blinded codes

The IWRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

The code for a particular subject may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Whenever a code is broken, the person breaking the code must print the Code Break Confirmation Notification generated by the IWRS, record the reason, and sign and date the document.

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IWRS is not accessible at the time of code break, the IWRS helpdesk should be contacted. Contact details are listed in [Attachment I](#). If the code has been broken, the subject must discontinue treatment with trial product and a treatment session must be completed in IWRS.

12 Adverse events, and technical complaints and pregnancies

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, i.e., an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example, change of medicine dose or more frequent follow-up due to the abnormality.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.

The following three definitions are used when assessing an AE:

- **Severity**
 - **Mild** – no or transient symptoms, no interference with the subject's daily activities.
 - **Moderate** – marked symptoms, moderate interference with the subject's daily activities.
 - **Severe** – considerable interference with the subject's daily activities; unacceptable.
- **Causality**

Relationship between an AE and the relevant trial product(s):

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

- **Final outcome**

- **Recovered/resolved** - The subject has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
- **Recovering/resolving** - The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
- **Recovered/resolved with sequelae** - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets a SAE criterion, the AE must be reported as a SAE.
- **Not recovered/not resolved** - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
- **Fatal** - This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as “recovered/resolved”, “recovering/resolving”, “recovered/resolved with sequelae” or “not recovered/not resolved”. An AE with fatal outcome must be reported as a SAE.
- **Unknown** - This term is only applicable if the subject is lost to follow-up.

12.1.2 Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

- Death.
- A life-threatening^a experience.
- In-patient hospitalisation^b or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity^c.
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening^a or require hospitalisation^b may be considered a SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE^d.

^a. The term “life threatening” in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

^b. The term “hospitalisation” is used when a subject:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
- Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial-related and social purposes

do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

^c A substantial disruption of a subject's ability to conduct normal life functions (e.g., following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

^d For example, intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasia or convulsions that does not result in hospitalisation, or development of drug dependency or drug abuse.

The following adverse events must always be reported as a SAE using the important medical event criterion if no other seriousness criteria are applicable:

- suspicion of transmission of infectious agents via the trial product
- risk of liver injury defined as alanine aminotransaminase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

12.1.3 Non-serious adverse event

A non-serious AE is any AE which does not fulfil the definition of a SAE.

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug or use of wrong device. Note: Use of wrong DUN is not considered a medication error
- Wrong route of administration, such as intramuscular instead of s.c.
- Administration of an overdose with the intention to cause harm, misuse or abuse of trial product
- Accidental administration of a lower or higher dose than intended. That is a dose lower or higher than 0.6, 1.2, 1.8, 2.4 and 3.0 mg respectively (within 24 hours). However, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur

If the subject discontinues trial product prematurely, this should not be reported as a medication error (see Section [8.4.2.1](#)).

Medication errors must be reported on an AE form and a specific event form for medication error.

12.1.5 Adverse events requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the product safety.

The below lists AEs that require completion of specific event forms in the eCRFs (see Section [8.4.2.2](#))

- Acute gallstone disease
- Neoplasm
- Pancreatitis
- Hepatic event (suspicion of DILI)
- Depression, suicidal ideation/behaviour

For details of these events, see Section [8.8](#).

12.1.6 Technical complaints

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:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (30 days). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below (see [Figure 12-1](#)).

During each contact with the trial site staff, the subject must be asked about AEs and technical complaints, for example, by asking: “Have you experienced any problems since the last contact?”

In addition, the subject should be asked about the mood for example – ‘How has your mood been since the last contact?’

All AEs, observed by the investigator or subject, must be reported by the investigator and evaluated.

All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the trial at the latest.

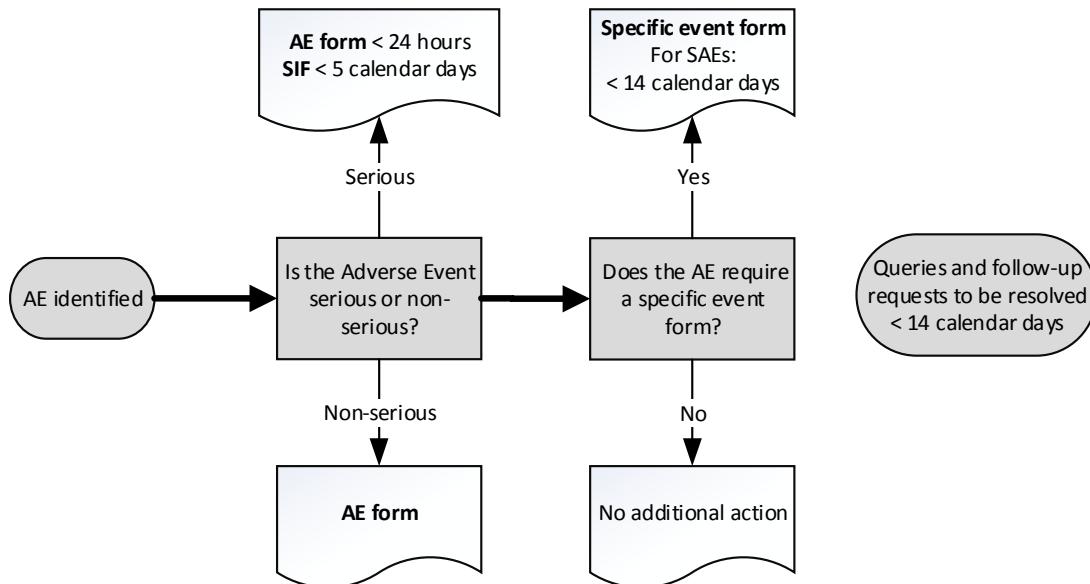
Timelines for initial reporting of AEs

The investigator must complete the following forms in the eCRF within the specified timelines:

- **SAEs:** The AE form **within 24 hours** and the safety information form **within 5 calendar days** of the investigator’s first knowledge of the SAE. Both forms must be signed **within 7 calendar days** from the date the information was entered in the eCRF.
- **For SAEs requiring reporting on a specific event form:** In addition to the above, the specific event form must be signed within **14 calendar days** from the investigator’s first knowledge of the AE.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the form into the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.



Timelines are for the completion of forms from the time of investigator's awareness.
AEs requiring specific event forms are described in Section 12.1.4 and 12.1.5.

AE: Adverse Event SIF: Safety Information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness

Novo Nordisk assessment of expectedness is performed according to the following reference documents: Company Core Data Sheet (CCDS), current version and any updates thereto.

Reporting of trial product-related SUSARs by Novo Nordisk

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP¹. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP¹, unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication

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

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.

Follow-up information must be reported to Novo Nordisk according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the event is “recovered/resolved”, “recovered/resolved with sequelae” or “fatal”, and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome “recovering/resolving” or “not recovered/not resolved”. Cases can be closed with the outcome of “recovering/resolving” when the subject has completed the follow-up period and is expected by the investigator to recover.

The SAE follow-up information should only include new (e.g., corrections or additional) information and must be reported within 24 hours of the investigator’s first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is “recovering/resolving”, “recovered/resolved” or “recovered/resolved with sequelae” or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome “recovering/resolving” or “not recovered/not resolved”. Cases can be closed with the outcome of “recovering/resolving” when the subject has completed the follow-up period and is expected by the investigator to recover.

The investigator must ensure that the recording of the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

SAEs after end of trial: If the investigator becomes aware of a SAE with a suspected causal relationship to the investigational medicinal product occurring to a subject after the subject has

ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Liraglutide 6 mg/ml, 3 ml PDS290 pen-injector
- Placebo PDS290 pen-injector
- Novo Nordisk needles for pen-injector

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in [Attachment I](#) to the protocol.

The investigator must assess whether the technical complaint is related to any AEs and/or SAEs.

Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each code or lot number must be completed

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaints **within 5 calendar days**
- Technical complaint assessed as related to a SAE **within 24 hours**

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in [Attachment I](#)) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the code or lot number, and, if available, the DUN. All parts of the DUN should be returned.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

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

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the trial. The investigator must report any pregnancy in subjects who have received trial product(s).

The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant is one month of age.

The investigator must report information about the pregnancy, pregnancy outcome, and health of the new born infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and new born infant.

The following must be collected and reported by the investigator to Novo Nordisk electronically (e.g., in PDF format), or by fax or courier:

1. Reporting of pregnancy information

Information about the pregnancy and pregnancy outcome/health of the new born infant(s) has to be reported on Maternal Form 1A and 1B, respectively.

When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

Initial reporting and follow-up information must be reported **within 14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. Reporting of AE information

The investigator has to report AEs in connection with the pregnancy as well as in the foetus and new born infant(s). The SAEs that must be reported include abnormal outcome, such as foetal

death (including spontaneous abortion), and congenital anomalies (including those observed at gross examination or during autopsy of the foetus), as well as other pregnancy complications fulfilling the criteria of a SAE.

