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Clinical Study Protocol	
EudraCT No.	2019-004545-32
Investigational Medicinal Product	EMP16-02
Sponsor study code	EP-002
Protocol Version and Date	Final version 3.0; 12NOV2020

Lean Efficacy Phase IIa Proof of concept trial (LEAAP)
A multi-centre, double-blind, placebo-controlled, randomised study in overweight and obese patients during twenty-six weeks, investigating the effect of EMP16-02 on body weight, safety and clinical biomarkers

Phase	IIa
Indication	Overweight and obesity
Test product and dose	EMP16-02 in two doses: • 120 mg orlistat/40 mg acarbose • 150 mg orlistat/50 mg acarbose
Unique ingredient identifier (UNII)	95M8R751W8/T58MSI464G
Sponsor signatory	Arvid Söderhäll, PhD Empros Pharma AB Fogdevreten 2 SE-171 65 Solna
Coordinating Investigator	Helena Litorp, MD PhD CTC Clinical Trial Consultants AB Dag Hammarskjölds väg 10B SE-752 37 Uppsala, Sweden
Clinical study conduct and management	CTC Clinical Trial Consultants AB Dag Hammarskjölds väg 10B SE-752 37 Uppsala, Sweden CTC Clinical Trial Consultants AB Uppsala University Hospital, Entrance 85, 2nd level SE-751 85 Uppsala, Sweden CTC Clinical Trial Consultants AB Brigadgatan 26 SE-587 58 Linköping, Sweden

The following amendments have been made to the first regulatory approved version of this Clinical Study Protocol (version 2.0):

Type of change (Substantial amendment/ non-substantial amendment)	**Summary of changes**	**Revised protocol version**
Substantial amendment	Addition of a voluntary, long-term follow-up visit 6 months after completion of the 26-weeks treatment period with EMP16 02 for assessment of weight, HbA1c and blood pressure. Addition of trough plasma concentration measurements of acarbose at steady state. Administrative changes, clarifications and corrections of typos.	Version 3.0

1 STUDY SYNOPSIS

Study title

Lean Efficacy Phase IIa Proof of concept trial (LEAAP). A multi-centre, double-blind, placebo-controlled, randomised study in overweight and obese patients during twenty-six weeks, investigating the effect of EMP16-02 on body weight, safety and clinical biomarkers

Study code	**EudraCT No**
EP-002	2019-004545-32
Planned study period	**Phase of development**
Main part (Visits 1 to 6): Q2 2020 to Q2 2021 Follow-up part (Visit 7): Q2 2021 to Q3 2021	Phase IIa

Coordinating Investigator

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Study design

This is an exploratory, randomised, double-blind, placebo-controlled study in overweight and obese patients in which the effect of two doses of EMP16-02 on body weight loss will be tested versus placebo. The main part of the study will be conducted during 26 weeks at two study centres in Sweden. Consenting subjects will continue in a 6 month follow-up part.

Objectives

Primary objective:

- To evaluate the effect of the study drug EMP16-02 (120 mg orlistat [O]/40 mg acarbose [A]) on relative body weight loss after a 26-week period of oral treatment as compared to placebo.

Secondary objectives:

- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on relative and absolute body weight loss during a 26-week period of oral treatment as compared to placebo.
- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on other anthropometric characteristics during a 26-week period of oral treatment as compared to placebo.
- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on satiety and meal pattern during a 26-week period of oral treatment as compared to placebo.
- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on fasting insulin, glucose metabolism markers, lipid metabolism markers and inflammation markers during a 26-week period of oral treatment as compared to placebo.

- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on blood pressure during a 26-week period of oral treatment as compared to placebo.
- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on quality of life during a 26-week period of oral treatment as compared to placebo.
- To assess the relationship between drop-out(s) and tolerability for two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) during a 26-week period of oral treatment as compared to placebo.
- To assess the safety and gastrointestinal (GI) tolerability of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) during a 26-week period of oral treatment as compared to placebo.