Forms and timelines for reporting AEs

Non-serious AEs:

- AE form^a **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

Serious AEs:

- AE form^a **within 24 hours** of the investigator's first knowledge of the SAE.
- Safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE.
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information.

^a It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or new born infant. If the AE occurred in the foetus or new born infant, the AE can only be reported on paper AE and safety information form.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

From clinical trials and marketed use of liraglutide overdoses have been reported up to 24 times the recommended dose (72 mg). One case of a 6-fold overdose (18 mg daily) given for 7 months has been reported. Generally, the patients reported severe nausea, vomiting and diarrhoea, but recovered without complications. None of the reports included severe hypoglycaemia.

In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. Please refer to the current approved US Saxenda[®] US prescribing information, for details concerning overdose.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal liraglutide safety committee to perform ongoing safety surveillance. The liraglutide safety committee may recommend unblinding of any data for further

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analysis, and in this case, an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g., is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms

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

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints that are not subject related. e.g., discovered at trial site before allocation)

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing “ND” (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g., is not applicable) indicate this by writing “NA” (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

13.1 Corrections to case report forms

Corrections to the eCRF data may be made by the investigator or the investigator’s delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction.

If corrections are made by the investigator’s delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

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13.2 Case report form flow

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

Site-specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. These data must be retained at the trial site.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FSFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LSLV at the trial site.

The monitor must be given direct access to all source documents (original documents, data and records). The monitor will ensure that the eCRFs are completed. Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone).

All data must be verifiable in source documentation other than the eCRF. For all data recorded, the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

The following data will be source data verified for screening failures:

- date for obtaining informed consent
- reason for screening failure
- SAEs (if any)

Source data generated by the trial site can be corrected by person other than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction. The original of the completed diaries or assessment tools must not be removed from the trial site. The COAs are completed electronically, thus entries at the site-pads are source data and a copy of the entries should be provided to site. The monitor will ensure that the eCRFs are completed and that paper CRFs are collected. Monitors will review the subject's medical records and other source data to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

15 Data management

Data management is the responsibility of Novo Nordisk.

Appropriate measures, including encryption of data files containing personally identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks. Data from central laboratories will be transferred electronically. In cases where data are transferred via non-secure electronic networks, data will be encrypted during transfer.

The subject and any biological material obtained from the subject will be identified by subject number and trial ID. Appropriate measures, such as encryption or leaving out certain identifiers, will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

17 Statistical considerations

Results from the statistical analysis will generally be accompanied by two-sided 95% confidence intervals and two-sided p-values.

Superiority will be claimed if the two-sided p-value is less than 5% and the estimated treatment difference/ratio favours liraglutide 3.0 mg.

Primary endpoints

The two primary endpoints (see Section [4.2.1](#)) are defined as:

- Change in body weight (%) from baseline to week 56
- Proportion of subjects losing at least 5% of baseline body weight at week 56

The primary objective is met if superiority of liraglutide 3.0 mg vs. placebo is demonstrated for each of the primary endpoints.

Definition of primary endpoint: % weight change

Change in body weight (%) from baseline to week 56, denoted % weight change, is calculated as body weight at week 56 minus body weight at baseline divided by body weight at baseline and multiplied by 100; therefore

$$\% \text{ weight change} = \frac{(\text{body weight at week 56} - \text{body weight at baseline})}{\text{body weight at baseline}} \times 100.$$

A negative value of % weight change indicates a body weight loss from baseline to week 56.

Definition of primary endpoint: 5% responders

The proportion of subjects having lost at least 5% of baseline body weight at week 56, denoted 5% responders, is defined as the proportion having

$$\% \text{ weight change} \leq -5\%.$$

A 5% responder is defined as a subject fulfilling this, therefore

$$5\% \text{ responder} = \begin{cases} 1 & \text{if } \% \text{ weight change} \leq -5\% \\ 0 & \text{if } \% \text{ weight change} > -5\% \end{cases}$$

Definition of estimands

Effectiveness estimand

The primary estimand is an effectiveness estimand (*de facto*) quantifying the average treatment effect of liraglutide 3.0 mg relative to placebo 56 weeks after randomisation, as adjunct to reduced caloric diet, increased physical activity and CMS-IBT, in all randomised subjects regardless of adherence to treatment.

Efficacy estimand

A secondary efficacy estimand (*de jure*) is quantifying the average treatment effect of liraglutide 3.0 mg relative to placebo 56 weeks after randomisation, as adjunct to reduced caloric diet, increased physical activity and CMS-IBT, if all randomised subjects had adhered to assigned treatment regimen for the entire duration of the trial.

Effectiveness estimand at week 16

In addition, an effectiveness estimand (*de facto*) is quantifying the average treatment effect of liraglutide 3.0 mg relative to placebo 16 weeks after randomisation, as adjunct to reduced caloric diet, increased physical activity and CMS-IBT, in all randomised subjects regardless of adherence to treatment.

Taxonomy of week 56 assessments being available or missing

A given assessment at week 56 may be available or missing and [Table 17-1](#) defines the taxonomy for this. Note this is done per assessment not per subject, as subjects may belong to different types for different assessments (a subject may have “available on treatment (AT)” for weight but “missing on treatment (MT)” for waist circumference).

Table 17–1 Taxonomy of week 56 assessments being available or missing

| Assessment at week 56 | On drug at week 56 | Type description | Type Abbreviation |
|-----------------------|--------------------|---|-------------------|
| Available | Yes | Available on randomised treatment: Subjects who did not discontinue randomised treatment prematurely. Include those that stop and restart trial product. | AT |
| | No | Available drop-outs: Subjects who discontinued randomised treatment prematurely but returned to have an assessment at week 56; so-called retrieved drop-outs. | AD |
| Missing | Yes | Missing on randomised treatment: Subjects who did not discontinue randomised treatment prematurely. Include those that stop and restart trial product. | MT |
| | No | Missing drop-outs: Subjects who discontinued randomised treatment prematurely and did not return to have an assessment at week 56; so-called non-retrieved drop-outs. | MD |

17.1 Sample size calculation

The sample size calculation is based on the analysis approach addressing the primary estimand for the primary endpoints change in body weight (%) from baseline to week 56 (% weight change) and proportion of subjects losing $\geq 5\%$ of baseline body weight at week 56 (5% responders).

The two primary endpoints will be tested in a hierarchical order.

The study design is a 1:1 randomisation with 282 subjects in total (141 subjects in each arm). Please see [Table 17–2](#) for general specifications on sample size and power calculation.

Table 17–2 General specifications for sample size and power calculation

| Endpoint | Statistical test | Minimum required power (%) |
|-----------------|--|----------------------------|
| % weight change | Two-group Satterthwaite unpooled t test on the mean difference with $\alpha=0.05$ assuming unequal variances | 90.0 (marginal) |
| 5% responders | Pearson chi-square test for two independent proportions with $\alpha=0.05$ | 90.0 (marginal) |

α : two-sided significance level

In the following paragraphs treatment differences and standard deviations (SD) are given without units.

Body weight measurements from returning discontinuing subjects will be used in the primary analysis. But for the sample size calculations, it is assumed that all subjects who discontinue will not return at week 56 and that they have a % weight change like placebo subjects who completed the trial. It is expected that % weight change for liraglutide 3.0 mg subjects who discontinue might be somewhere in between completing placebo subjects and completing liraglutide 3.0 mg subjects. The assumption is thus expected to lead to a conservative effect estimate. In trial NN8022-1839 in non-diabetic subjects and with obesity, around 31% treatment discontinuations were observed in the placebo group, around 25% in the liraglutide 3.0 mg group. The calculated sample size ensures adequate power if the proportion of discontinuing subjects should be as high as 30%.

Based on findings from NN8022-1839, a difference in % weight change between liraglutide 3.0 mg and placebo of -5 (-9% vs. -4%, SD=7) is assumed among completing subjects. For sample size calculation, a common SD of 7 was assumed for completers of liraglutide 3.0 mg or placebo. In NN8022-1839, a SD of 6.65 was seen for % weight change among subjects completing liraglutide 3.0 mg at week 56; 5.88 was observed among subjects completing placebo. Adjusting for 30% discontinuation and using a mixture distribution, a difference of -3.5 is expected in the primary analysis. A sample size of 282 subjects (141 in each arm), gives a marginal power of 98.3%.

For the primary endpoint 5% responders, the expected proportions were calculated based on the same assumptions as above. Adjusting for 30% discontinuation gives an expected 5% responders proportion of 63% in the liraglutide 3.0 mg arm and 44% in the placebo arm. With 282 subjects, this results in a marginal power of 90%.

Given these assumptions, the sample size of 282 subjects (141 in each arm), results in a combined power of 88.5%.

The tests of superiority of liraglutide 3.0 mg to placebo for each of the confirmatory endpoints are performed hierarchically in the order in which the endpoints are presented (see Sections [4.2.1](#) and [4.2.2.1](#)). The two primary endpoints are included in the statistical testing hierarchy, and the primary objective will be met if superiority of liraglutide 3.0 mg vs. placebo is demonstrated for each of the primary endpoints. The test hierarchy is given in [Table 17-3](#) with underlying assumptions, marginal power and effective power. The effective was calculated using a naïve and conservative approach, which assumes no correlation of endpoints by multiplying the respective marginal powers. Assumptions made to calculate the power for the two primary endpoints and all confirmatory secondary endpoints are also presented in [Table 17-3](#).

Table 17–3 Assumptions, marginal power and effective power for each confirmatory endpoint in the hierarchical testing procedure given an anticipated number of 282 randomised subjects

| | Assumed mean (\pm SD) / proportion for completers liraglutide 3.0 mg placebo | | Expected mean (\pm SD) / proportion for liraglutide 3.0 mg # | Expected difference # | Marginal power (%) | Effective power (%) |
|---|---|--------------------|---|-----------------------|--------------------|---------------------|
| % weight change | -9.0 (\pm 7.0) | -4.0 (\pm 7.0) | -7.5 (\pm 7.4) | -3.5 | 98.3 | 98.3 |
| 5% responders | 72% | 44% | 63% | 19% | 90.0 | 88.5 |
| 10% responders | 44% | 20% | 37% | 17% | 90.3 | 79.9 |
| 15% responders | 20% | 6% | 15% | 9% | 75.0 | 59.9 |
| 4% responders at week 16 | 70% | 45% | 63% | 18% | 84.2 | 50.4 |
| WC change | -9.0 (\pm 7.0) | -5.0 (\pm 7.0) | -7.8 (\pm 7.2) | -2.8 | 90.8 | 45.8 |
| sBP change | -5.0 (\pm 13.0) | -3.0 (\pm 13.0) | -4.4 (\pm 13.0) | -1.4 | 14.7 | 6.7 |
| 6MWT change | 8.2 (\pm 12.0) | 5.8 (\pm 12.0) | 7.5 (\pm 12.1) | 1.7 | 21.5 | 1.4 |
| IWQoL-Lite for CT physical change | 16.0 (\pm 18.0) | 11.0 (\pm 18.0) | 14.5 (\pm 18.1) | 3.5 | 36.7 | 0.5 |
| IWQoL-Lite for CT mental/emotional change | 14.0 (\pm 20.0) | 11.0 (\pm 20.0) | 13.1 (\pm 20.0) | 2.1 | 14.2 | 0.1 |

SD standard deviation, sBP systolic blood pressure, WC waist circumference, 6MWT six minutes walking test, IWQoL-Lite for CT Impact of Weight on Quality of Life-Lite for Clinical Trial Version; # Adjusted for 30% discontinuation; Assumptions are based on findings from NN8022-1839.

17.2 Definition of analysis sets

Two analysis sets are defined:

- The *full analysis set* (FAS) includes all randomised subjects according to the intention-to-treat (ITT) principle. Subjects in the FAS will be analysed as randomised.
- The *safety analysis set* includes all randomised subjects exposed to at least one dose of trial drug. Subjects will be analysed as treated.

Any observation excluded from the analysis database will be documented before database lock with the reason for exclusion provided.

17.3 Primary endpoints

The two primary endpoints are as mentioned previously (see start of Section [17](#)):

- % weight change
- 5% responders

17.3.1 Analytical methods addressing the effectiveness estimand for the primary endpoints

These analyses will use the FAS. The analyses of the primary endpoints use baseline body weight and body weight at week 56, and assessments at week 56 may be missing (“missing on treatment [MT]” and “missing drop-outs [MD]”). First, a description of the statistical models for the primary endpoints is given under the assumption of no missing values (i.e. all subjects have body weight measurements at baseline and week 56). Subsequently, handling of missing data is described.

17.3.1.1 Statistical model for the primary endpoint % weight change

The primary endpoint % weight change will be analysed using analysis of covariance (ANCOVA) including the factors and covariates listed in [Table 17–4](#).

Table 17–4 Factors and covariates for the analysis of the primary endpoints

| Factors and covariates at baseline | Type | Categories |
|------------------------------------|-----------|-----------------------------|
| Randomised treatment | Factor | Liraglutide 3.0 mg, placebo |
| Gender | Factor | Male, female |
| BMI (kg/m ²) | Factor | [30,35[, [35,40[, ≥40 |
| Body weight (kg) | Covariate | <i>Not applicable</i> |

The factors and covariates will be included in the model as main effects in an additive structure. The estimated treatment difference between liraglutide 3.0 mg and placebo will be reported together with the associated two-sided 95% CI and corresponding p-value.

The superiority test of liraglutide 3.0 mg vs. placebo will be carried out as follows:

Let $\mu_{\text{liraglutide}}$ and μ_{placebo} denote the true mean of % weight change for liraglutide 3.0 mg and placebo group, respectively. The hypothesis and the alternative are:

H: $\mu_{\text{liraglutide}} \geq \mu_{\text{placebo}}$ against the alternative $H_A: \mu_{\text{liraglutide}} < \mu_{\text{placebo}}$.

The hypothesis will be rejected and superiority claimed, if the upper limit of the estimated two-sided 95% CI of the treatment difference is below 0.

17.3.1.2 Statistical model for the primary endpoint 5% responders

This binary endpoint will be analysed using a logistic regression model. Factors and covariates will be those listed in [Table 17–4](#). The estimated odds ratio (OR) between liraglutide 3.0 mg and placebo will be reported together with the associated two-sided 95% CI and corresponding p-value.

Let $OR_{\text{liraglutide/placebo}}$ denote the true odds ratio between liraglutide 3.0 mg and placebo. The hypothesis and the alternative are:

H: $OR_{\text{liraglutide/placebo}} \leq 1$ against the alternative H_A : $OR_{\text{liraglutide/placebo}} > 1$

The hypothesis will be rejected and superiority claimed, if the lower limit of the estimated two-sided 95% CI is above 1.

17.3.2 Handling of missing values for the effectiveness estimand

17.3.2.1 Handling of missing values at baseline

If an assessment has been made both at screening and randomisation, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment has been made at screening, then the screening value will be used as the baseline value.

17.3.2.2 Handling of missing values at week 56

Missing values at week 56 will be imputed and the relevant endpoints will be derived from the imputed values. Several approaches for imputation of missing values at week 56 will be applied. First, a description of the primary imputation approach used to address the effectiveness estimand for the primary endpoints is given. This is followed by a description of a number of sensitivity analyses.

Primary approach for handling of missing values

The primary approach for multiple imputations of missing values of body weight at week 56 (type MT+MD) for both the liraglutide 3.0 mg and placebo group is by sampling among all available assessments at week 56 in the placebo group (type AT+AD). This approach is also known as jump to reference and makes the assumption that subjects instantly after discontinuation lose any effect of randomised treatment beyond what can be expected from placebo treatment as adjunct to diet and exercise⁵⁵. Body weight measurements at visits between baseline and week 56 are not used for this imputation approach. The multiple imputation approach is done in three steps.

- **Imputation:** Step 1 defines an imputation model based on placebo subjects, which is used to impute missing body weight values at week 56 in both arms. This will be done 100 times

and results in 100 complete data sets. A more detailed explanation of this step is given below.

- **Analysis:** Step 2 analyses each of the 100 complete data sets, using the statistical model defined in Section [17.3.1.1](#) and [17.3.1.2](#), and saves the 100 estimation results.
- **Pooling:** Step 3 integrates the 100 estimation results into a final result using Rubin's formula.

The imputation model in step 1, uses placebo subjects from FAS with non-missing body weight measurements at baseline and week 56. The imputation model is a linear regression of body weight (kg) at week 56 on the factors and covariates listed in [Table 17-4](#) (except randomised treatment) with no interactions. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation model is then used to impute missing week 56 body weight values for both randomised treatment arms.

If 100 copies are not sufficient to establish stable results, a higher number will be used. The multiple imputations will be generated using Novo Nordisk trial number 80224274 as seed number.

Sensitivity analyses of the primary endpoints for the effectiveness estimand

The sensitivity analyses will address the robustness of the primary approach for handling of missing values. In particular the sensitivity analyses address how assumptions on how body weight progresses after discontinuation of randomised treatment impact the estimated treatment difference between liraglutide 3.0 mg and placebo. The sensitivity analyses include the following.