Exploratory objectives:

- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O /50 mg A) on fasting plasma/serum levels of apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB) during a 26-week period of oral treatment as compared to placebo.
- To assess the pre-dose plasma level of orlistat and acarbose at steady state.
- To evaluate the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O /50 mg A) on relative and absolute body weight loss 6 months after completion of a 26-week period of oral treatment as compared to placebo.
- To evaluate the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O /50 mg A) on HbA1c concentration 6 months after completion of a 26-week period of oral treatment as compared to placebo.
- To evaluate the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O /50 mg A) on blood pressure 6 months after completion of a 26-week period of oral treatment as compared to placebo.

Endpoints

Primary endpoint:

- Relative (%) change from baseline in body weight after 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A) as compared to placebo.

Secondary endpoints:

- Absolute change from baseline in body weight after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A) as compared to placebo.
- Relative (%) and absolute change from baseline in body weight after 14 and 26 weeks of treatment with EMP16-02 (150 mg O/50 mg A) as compared to placebo.
- Proportion of patients with ≥5% and ≥10% decrease in body weight compared to baseline after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Relative (%) and absolute change from baseline in body mass index (BMI) after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Absolute change from baseline in waist circumference after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Absolute change from baseline in sagittal diameter after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.

- Relative (%) and absolute change from baseline in percentage body fat after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Satiety and craving after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo, corrected for satiety and craving after standardised breakfast at baseline.
- Relative (%) and absolute change from baseline in fasting haemoglobin A1c (HbA1c), glucose, insulin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, liver enzymes, albumin and high-sensitivity C-reactive protein (hs-CRP) after 7, 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Change from baseline in the proportion of diabetic (fasting glucose ≥ 7.0 mmol/L) and prediabetic patients (fasting glucose ≥ 6.1 mmol/L and < 7.0 mmol/L) after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Relative (%) and absolute change from baseline in blood pressure after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Change from baseline in quality of life after 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Dropout rate (overall and GI-related) following treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Frequency and severity of adverse events (AEs) during 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Clinically significant relative (%) and absolute changes from baseline in safety laboratory parameters and ECG after 26 weeks of treatment, and in vital signs after 7, 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.
- GI tolerability after 2, 4, 6, 8, 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Compliance after 7, 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.

<u>Exploratory endpoints:</u>

- The absolute difference in fasting plasma/serum levels of ApoA1 and ApoB from baseline after 7, 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Pre-dose plasma concentrations of orlistat and acarbose after 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A).
- Relative (%) and absolute change in body weight from baseline, and from end of treatment at 26 weeks, to 6 months after end of treatment with EMP16-02 (120 mg O/ 40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Relative (%) and absolute change in HbA1c from baseline, and from end of treatment at 26 weeks, to 6 months after end of treatment with EMP16-02 (120 mg O/ 40 mg A and 150 mg O/50 mg A) as compared to placebo.
- Relative (%) and absolute change in blood pressure from baseline, and from end of treatment at 26 weeks, to 6 months after end of treatment with EMP16-02 (120 mg O/ 40 mg A and 150 mg O/50 mg A) as compared to placebo.

The exploratory analyses may not be reported in the clinical study report (CSR). 6-month data will be reported in an addendum to the CSR.

Number of patients planned

A total of 156 patients will be randomised in the study. Assuming a dropout rate of 20%, a total of 52 patients will be randomised to each treatment arm to achieve at least 41 evaluable patients per arm.

An evaluable patient in the main part is defined as a patient who has completed 26 weeks of treatment with investigational medicinal product (IMP). An evaluable patient in the follow-up part is defined as a patient who has completed 26 weeks of treatment with IMP and the 6 months follow-up visit.

Diagnosis and main eligibility criteria

- Male and female patients with overweight or obesity, defined as BMI ≥ 30, or ≥ 28 kg/m² in the presence of other risk factors (*e.g.*, hypertension, glucose dysregulation such as impaired glucose tolerance and type 2 diabetes mellitus (T2DM), and/or dyslipidaemia).
- Aged ≥ 18 and ≤75 years.
- Willing and able to give written informed consent for participation in the study.
- Body weight stable (<5% reported change during the three months preceding screening and randomisation).

Methodology

This is an exploratory randomised, double-blind, placebo-controlled study in which EMP16-02 or placebo will be taken orally three times daily (TID) together with the three main daily meals during 26 weeks. EMP16-02 will be given to obese patients with an initial BMI ≥ 30 kg/m² or ≥ 28 kg/m² in the presence of other risk factors (*e.g.*, hypertension, glucose dysregulation such as impaired glucose tolerance and T2DM, and/or dyslipidaemia). Prior to any study assessments, patients will be asked to provide signed informed consent to participate in the study. The main part of the study consists of 6 visits to the research clinic, including screening and a safety follow-up visit. Visit 7 will be a long-term follow-up visit scheduled 6 months after completion of the 26-weeks treatment. All patients completing the treatment period will be asked to participate in the long-term follow-up and a separate consent will be collected. There will be no overnight stays at the clinic. Screening (Visit 1) will take place from Day -28 to Day -1. An electronic diary will be used to provide the patients with questionnaires to be filled in during or shortly before/after the visits. At two extra occasions between Visit 4 and 5, the electronic diary will be used for collecting information on IMP compliance, AEs and use of concomitant medication.

Eligible and consenting patients will arrive at the research clinic in the morning of the first dosing day (Day 1, Visit 2) after at least 8 hours overnight fasting. A re-check of eligibility including a brief physical examination, vital signs and assessment of body weight will be conducted.

The patients will be randomised to either of two doses of EMP16-02 or placebo:

1. EMP16-02 120 mg O/40 mg A
2. EMP16-02 150 mg O/50 mg A
3. Placebo (identical capsules)

Blood sampling (fasting), and anthropometric measurements will be performed. Patients will receive electronic diary instructions and will be asked to fill in a satiety and craving questionnaire before breakfast (at the clinic), and then once every hour for 4 hours until before lunch (at home). A standardised breakfast will be served at the clinic. Halfway through breakfast at Visit 2, all patients will receive a placebo capsule independent of the treatment arm to which the patients have been randomised, to provide patients with the opportunity to train on self-administering the IMP under supervision of clinic staff. The patients will also receive instructions for filling in more questionnaires

regarding health and quality of life, meal pattern, activity and sleep, and gastrointestinal symptoms (gastrointestinal rating scale [GSRS]).

The patients will be instructed to take EMP16-02 or placebo halfway through each meal, together with approximately 100-200 mL water (or other drink) on all subsequent treatment days. Once IMP has been handed out, the patients are free to leave the clinic. The first randomised IMP dose will be taken during lunch (or the next meal) at home.

Patients randomised to EMP16-02 will start with a run-in period of 6 weeks during which the dose is sequentially increased. From week 7, all patients will have reached their final intended dose and a 20-week treatment and observation period will start. The run-in phase will start at a dose of 60 mg O and 20 mg A TID, which will sequentially be increased with 30 mg O/10 mg A every two weeks until the target doses of 120 mg O/40 mg A TID (for the lower dose group) and 150 mg O/50 mg A TID (for the higher dose group) are reached. The dosing regimen is as follows:

Target dose	**Week 1 and 2**	**Week 3 and 4**	**Week 5 and 6**	**Week 7 to 26**
EMP16-02 120 mg O/40 mg A	60 mg O/20 mg A	90 mg O/30 mg A	120 mg O/40 mg A	120 mg O/40 mg A
EMP16-02 150 mg O/50 mg A	60 mg O/20 mg A	90 mg O/30 mg A	120 mg O/40 mg A	150 mg O/50 mg A

Placebo treatment consists of matching oral capsules. Placebo and EMP16-02 capsules need to be taken TID together with three daily meals.

Patients will come to the clinic at Visit 3 (week 7), Visit 4 (week 14) and Visit 5 (week 26) for safety assessments and assessments of weight and anthropometric measurements. Patients will arrive in the morning after at least 8 hours overnight fasting. All visits will start with a brief physical examination followed by blood sampling (fasting) and assessment of body weight and body composition. A standardised breakfast will be served during which the patient will take the IMP. All or a selection of the questionnaires, including the satiety and craving questionnaire, will be filled in in a similar way as during Visit 2.