- A multiple imputation approach as described by McEvoy⁵⁶ where missing body weight measurement at week 56 for non-retrieved drop-outs (type MD) are imputed by sampling from values obtained from retrieved drop-outs (type AD) in each randomised treatment arm and according to the timing (monthly) of last available observation (of body weight) on randomised treatment (LAO-OT). Missing body weight measurements at week 56 for subjects on drug treatment (type MT) are imputed by sampling from type AT in the relevant randomised treatment arm. Thus, the imputation model for each randomised treatment arm and timing of LAO-OT is a linear regression of body weight (kg) at week 56 on the factors and covariates listed in [Table 17-4](#) (except randomised treatment arm) with no interactions and LAO-OT of body weight. If timing by month is too restrictive, quarters, half-years, or excluding timing will be used.
- A weighted ANCOVA (wANCOVA) where returning drug discontinuing subjects (AD) are up-weighted relative to their proportion of all drug discontinuing subjects (AD+MD) to account for the subjects not returning for assessments at week 56⁵⁶. Similarly, AT subjects are up-weighted relative to their proportion of all drug continuing subjects (AT+MT). The up-weighting is done by randomised treatment arm and the timing of LAO-OT. Subjects who

are missing the weight measurement at week 56 (MD+MT) are assigned a weight of 0 (zero).

- A single imputation approach as done by Sacks⁵⁷. Missing weight measurement at week 56 for subjects who drop-out (type MD) are imputed using a weight regain rate of 0.3 kg/month after last available observation (LAO) of body weight. Change from baseline is truncated whenever the extrapolation would lead to a positive weight gain relative to baseline. LAO does not need to be the same as LAO-OT as subjects are allowed to come to scheduled visits after discontinuing randomised treatment. When a subject's LAO represents a gain in weight relative to baseline, no additional gain will be imputed, and the unfavourable gain is carried forward to week 56. Missing weight measurement at week 56 for subjects on treatment (type MT) will be imputed using the LAO. The weight regain imputation will be done for both randomised treatment arms. Additionally, a version where only the liraglutide 3.0 mg arm uses the regain rate while the placebo arm uses LAO (corresponding to a weight regain rate of 0 kg/month) will be performed.
- Tipping point analysis. In a similar manner as above for a range of weight regain rates (starting from 0.1 kg/month and in intervals of 0.1 kg/month) for MD in liraglutide 3.0 mg arm will be used to define a tipping point in which superiority of liraglutide 3.0 mg disappears. In this analysis, the placebo arm will be imputed by LAO.

[Figure 17-1](#) and [Table 17-5](#) give an overview of the handling of missing values at week 56 assessments.

Additional sensitivity analyses

Additional analyses will investigate how sensitive the primary statistical models (for primary endpoints) are to the choice of factors and covariates in the model as follows: A model resembling the primary analysis models using the same imputation method (jump to reference) adjusting only for baseline body weight and randomised treatment arm. The imputation model (step 1) will be same as for the primary approach.

For the binary primary endpoint, the risk difference (unadjusted for any factors and covariates) and corresponding 95% CI will also be calculated.

17.3.3 Analysis method addressing the efficacy estimand for the primary endpoints

The efficacy estimand for % weight change will be assessed using a mixed model for repeated measurements (MMRM). The MMRM will use assessments only from subjects who are taking the randomised treatment until end of trial or at first discontinuing of trial drug (either temporarily or permanently). A pause of less than three consecutive days is not regarded as discontinuation for this analysis. This means that assessments at week 56 for retrieved drop-outs (type AD) will be

discarded. The MMRM will be fitted using % weight change and the same factors and covariates ([Table 17-4](#)) as for the primary analyses all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

The efficacy estimand for 5% responders will be assessed using the same MMRM. From the MMRM individually predicted values for % weight change at week 56 will be used to classify each subject as 5% responder or not. This classification will then be analysed using a logistic regression model with treatment as the only factor.

17.3.4 Subgroup analyses for primary endpoints

For the primary estimand, subgroup analyses will be done for the factors listed and categorised as in [Table 17-4](#). For baseline weight, categories based on quartiles will be used. The subgroup analyses will be done separately for each of these by including interaction term(s) with randomised treatment arm in the respective models (ANCOVA or logistic regression).

Figure 17–1 Illustration of imputation approaches for the effectiveness estimand

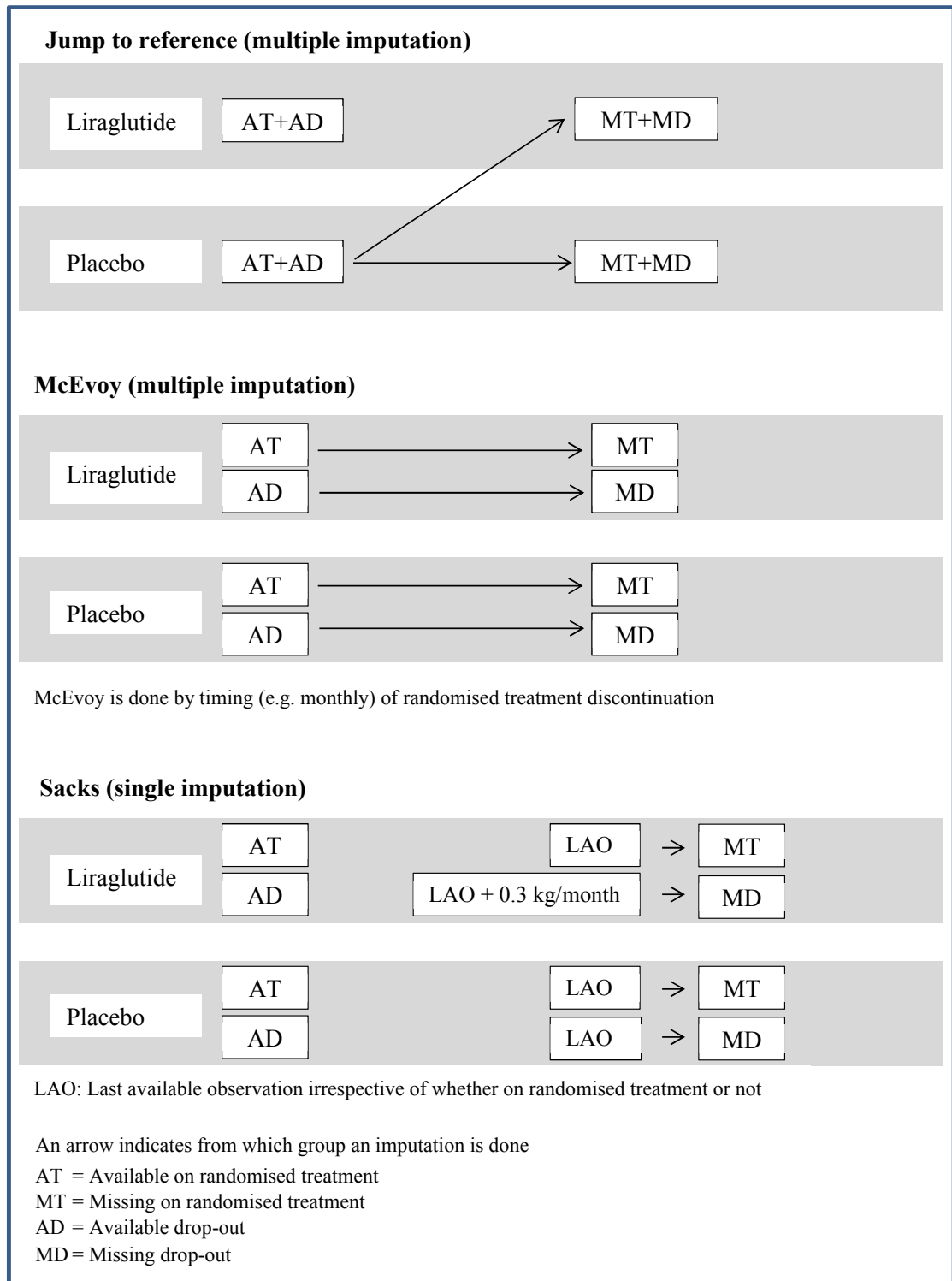


Table 17–5 Overview of handling of missing values

| Approach | Description | Assumptions |
|---|--|---|
| Jump to reference (multiple imputation) | Liraglutide and placebo MT+MD imputed from placebo AT+AD (i.e., all available placebo assessments at week 56) | - Liraglutide MD lose any treatment effect instantly after drop-out - Placebo AT and placebo AD are assumed to have the same weight loss |
| McEvoy (multiple imputation) | Separately for the two randomised treatment arms: MD imputed from AD by matching on time (month) of drop-out MT imputed from AT | - AD is representative of the MD for each randomised treatment arm - AT is representative of the MT for each randomised treatment arm |
| Weighted ANCOVA (wANCOVA) | No imputation. Separately for the two randomised treatment arms: AD subjects are up-weighted relative to their proportion of AD+MD and timing of drop-out AT subjects are up-weighted relative to their proportion of AT+MT | - AD is representative of the MD for each randomised treatment arm - AT is representative of the MT for each randomised treatment arm |
| Sacks (single imputation) | Liraglutide MD imputed by minimum of LAO+0.3 kg and baseline value for each month from drop-out to week 56 and either a) Placebo MD imputed by minimum of LAO+0.3 kg and baseline value for each month from drop-out to week 56 or b) MT (both randomised treatment arms) and placebo MD are imputed by LAO | a) Liraglutide and placebo MD lose any treatment effect linearly after drop-out. b) Only liraglutide MD lose any treatment effect linearly after drop-out. No change in treatment effect since LAO for others. |
| Tipping point (single imputation) | Liraglutide MD imputed by minimum of LAO+X kg (X in steps of 0.1) and baseline value for each month from drop-out to week 56. MT (both randomised treatment arms) and placebo MD are imputed by LAO | Only liraglutide MD lose any treatment effect linearly after drop-out. No change in treatment effect since LAO for others |

AT available on randomised treatment, MT missing on randomised treatment, AD available drop-out, MD missing drop-out, LAO last available observation, LAO-OT last available observation on randomised treatment.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoints

Confirmatory secondary endpoints are listed in Section [4.2.2.1](#).

All confirmatory secondary endpoints, except proportion of subjects losing at least 4% of baseline body weight at week 16, are planned to be assessed at week 56 and will be analysed using the same primary MI approach as used for the primary endpoints and to address the effectiveness estimand. The statistical model for continuous confirmatory secondary endpoints will be ANCOVA with covariates listed in [Table 17-4](#) with baseline body weight replaced by baseline measurement of endpoint to be analysed. Binary confirmatory secondary endpoints will be analysed using logistic regression in the same way as for 5% responders.

The effectiveness estimand at week 16 will be assessed using the confirmatory secondary endpoint of proportion of subjects losing at least 4% of baseline body weight at week 16. Subjects with missing values for weight at week 16 will be considered non-responders.

Sensitivity analyses will be carried out for all confirmatory secondary endpoints, except for proportion of subjects losing at least 4% of baseline body weight at week 16. See [Table 17-6](#) for details on planned analysis methods, multiple imputation approach and sensitivity analyses.

The efficacy estimand will also be assessed for confirmatory secondary endpoints, except for proportion of subjects losing at least 4% of baseline body weight at week 16, using MMRM as described for the primary endpoints.

17.4.2 Description of the hierarchical testing procedure to address the effectiveness estimand for primary and confirmatory secondary endpoints

The tests of superiority of liraglutide 3.0 mg to placebo for each of the endpoints are tested in a hierarchical manner in the order in which the endpoints are presented. The two primary endpoints are included in the statistical testing hierarchy below, even though the primary objective will only be met if superiority of liraglutide 3.0 mg vs. placebo is demonstrated for each of the primary endpoints. The test hierarchy is given in [Table 17-6](#). The first endpoints to be tested are all assessing aspects of weight loss (e.g., relative change in body weight, achieving a certain magnitude of weight loss, and change in waist circumference); these endpoints are followed by endpoints assessing change in weight-related comorbidities and/or consequences of excess body weight and 'feeling and function' indicators.

Table 17–6 Hierarchical order and type of statistical method to address the effectiveness estimands for primary and confirmatory secondary endpoints

| Test order | Endpoint | Endpoint Type | Statistical model | MI approach | Sensitivity analyses # |
|---|---|---------------|---------------------|---|--|
| Primary endpoints | | | | | |
| 1 | Change in body weight (%) from baseline to week 56 | Continuous | ANCOVA | Jump to reference | McEvoy wANCOVA Sacks Tipping point Unadjusted ANCOVA |
| 2 | Proportion of subjects losing at least 5% of baseline body weight at week 56 | Binary | Logistic Regression | Jump to reference | McEvoy Sacks Tipping point Risk difference |
| Confirmatory secondary endpoints | | | | | |
| 3 | Proportion of subjects losing more than 10% of baseline body weight at week 56 | Binary | Logistic Regression | Jump to reference | McEvoy Tipping point |
| 4 | Proportion of subjects losing more than 15% of baseline body weight at week 56 | Binary | Logistic Regression | Jump to reference | McEvoy Tipping point |
| 5 | Proportion of subjects losing at least 4% of baseline body weight at week 16 (addresses the effectiveness estimand for week 16) | Binary | Logistic Regression | Not needed, as subjects with missing body weight values at week 16 will be considered non-responders. | |
| 6 | Change from baseline to week 56 in waist circumference (cm) | Continuous | ANCOVA | Jump to reference | McEvoy wANCOVA Tipping point |
| 7 | Change from baseline to week 56 in systolic blood pressure (sBP) (mmHg) | Continuous | ANCOVA | Jump to reference | McEvoy wANCOVA Tipping point |
| 8 | Change in six-minute walking distance (m) from baseline to week 56 | Continuous | ANCOVA | Jump to reference | McEvoy wANCOVA Tipping point |
| 9 | Change in total quality of life score from baseline to week 56 as assessed by IWQoL-Lite | Continuous | ANCOVA | Jump to reference | McEvoy wANCOVA Tipping point |
| 10 | Change in physical function score from baseline to week 56 as assessed by IWQoL-Lite | Continuous | ANCOVA | Jump to reference | McEvoy wANCOVA Tipping point |

MI Multiple Imputation;

See [Table 17–5](#).

17.4.3 Supportive secondary endpoints

17.4.3.1 Efficacy endpoints

Supportive secondary efficacy endpoints addressing the secondary efficacy objectives are listed in Section [4.2.2.2](#).

Secondary endpoints addressing the first of the secondary efficacy objectives

Supportive secondary endpoints will be evaluated to address the effectiveness estimand. These endpoints will be analysed using the same MI approach as used for the primary and confirmatory endpoints and to address the effectiveness estimand.

The statistical model for continuous endpoints will be ANCOVA with covariates listed in [Table 17-4](#) with baseline body weight replaced by baseline measurement of endpoint to be analysed. The statistical model for proportions will be analysed using logistic regression.

Secondary endpoints addressing the second of the secondary efficacy objectives

Adherence, used both as an endpoint and as a factor for weight loss will be investigated in an exploratory manner. In addition to the adherence definitions, analyses and displays presented below, alternative definitions, analyses and displays may be made if deemed relevant. These will be described as post-hoc analyses when reporting the trial.

- Adherence to trial product is defined as at least one administration of trial product per week
- Adherence to caloric diet is defined as at least one food diary entry for five days per week
- Adherence to physical activity is defined as at least 50% of the target minutes per week
- Adherence to caloric diet and physical activity is defined as being adherent to both caloric diet and physical activity
- Adherence to trial product, caloric diet and physical activity is defined as being adherent to all three randomised trial product, caloric diet and physical activity

Number of weeks adherent to treatment will be analysed by fitting a regression model for count data (e.g. negative binomial) with factors and covariates listed in [Table 17-4](#).

Further, the association of adherence to trial product, caloric diet and/or physical activity with relative change of body weight will be explored across the total planned treatment duration. For that purpose, the following variables will be derived: First, the total treatment period (from randomisation to end-of-treatment visit) will be divided into four periods (each e.g. 12 (visit 2 to 10), 12 (visit 10 to 16), 16 (visit 16 to 20) and 16 (visit 20 to 24) weeks). Second, number of weeks adherent to trial product, caloric diet or physical activity during each of the four periods will be divided by total number of weeks of the respective period. Then, MMRM will be performed

including randomised treatment, BMI, gender, baseline body weight, period, normalised adherence to trial product, caloric diet and physical activity as factors and covariates as well as the interaction terms between randomised treatment, period and normalised adherence to trial product, caloric diet and physical activity.

In addition, relative change of body weight will be summarized descriptively stratified by visits and different adherence categories, which will be defined based on the distribution of observed data.

Exploratory analysis of week 16 responders

In this exploratory analysis, subjects who lost $\geq 4\%$ of their baseline body weight at week 16 after randomisation are considered as ‘week 16 responders’. Subjects who lost $< 4\%$ of their baseline body weight at week 16 after randomisation are considered as ‘week 16 non-responders’. Hence, four ‘week 16 response’ groups can be defined:

1. $\geq 4\%$ weight loss at 16 weeks (liraglutide 3.0 mg)
2. $< 4\%$ weight loss at 16 weeks (liraglutide 3.0 mg)
3. $\geq 4\%$ weight loss at 16 weeks (placebo)
4. $< 4\%$ weight loss at 16 weeks (placebo)

The change in body weight (%) from baseline to week 56 will be explored among the four ‘week 16 response’ groups based on descriptive statistics only. Since the comparisons of the four ‘week 16 response’ groups are influenced by post-randomisation factors, no formal testing will be done.

17.4.3.2 Safety endpoints

Descriptive statistics for all safety endpoints will be provided with the aim to compare liraglutide 3.0 mg and placebo. All analyses and tabulations will be done using the safety analysis set. Unless otherwise stated, no formal statistical analyses are planned for the safety endpoints.

Adverse events

AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be presented based on system organ class, high level group term and preferred terms.