After 18 and 22 weeks of treatment (Day 123 ± 3 days and Day 151 ± 3 days, respectively), patients will be asked to answer questions about IMP compliance, occurrence of AEs and use of concomitant medication using an electronic diary.

New IMP will be handed out to the patients at Visit 2, 3 and 4.

At Visit 5 (week 26), the patients will take the last dose during breakfast at the clinic. Visit 6 is a safety follow up visit. Visit 7 is a 6 month follow-up visit for consenting patients who has completed the 26-week treatment period with active EMP16-02 treatment (120 mg O/40 mg A and 150 mg O/50 mg A) or placebo.

Investigational Medicinal Product (IMP), dosage and mode of administration

EMP16-02 is an oral, modified-release (MR) fixed dose combination (FDC) of orlistat and acarbose formulated in capsules, available in two strengths:

- EMP16-02-90/30, containing 90 mg O/30 mg A
- EMP16-02-60/20, containing 60 mg O/20 mg A

Two different doses of EMP16-02 will be used in the study (after a 6-week run-in period):

- 120 mg O/40 mg A (2 capsules EMP16-02-60/20)
- 150 mg O/50 mg A (1 capsule EMP16-02-90/30 and 1 capsule EMP16-02-60/20)

Placebo is a matching, oral capsule. EMP16-02 and placebo should be taken three times daily (TID) together with three main daily meals.
Duration of treatment Each patient will receive three daily doses of EMP16-02 or matching placebo during 26 weeks. The IMP will be taken together with the main daily meals.
Duration of each patient's involvement in the study Each patient in the main part of the study will participate in the study for approximately 32 weeks including a screening period of up to 4 weeks, 26 weeks of treatment and a safety follow-up visit 2 weeks after the last treatment. Patients giving their consent to participate in a 6 month follow-up evaluation will participate in the study for 58 weeks including a screening period of up to 4 weeks, 26 weeks of treatment, a safety follow-up visit 2 weeks after the last treatment and a follow-up visit 26 weeks after the last treatment.
Efficacy assessments Weight, other anthropometric measurements (BMI, waist circumference, sagittal diameter, bio-impedance), blood sampling for fasting lipid metabolism, glucose metabolism and inflammations markers, blood pressure, questionnaires (meal pattern, GSRS, satiety and craving, activity and sleep and health and quality of life [RAND-36]), drop-out rate (assessed both in terms of safety and efficacy).
Safety assessments AE recording, vital signs (blood pressure assessed both in terms of safety and efficacy), ECG, fasting safety laboratory blood sampling, physical examination, GSRS (assessed both in terms of safety and efficacy).
Exploratory assessments Fasting blood sampling for ApoA1 and ApoB, pre-dose blood sampling for orlistat and acarbose plasma concentrations at steady state. Weight, HbA1c and blood pressure 6 months after end of treatment.
Statistical methods The primary endpoint, relative (%) change from baseline in body weight after 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A) as compared to placebo, will be analysed using analysis of variance with treatment as independent variable. The absolute change from baseline in body weight after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A) as compared to placebo will be analysed using analysis of covariance with treatment and body weight at baseline as covariates. The relative (%) change from baseline in body weight after 14 and 26 weeks of treatment with EMP16-02 (150 mg O/50 mg A) as compared to placebo will be analysed using analysis of variance with treatment as independent variable. The relative and absolute change in body weight from baseline, and from end of treatment at 26 weeks, to 6 months after completion of the 26-week treatment period will be analysed by corresponding means. The proportion of patients with ≥5% and ≥10% decrease in body weight compared to baseline after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using Chi-square test without continuity correction. Other anthropometric parameters, glucose metabolism markers, lipid metabolism markers, inflammation markers and blood pressure will also be analysed using analysis of variance. For

relative changes from baseline, treatment will be used as independent variable. For absolute changes from baseline, treatment and body weight will be used as covariates.

The proportions of diabetic patients, prediabetic patients and non-diabetic patients after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) will be presented using shift tables. The change from baseline in the proportion of diabetic and prediabetic patients after 14 and 26 weeks of treatment with EMP16-02 as compared to placebo will be analysed using Chi-square test without continuity correction.

Meal pattern, satiety and craving and health and quality of life (RAND-36) questionnaires will be analysed using the Wilcoxon Rank Sum test. The GSRS questionnaire will be analysed using analysis of covariance while the activity and sleep questionnaire will be analysed using a Chi-square test. The drop-out rate (overall and GI-related) following treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using Chi-square test without continuity correction.

Continuous data will be presented in terms of evaluable and missing observations, arithmetic mean, standard deviation (SD), median, minimum and maximum value.

Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by treatment, and by assessment time. Individual patient data will be listed by treatment, patient number, and, where applicable, by assessment time.

All descriptive summaries and statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute, Inc., Cary, NC).

Baseline is defined as the visit with last data collection point prior to the first administration of IMP.

All hypothesis testing will use a significance level of 5%.

Comparisons will be made pairwise and analysed at each visit if not stated otherwise.

Study reporting

After completion of the main part of the study (including Visit 6), an International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 compliant CSR will be prepared. The exploratory analyses may not be reported in the CSR. 6-month data will be reported an addendum to the CSR.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or term	Explanation
A	Acarbose
ADL	Activities of daily living
AE	Adverse event
ADR	Adverse drug reaction
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CA	Competent authority
CIOMS	Council for International Organisations of Medical Sciences
CSP	Clinical study protocol
CSR	Clinical study report
CTC	Clinical Trial Consultants AB
CTCAE	Common terminology criteria for adverse events
CTC PV	CTC's Pharmacovigilance department
DALY	Disability-adjusted life-years
DBP	Diastolic blood pressure
DMP	Data management plan
DSUR	Development safety update report
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EMA	European Medicines Agency

ePRO	Electronic patient reported outcomes
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FDC	Fixed dose combination
FFA	Free fatty acid
FSH	Follicle stimulating hormone
GBP	Gastric by-pass surgery
GCP	Good clinical practice
GDPR	General data protection regulation
GERD	Gastroesophageal reflux disease
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GMP	Good manufacturing practice
GSRS	Gastrointestinal symptom rating scale
h	hour
H2	Histamine type 2 receptor
Hb	Haemoglobin
HbA1c	Haemoglobin A1c
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
hs-CRP	High sensitivity C-reactive protein
IB	Investigator's brochure
IBS	Irritable Bowel Syndrome
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IME	Important medical event
IMP	Investigational medicinal product
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system

LDL	Low-density lipoprotein
MedDRA	Medical dictionary for regulatory activities
MEN 2	Multiple Endocrine Neoplasia syndrome type 2
mmHg	Millimetre of Mercury (unit of pressure)
MPA	Medical products agency
MR	Modified-release
MTC	Medullary Thyroid Carcinoma
N	number
NIH	National Institute of Health
NSAID	Non-steroidal anti-inflammatory drug
O	Orlistat
PII	Personally Identifiable Information
PK (INR)	Prothrombin complex international normalised ratio
PPI	Proton pump inhibitor
PPS	Per protocol analysis set
PT	Preferred term
PV	Pharmacovigilance
QA	Quality assurance
QC	Quality control
RBC	Red blood cell
RBM	Risk-based monitoring
RSI	Reference safety information
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SDV	Source data verification
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard operating procedures
SSRI	Selective serotonin re-uptake inhibitor
SUSAR	Suspected unexpected serious adverse reaction

T2DM	Type 2 diabetes mellitus
TID	*ter in die* (three times per day)
TMF	Trial master file
UK	United Kingdom
ULN	Upper limit of normal
US	United States (of America)
WBC	White blood cell
WHO	World Health Organisation
WOCBP	Women of childbearing potential

4 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

4.1 Medical emergencies contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes a serious adverse event (SAE) and is to be reported as such. Detailed SAE reporting procedures are described in Section 11.6.1.13.

In the case of a medical emergency the Investigator may contact the Medical Monitor.