Adverse events will be classified and analysed as ‘in trial’ and ‘on drug’ defined in terms of patient years of observation (PYO) and patient years of exposure (PYE), respectively. For each subject, PYO is defined as number of days from date of randomisation until and including date of follow-up visit or date of last contact. For each subject PYE is defined as time intervals of exposure to trial drug including an ascertainment window of 14 days for each exposure interval.

AEs, which occurred while the subject was in trial or on drug will be summarised descriptively, whereas AEs, which occurred before first exposure to trial drug or after the follow-up visit will only be presented in listings. AEs will be displayed in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). Furthermore, AEs will be summarised by seriousness, severity, relation to trial drug, premature treatment discontinuation due to AE and outcome.

Summary tables by system organ class, high level group term and preferred term will be made for all AEs, SAEs, AEs possibly or probably related to trial drug, severe AEs, AEs occurring in at least 5% of the subjects in any arm, and AEs occurring in at least 1% of the subjects in any treatment arm.

AEs requiring completion of specific event forms will be presented in tables and listings. In addition, time to occurrence of these AEs will be presented in cumulative incidence plots.

Physical examination

Outcome of the physical examination at screening and change in the physical examination category at week 56 will be summarised in tables.

Pulse

Pulse (beats/min) at baseline and change of pulse at week 56, will be summarised in tables by week and treatment. Additionally, categories based on the maximum change from baseline until week 56 (>0, >5, >10, >20 beats/min) and categories based on the maximum value until week 56 (>80, >90, >100 beats/min) will be included in summary tables. Additionally, change in pulse from baseline to week 56 will be evaluated in the trial observation period similar to the primary analysis for the primary estimand but using the safety analysis set.

ECG

Shifts in the ECG category from screening to week 56 will be summarised in tables.

Laboratory measurements

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

Laboratory safety parameters are measured throughout the trial and comprise haematology and biochemistry as defined in the flow chart.

The distribution of each continuous laboratory parameter will be presented using box plots by treatment and week. Continuous laboratory parameters will be compared to the relevant reference ranges and results will be presented.

Amylase and lipase

Shifts from baseline to highest value in trial period to UNL, 2xUNL and 3xUNL will be summarised in tables.

Mean plots, geometric mean plots and box plots by gender, visit and treatment will be prepared. Change from week 0 to week 56 will also be presented by empirical distribution plots.

Number and percentage of subjects with amylase and lipase levels \geq UNL, \geq 2xUNL or \geq 3xUNL will be tabulated by week and treatment. Subjects with values \geq 2xUNL will additionally be presented with spaghetti plots.

Additionally, change in amylase and lipase from baseline to week 56 will be evaluated in the in trial observation period similar to the primary analysis for the primary estimand but using the safety analysis set.

Calcitonin

Number, percentage and incidence of subjects with persistent (all post-baseline measurements) and incidental (at least one post-baseline measurement) increases in calcitonin for the criteria below will be tabulated for all subjects, males and females.

- From baseline $<$ UNL to \geq UNL
- From baseline $<$ UNL to \geq 20 ng/L
- From baseline $<$ UNL to \geq 50 ng/L
- From baseline $<$ 20 ng/L to \geq 20 ng/L
- From baseline $<$ 50 ng/L to \geq 50 ng/L

Number and percentage of subjects with calcitonin levels \geq UNL, \geq 1.5xUNL or \geq 20 ng/L and \geq 50 ng/L will be tabulated by visit and treatment.

A summary table showing number and percentage of observations $<$ and \geq LLOQ, minimum, Q25, median, Q75, maximum and geometric mean will be prepared by gender, visit and treatment.

The distribution of the calcitonin values across treatment group and time will be shown in plots by gender and total actual levels. Geometric means will be plotted by visit and treatment in order to assess the pattern of the longitudinal changes.

In addition, a scatter plot of baseline vs. maximum post-baseline calcitonin value will be prepared.

Longitudinal changes with calcitonin \geq 20ng/L will be evaluated with spaghetti plots.

Subjects with at least one post-baseline calcitonin value above 20 ng/L will be listed.

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UTN: U1111-1177-5059
EudraCT no.: 2015-005592-24

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| Version: | 4.0 | |
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The listings will include treatment, age, gender, smoking habits at baseline, risk factor information (use of relevant concomitant medication at time of assessment [proton pump inhibitors and H2 blockers] and medical history of thyroid disorder) and calcitonin values.

18 Ethics

18.1 Benefit-risk assessment of the trial

The trial will be conducted in compliance with ICH GCP [1](#), applicable regulatory requirements and in accordance with the Declaration of Helsinki [2](#).

Risks and precautions

The sections below describe identified and potential risks associated with liraglutide treatment. The identified/potential risks are based on findings in non-clinical and clinical trials with liraglutide as well as other GLP-1 RAs. For each of these risks, mitigating actions have been implemented to minimise the risks for subjects enrolled in this trial.

Neoplasms

Subjects with overweight and obesity have an increased risk of certain types of cancer. In the clinical development programme for liraglutide 3.0 mg, the reporting rate of neoplasm events confirmed by external independent event adjudication committee was similar with liraglutide and placebo. Thus, the overall risk of neoplasms and cancer in the weight management trials was low and balanced between treatment groups.

Thyroid C-cell tumours

Liraglutide causes thyroid C-cell tumours (MTC) at clinically relevant exposures in both genders of rats and mice. Studies in mice demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the rearranged during transfection (RET) protooncogene in thyroid C-cells. Human relevance of thyroid C-cell tumours in mice and rats is unknown and has not been determined by clinical or nonclinical studies. Data from the intensive monitoring of calcitonin (a marker for MTC) in plasma in the liraglutide clinical development programme, do not support an effect of liraglutide on calcitonin levels in humans. As a precaution subjects with personal or family history of MTC, or MEN2 will not be enrolled in the trial. Calcitonin will be monitored as per flow chart, see Section [2](#). Subjects with elevated calcitonin (≥ 100 ng/L) will be discontinued on liraglutide 3.0 mg and appropriate clinical follow-up will be initiated, see [Appendix A](#).

Breast and colon tumours

Based on a limited number of reports in the clinical development programme for liraglutide 3.0 mg, a numerical imbalance was observed for events of breast neoplasms in females and colorectal adenomas in males. There were too few cases to determine whether these cases were related to liraglutide. In addition, there are insufficient data to determine whether liraglutide has an effect on pre-existing breast neoplasia. Two positively adjudicated cases of malignant colorectal carcinoma were reported in liraglutide-treated subjects and none in placebo-treated subjects.

Heart rate increase

In the clinical development programme, mean increase in resting heart rate (by 2-3 beats per minute) as well as a slight decrease in systolic blood pressure has been observed. The long-term clinical effects of the increase in resting heart rate have not been established. There is no indication that the effect on resting heart rate is dose dependent and the increase in heart rate disappears upon treatment discontinuation. When initiating treatment with liraglutide 3.0 mg, heart rate should be monitored at regular intervals consistent with usual clinical practice.

Allergic reactions

As in the case with all protein-based pharmaceuticals, treatment with liraglutide may evoke allergic reactions. These may include urticaria, rash, pruritus as well as anaphylactic reactions. As a precaution, subjects with known or suspected hypersensitivity to trial product(s) or related products will not be enrolled in the trial. In addition, subjects will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction occurs

Pancreatitis

An association between the use of GLP-1RAs and pancreatitis has been suggested based on case reports received in clinical trials and during the post-marketing experience with liraglutide (in T2DM) and other GLP-1RAs. Few events of pancreatitis have been reported in clinical trials with liraglutide in weight management. After initiation of liraglutide 3.0 mg, subjects must be observed carefully for signs and symptoms of pancreatitis (see Section [8.8.1](#)). If pancreatitis is suspected, liraglutide 3.0 mg should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, liraglutide 3.0 mg should not be restarted. Subjects with a history of pancreatitis are excluded from participation in the trial.

Acute gallstone disease

Cases of gallstones (cholelithiasis) and inflammation of the gallbladder (cholecystitis) were reported more commonly in adult subjects treated with liraglutide 3.0 mg compared to placebo in the clinical development programme for liraglutide 3.0 mg. From literature, it is well-known that obesity carries an increased risk of cholelithiasis and that an association between rapid and/or marked weight loss and the development of cholelithiasis is present⁵⁸. If cholelithiasis is suspected, treatment should be discontinued and gallbladder examination and appropriate clinical follow-up should be initiated.

Gastrointestinal adverse events

The most frequently reported adverse events in subjects treated with liraglutide 3.0 mg were gastrointestinal (nausea and diarrhoea), with onset during the first weeks; these were mostly mild to moderate, and transient. Other gastrointestinal adverse events (GI AEs) included: dyspepsia, vomiting, constipation, and abdominal pain. Clinical trials have indicated that a low starting dose

with gradual dose escalation diminishes GI AEs compared with more aggressive dosing regimens. If subjects do not tolerate an increased dose during dose escalation, dose escalation may be delayed for approximately one additional week.

Renal impairment

GLP-1 RAs may cause nausea, vomiting or diarrhoea leading to loss of fluids (dehydration). Dehydration may cause renal impairment and acute renal failure. Subjects treated with liraglutide 3.0 mg should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Benefits

In the present trial, subjects will be treated with a regimen anticipated to be better than or equal to the weight management they receive at the time of entry into the trial. In the clinical development programme, approximately 2/3 of the subjects lost more than 5% of their initial body weight and approximately 1/3 lost more than 10% of their initial body weight. Even a modest weight loss decreases the risk of type 2 diabetes mellitus (T2DM), hypertension and premature cardio-vascular death in patients with obesity (see Section 3.1). Furthermore, improvements in patient reported health-related quality of life and physical function have been observed with weight loss. Although subjects will have to spend time on site visits and procedures required by trial participation, it is expected that all subjects (including those subjects randomised to placebo) will benefit from the behavioural counselling and increased physical activity, with close follow-up of their obesity and a careful medical examination. All of which will result in an intensified management of their obesity.

Conclusion

Necessary precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of participation in the trial. These precautions include thorough information regarding the correct administration of the trial products and gradual dose adjustment. It is important to note that the target population for liraglutide 3.0 mg is already at serious risk from obesity and its associated major co-morbidities. The overall efficacy and safety results from the weight management programme demonstrated that the benefit-risk balance is in favour of liraglutide 3.0 mg, as an adjunct to a reduced-calorie diet and increased physical activity, within the investigated population of subjects with overweight and obesity.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP ¹ and the requirements in the Declaration of Helsinki².

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand. This includes the use of an impartial witness where required according to local requirements.

The subjects must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products. A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

The investigator must ensure the subject has ample time to come to a decision whether or not to participate in the trial. The responsibility for 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. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

The responsibility for 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. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the investigator must inform the subject in a timely manner, and a revised written subject information must be provided and a new informed consent must be obtained.

18.3 Data handling

If the subject withdraws from the trial or is lost to follow-up, then the subject's data will be handled as follows:

- Data already collected and any data collected at the end-of-trial visit including follow-up visits will be retained by Novo Nordisk, entered into the database and used for the CTR.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data are used, it will always be in accordance with local regulations and IRBs/IECs.

18.4 Information to subjects during trial

During the trial, the subjects may receive information that could include a “welcome to the trial letter”, newsletter(s) and a “thank you for your participation letter” after completion of the trial, if locally acceptable.

Initiatives for subject retention will be instituted for this trial. These may include retention activities, materials and items, if locally acceptable. The retention items will be relevant for the subjects’ participation in the trial and/or their obesity and will not exceed local fair market value.

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

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If the trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of subjects who have participated in the trial. If it has an impact, the actions needed to inform and protect the subjects should be described.

19 Protocol compliance

19.1 Protocol deviations

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor 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. Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

19.2 Prevention of missing data

Considerable effort must be made by the investigator to avoid missing data, including minimising the number of subjects withdrawing from the trial.

The importance of subject retention will be addressed by Novo Nordisk in the training and communication with the trial sites. The subjects will be carefully informed about the trial procedures before signing informed consent, so that they are fully aware of the implications of participating in the trial.

Measures will be implemented during trial conduct to encourage subjects to complete the trials; these will be described in detail in trial specific retention mitigation plans and may include subject newsletters, appreciation items and various local initiatives.

For subjects discontinuing treatment, the investigator should encourage continued attendance to the CMS-IBT visits until the primary outcome measure at 56 weeks. Furthermore, re-initiation of treatment is allowed at the discretion of investigator, as described (Section [8.1](#)).

Surveillance of subject retention will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial product or withdrawal of consent to initiate mitigations as needed in collaboration with the trial sites.

20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

Before a trial site is allowed to start screening subjects, written notification from Novo Nordisk must be received and the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of investigator's brochure, SmPC or similar labelling as appropriate
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

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

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP¹ applicable regulatory requirements and the Declaration of Helsinki²

By signing the protocol agreement, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 Responsibilities

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

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

The investigator will follow instructions from Novo Nordisk when processing data.

The investigator is responsible for filing essential documents (i.e., those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents including the subject identification code list must be kept in a secure locked facility, so no unauthorized 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. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

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

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

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

23 Reports and publications

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

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

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

One investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications⁵⁹.

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure⁴⁰.

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example, when the CTR is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

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

In all cases, the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

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

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors⁵⁹ (sometimes referred to as the Vancouver Criteria).

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

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 Investigator access to data and review of results

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

24 Retention of clinical trial documentation

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

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g., the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

The files from the trial site/institution must be retained for 15 years after end of trial as defined in Section [7](#), or longer if required by local regulations or Novo Nordisk. In any case, trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to investigator's brochure, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the CTR synopsis to the IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the subjects.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities

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

26 Indemnity statement

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

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

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Appendix A

NN8022-4274

Monitoring of calcitonin

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Background

Treatment with GLP-1 receptor agonists has shown to be associated with thyroid C-cell changes in rodents but not in non-human primates. The human relevance of this finding is unknown. However, based on the findings in rodents, monitoring of serum calcitonin (a sensitive biomarker for C-cell activation) is currently being performed in clinical trials with liraglutide.

While there is general agreement on the clinical interpretation of substantially elevated calcitonin levels (greater than 100 ng/L) is likely indicative of C-cell neoplasia; the interpretation of values between upper normal range (5.0 and 8.4 ng/L for women and men, respectively) and 100 ng/L is less clear with regards to indication of the neoplasia.

There are several known confounding factors affecting calcitonin levels, e.g.:

- renal dysfunction
- smoking
- autoimmune thyroiditis
- several drug classes (e.g. proton pump inhibitors, beta-blockers, H₂-blockers and glucocorticoids)

Physiology of C-cell activation in various clinical conditions and in different patient populations (i.e. with various co-morbidities) is poorly understood. There may be various clinical conditions not identified so far which mildly or moderately affect calcitonin secretion by C-cells.

1 Calcitonin monitoring

A blood sample will be drawn at pre-specified trial visits for measurement of calcitonin.

In case a subject has a calcitonin value ≥ 10 ng/L, the algorithm outlined below should be followed. The algorithm applies for all calcitonin values including screening values.

Please report clinically significant abnormal values as an adverse event (see Section 12 in the protocol).

1.1 Calcitonin ≥ 100 ng/L

Action: The subject (even if a screen failure) must immediately be referred to a thyroid specialist for further evaluation and the trial product must be discontinued (see protocol section 6.5 premature discontinuation of trial product). The subject can remain in the trial; however, all suspected medications must be discontinued until diagnosis has been established.

Background: These values were found in 9 (0.15%) of a population of 5817 patients with thyroid nodular disease.¹ All of these patients were diagnosed with MTC resulting in a positive predictive value of 100 %.

Diagnostic evaluation should include:

- thyroid ultrasound
- fine needle aspiration of any nodules >1 cm
- potentially surgery with neck dissection

In case a subject is diagnosed with MTC, it is common clinical practice to explore the family history of MTC or MEN2 and perform a genetic test for RET proto-oncogene mutation.

1.2 Calcitonin ≥ 50 and < 100 ng/L

Action: The subject (even if a screen failure) must be referred to a thyroid specialist for further evaluation. The subject can remain in the trial and continue on trial product.

Background: These values were found in 8 (0.14%) of the population of 5817 patients with thyroid nodular disease.¹ Two of these subjects were diagnosed with MTC and two were diagnosed with C-cell hyperplasia, resulting in a positive predictive value of a C-cell anomaly of 50%.

Diagnostic evaluation should include:

- thyroid ultrasound examination
- if available and there are no contraindication, a pentagastrin stimulation test. Subjects with positive pentagastrin stimulation tests should be considered to undergo surgery

- if pentagastrin is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information about the need for surgery.

1.3 Calcitonin ≥ 10 and <50 ng/L

Action: The subject can continue in the trial on trial product. Continue sampling of calcitonin according to the protocol.

If the subject is a screen failure, or if the value is from the last sample taken in the trial, the subject should be referred to a thyroid specialist for further evaluation.

Background: Calcitonin values from 20-50 ng/L were found in up to 1% of subjects of the population of 5817 patients with thyroid nodular disease.¹ The predictive value of a C-cell anomaly for this calcitonin level was 8.3%. However, the likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.