Name	Function in the study	Telephone number and e-mail
Cornelia Lif-Tiberg	Medical monitor	Telephone: +46 (0)73 978 94 45 E-mail: cornelia-lif-tiberg@ctc-ab.se

5 INVESTIGATOR(S) AND STUDY ADMINISTRATIVE STRUCTURE

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Laboratory (Bioanalysis)	Lablytica Life Science AB Virdings allé 18 SE-754 50 Uppsala, Sweden Recipharm OT Chemistry Virdings allé 32b SE-754 50 Uppsala, Sweden

Investigational medicinal product (IMP) manufacturing, packaging and release	Recipharm Pessac Avenue Gustave Eiffel FR-33600 Pessac, France
IMP labelling and secondary packaging	Recipharm Pharmaceutical Development AB Gårdsvägen 10A SE-169 70 Solna, Sweden
Questionnaires	**RAND-36** Health and Quality of Life instrument RAND Corporation USA Swedish translation by: RCSO (Registercentrum SydOst) info@rcso.se **GSRS** Gastrointestinal Symptoms Rating Scale AstraZeneca Forskargatan 18 151 85 Södertälje **Satiety and craving** (generated by Empros Pharma AB) **Meal pattern** (generated by Empros Pharma AB) **Activity and sleep** (generated by Empros Pharma AB)
Electronic data capture (EDC) system provider:	PCG Solutions AB S:t Persgatan 6 SE-753 20 Uppsala, Sweden

Signatures are provided in Section 19.

6 INTRODUCTION

6.1 Background

6.1.1 *Obesity and overweight*

Obesity is a worldwide health problem and major risk factor for cardiovascular diseases, diabetes, musculoskeletal disorders, and some cancers. From 1980 to 2014, the worldwide prevalence of obesity more than doubled, with over 1.9 billion adults being overweight (defined as a body mass index [BMI] of ≥25 kg/m^2) and over 600 million being obese (defined a s a BMI of ≥30 kg/m^2) [1]. In the US, over 70% of adults are overweight or obese [2], while in the UK the proportion of overweight and obese adults constitutes 64% [3]. Among the most troubling obesity-related trends is the almost 50% increase of overweight among children and adolescents during the last decades of the 20th century. Consequently, children are increasingly being diagnosed with traditionally adult-onset diseases such as type 2 diabetes mellitus (T2DM) and heart disease [4].

In 2010, overweight and obesity were estimated to cause 3.4 million deaths, 3.9% years of life lost, and 3.8% of disability-adjusted life-years (DALYs) worldwide [5]. In addition, 44% of diabetes burdens, 23% of ischemic heart disease burdens and between 7% and 41% of certain cancer burdens are attributable to overweight and obesity [6]. Obesity is also associated with hypertension, hyperglycaemia, dyslipidaemia, obstructive sleep apnoea, atherosclerosis, physical problems as joint pain, psychosocial problems and a reduced life expectancy of about 5-10 years. The many serious health consequences make obesity a public health priority. Lifestyle intervention affecting dietary intake and energy expenditure are important, however, often not enough. Therefore, there is a great medical need for safe and efficient medical treatments [7,8,9].

Current treatments that aim to induce rapid body weight loss are different types of gastrointestinal (GI) surgery, among which gastric bypass surgery (GBP) is most common [10]. Several pharmacological treatment principles have been considered including, among others, increasing energy expenditure (stimulants), suppressing caloric intake (anorectic agents), limiting nutrient absorption and modulating insulin production and/or action [11,12]. Two of the drugs that function by affecting the uptake of nutrients through inhibition of intestinal digestion are orlistat and acarbose.

6.1.2 *EMP16-02 mechanism of action*

EMP16-02 consists of a fixed dose combination (FDC) of orlistat and acarbose.