For calcitonin values 10-20 ng/L Costante et al¹ identified 216 (3.7%) patients. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin of 33 ng/L, and had C-cell hyperplasia at surgery. Two other studies used a cut-off of CT > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT >10 and <20 ng/L to allow conclusions^{2,3}

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Liraglutide 3.0 mg
Trial ID: NN8022-4274
Clinical Trial Report
Appendix 16.1.1

~~CONFIDENTIAL~~

Date:
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Novo Nordisk

Global and country key Novo Nordisk staff

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff

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Novo Nordisk

Protocol Amendment

no 1

**to Protocol, version 4.0
dated 14 September 2016**

Trial ID: NN8022-4274

SCALE™ IBT

**Effect and safety of liraglutide 3.0 mg as an adjunct to intensive behaviour therapy for obesity
in a non-specialist setting**

Trial phase: 3b

Applicable to all countries

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1 Introduction including rationale for the protocol amendment

Rationale for the changes:

- To reflect the outcome of the Impact of Weight on Quality of Life-Lite for Clinical Trials (IWQoL-Lite for CT) questionnaire validation and the recommendations from regulatory authorities to include the Short-form 36 (SF-36) questionnaire as a confirmatory secondary endpoint; the endpoint section and statistical hierarchy have been updated.
- Due to the low power to demonstrate a difference between active treatment and placebo, systolic blood pressure has been added as a supportive secondary endpoint and removed as a confirmatory secondary endpoint.
- To reflect the degree of uncertainty, the six minute walking distance test (6MWT) has been moved to the bottom of the statistical hierarchy.
- Minor edits to Flow chart for clarity and accuracy.

In this protocol amendment:

- Any new text is written *in italics*.
- Any text deleted from the protocol is written using ~~strike through~~.
- Any new text in the Flow chart is written in *italics* and highlighted with yellow

2 Changes

2.1 Section 1 Key secondary endpoints

Change from baseline to week 56 in:

- Waist circumference (cm)
- ~~Systolic blood pressure (mmHg)~~
- ~~Six minutes walking distance (m)~~
- *Short Form-36 (SF-36) v2.0 acute, physical functioning score*
- Impact of Weight on Quality of Life-Lite for Clinical Trial Version (IWQoL-Lite for CT), physical functioning domain (5-items) score
- ~~IWQoL-Lite for CT, mental/emotional functioning score~~
- *Six minute walking distance test (m)*

2.3 Section 4.2.2.1 Confirmatory secondary endpoints

Confirmatory secondary endpoints addressing the first and second of secondary objectives:

- Proportion of subjects losing more than 10% of baseline body weight at week 56
- Proportion of subjects losing more than 15% of baseline body weight at week 56
- Proportion of subjects losing $\geq 4\%$ of baseline body weight at week 16

Change from baseline to week 56 in:

- Waist circumference (cm)
- ~~Systolic blood pressure (mmHg)~~
- ~~Six minutes walking distance (m)~~
- *Short Form-36 (SF-36) v2.0 acute, physical functioning score*
- Impact of Weight on Quality of Life-Lite for Clinical Trial Version (IWQoL-Lite for CT), physical functioning domain (5-items) score
- ~~IWQoL-Lite for CT, mental/emotional functioning score~~
- *Six minute walking distance test (m)*

2.4 Section 4.2.2.2 Supportive secondary endpoints

Change from baseline to week 56 in:

- HbA_{1c} (%)
- Fasting plasma glucose (mg/dL)
- *Systolic blood pressure (mmHg)*
- Diastolic blood pressure (mmHg)
- Lipids (total cholesterol [TC], low density lipoprotein cholesterol [LDL cholesterol], high density lipoprotein cholesterol [HDL cholesterol], very low density lipoprotein cholesterol [VLDL cholesterol], triglycerides [TG], free fatty acids [FFA])
- ~~Short Form-36 v2.0 acute (SF-36) (physical component summary (PCS), mental component summary (MCS) and subdomains)~~
- *SF-36 v2.0 acute:*
 - *role-physical score*
 - *bodily pain score*
 - *general health score*
 - *vitality score*
 - *social functioning score*
 - *role-emotional score*
 - *mental health score*
 - *physical component summary (PCS)*
 - *mental component summary (MCS)*

- *IWQoL-Lite for CT*
 - *pain/discomfort domain score*
 - *psychosocial domain score*
 - *total score*
- Weight related sign and symptom (WRSS) measure, total score

~~Proportion of subjects with the following at week 56:~~

Subjects who after 56 weeks achieve (yes/no):

- ≥ 4.3 T-score points increase from baseline in SF-36 physical functioning score
- ≥ 2 3.8 T-score points increase from baseline in SF-36 PCS
- ≥ 3 4.6 T-score points increase from baseline in SF-36 MCS
- Responder definition value for IWQoL-Lite for CT physical function domain (5-items) score

2.5 Section 8.5.2 Laboratory assessments for safety

Biochemistry

*If TSH levels are out of normal range, the investigator must perform additional testing:

- Total and free T3 and T4 and Free Thyroid Thyroxine Index
- Thyroid peroxidase antibodies

2.6 Section 17.1 Sample size calculation

Table 17.3 Assumptions, marginal power and effective power for each confirmatory endpoint in the hierarchical testing procedure given an anticipated number of 282 randomised subjects

| | Assumed mean (\pm SD) / proportion for completers liraglutide 3.0 mg placebo | | Expected mean (\pm SD) / proportion for liraglutide 3.0 mg # | Expected difference # | Marginal power (%) | Effective power (%) |
|---|--|--------------------|--|-----------------------|--------------------|---------------------|
| % weight change | -9.0 (\pm 7.0) | -4.0 (\pm 7.0) | -7.5 (\pm 7.4) | -3.5 | 98.3 | 98.3 |
| 5% responders | 72% | 44% | 63% | 19% | 90.0 | 88.5 |
| 10% responders | 44% | 20% | 37% | 17% | 90.3 | 79.9 |
| 15% responders | 20% | 6% | 15% | 9% | 75.0 | 59.9 |
| 4% responders at week 16 | 70% | 45% | 63% | 18% | 84.2 | 50.4 |
| WC change | -9.0 (\pm 7.0) | -5.0 (\pm 7.0) | -7.8 (\pm 7.2) | -2.8 | 90.8 | 45.8 |
| sBP change | -5.0 (\pm 13.0) | -3.0 (\pm 13.0) | -4.4 (\pm 13.0) | -1.4 | 14.7 | 6.7 |
| 6MWT change | 8.2 (\pm 12.0) | 5.8 (\pm 12.0) | 7.5 (\pm 12.1) | 1.7 | 21.5 | 1.4 |
| SF-36 PF | 3.7 (\pm 8.0) | 2.4 (\pm 8.0) | 3.3 (\pm 8.0) | 0.9 | 15.8 | 7.2 |
| IWQoL-Lite for CT physical change IWQoL-Lite for CT PF | 16.0 (\pm 18.0) | 11.0 (\pm 18.0) | 14.5 (\pm 18.1) | 3.5 | 36.7 | 0.5-2.7 |
| IWQoL-Lite for CT mental/emotional change | 14.0 (\pm 20.0) | 11.0 (\pm 20.0) | 13.1 (\pm 20.0) | 2.1 | 14.2 | 0.1 |
| 6MWT change | 8.2 (\pm 12.0) | 5.8 (\pm 12.0) | 7.5 (\pm 12.1) | 1.7 | 21.5 | 0.6 |

SD standard deviation, sBP systolic blood pressure, WC waist circumference, 6MWT six minutes walking test, SF-36 PF Short Form-36 v2.0 acute physical functioning score, IWQoL-Lite for CT PF Impact of Weight on Quality of Life-Lite for Clinical Trial Version Physical function domain (5- items) score, IWQoL-Lite for CT Impact of Weight on Quality of Life-Lite for Clinical Trial Version, 6MWT six minute walking distance test;

Adjusted for 30% discontinuation;

Assumptions are based on findings from NN8022-1839

2.7 Section 17.4.2 Description of the hierarchical testing procedure to address the effectiveness estimand for primary and confirmatory secondary endpoints

Table 17.6 Hierarchical order and type of statistical method to address the effectiveness estimands for primary and confirmatory secondary endpoints

| Test order | Endpoint | Endpoint Type | Statistical model | MI approach | Sensitivity analyses # |
|---|---|---------------|-------------------|-------------------|------------------------------------|
| Confirmatory secondary endpoints | | | | | |
| 7 | Change from baseline to week 56 in systolic blood pressure (sBP) (mmHg) | Continuous | ANCOVA | Jump to reference | McEvoy wANCOVA Tipping point |
| 87 | Change in six minute walking distance (m) from baseline to week 56 Change from baseline to week 56 in Short Form-36 (SF-36) v2.0 acute physical functioning score | Continuous | ANCOVA | Jump to reference | McEvoy wANCOVA Tipping point |
| 98 | Change in total quality of life score from baseline to week 56 as assessed by IWQoL-Lite Change from baseline to week 56 in impact of Weight on Quality of Life-Lite (IWQoL-Lite for CT), physical function domain (5-items) score | Continuous | ANCOVA | Jump to reference | McEvoy wANCOVA Tipping point |
| 109 | Change in physical function score from baseline to week 56 as assessed by IWQoL-Lite Change in six minute walking distance test (m) from baseline to week 56 | Continuous | ANCOVA | Jump to reference | McEvoy wANCOVA Tipping point |