Orlistat is an anti-obesity drug that is administered orally during a meal and acts by preventing intestinal digestion of dietary fats and subsequent absorption of free fatty acids (FFAs) through inhibition of gastric and pancreatic lipases in the GI lumen [13,14]. Although safe, orlistat is associated with side-effects and tolerability issues that severely hamper compliance. Previous clinical trials showed that around 25% or more of the patients complain about GI side-effects including diarrhoea, oily spottings and faecal urgency [15]. Efficacy of orlistat treatment was rather modest, inducing a 10% relative body weight loss at best, while placebo induced a 6% loss of weight [16]. Orlistat in conventional form seems to have a direct effect on the stomach by increasing gastric emptying, which may lead to increased appetite

[17]. The modest effect on body weight together with the tolerability issues make orlistat given in a conventional dosage form (such as Xenical®) unattractive for most obese patients.

Acarbose is a competitive α-glucosidase and pancreatic α-amylase inhibitor that acts by inhibiting the hydrolysis of oligosaccharides in the GI lumen and subsequently delays the intestinal absorption rate of monosaccharides [18]. Acarbose binds to the carbohydrate binding sites of α-glucosidases with significantly higher affinity than the normal substrates. Because of the reversible nature of the inhibitor-enzyme interaction, the conversion of oligosaccharides to monosaccharides is only delayed rather than completely blocked. Acarbose is currently used as a T2DM drug, mainly in Asia, but only scarcely in Western countries. By locally inhibiting the luminal digestion of carbohydrates, the blood sugar increases slower postprandially, and the patient's insulin need is reduced [19]. Clinical studies showed a small effect on body weight: only 1% relative weight loss was observed after 12 months daily treatment with 600 mg acarbose [20,21,22]. As with orlistat, a large part of the patients using acarbose in conventional oral dosage form (Glucobay®) report GI side effects, such as flatulence, diarrhoea and abdominal pain [18]. These side effects originate from bacterial fermentation of undigested carbohydrates in the colon [23] and limit the clinical use of acarbose mainly in Western countries.

Orlistat has very lipophilic molecular properties which limit its solubility, dissolution rate and subsequent intestinal absorption and plasma exposure. More than 83% of a given oral dose is recovered unchanged in the faeces [13,24]. The fraction of the dose of conventional orlistat absorbed from the GI tract is low (<3%) and accordingly the plasma exposure is low and variable [25,26]. Like orlistat, acarbose also has a low absorption rate. Less than 2% of an oral dose of acarbose is absorbed intact and becomes available (mostly as parent drug), resulting in low plasma exposure. As both drugs are intended to act locally in the GI tract, their pharmacokinetic properties are well suited towards their pharmacological action directed exclusively towards the intestinal lipases, amylases and glucosidases [27].

In EMP16-02, orlistat and acarbose are formulated in an oral FDC multiple-unit modified-release (MR) dosage form. The major differences between EMP16-02 and the conventional oral dosage forms for orlistat and acarbose are the multiple unit properties and the release patterns of both drugs in the intestine, that are designed to increase efficacy and improve GI tolerability. EMP16-02 is composed of three fractions that contain different amounts of orlistat and/or acarbose and release the drugs at different rates. The purpose of these pharmaceutical properties is to release orlistat and acarbose in the distal jejunum and this way delay normal food digestion and absorption of free fatty acids and hexoses to the more distal parts of the small intestine (the ileum). Exposure of specialised enteroendocrine cells in the ileum to digested food leads to an increased secretion of several gut hormones that act locally on the motility of the GI tract as well as on the brain centre regulating satiety. This effect is commonly known as the ileal brake. By delaying food digestion and absorption to the ileum, EMP16-02 activates the ileal brake, leading to increased satiety levels and reduced food intake.

For more details, refer to the EMP16-02 Investigator's Brochure (IB).

6.2 Study rationale

EMP16-02 is an FDC of orlistat and acarbose, formulated in an MR form. By using a combination of both orlistat and acarbose, the digestion of both dietary fats and carbohydrates can be inhibited. However, because of the risk of profound and synergistic GI side effects when used together, the combination of orlistat and acarbose in conventional dosage form is currently not recommended. The multiple-unit MR formulation of EMP16-02 will substantially reduce the risk for these negative synergistic effects: the acarbose side effects will be minimised by optimising mixing of the multiple-unit granules containing acarbose with the ingested food before acarbose becomes active, and the orlistat side effects will be minimised by delaying orlistat release to after the stomach, thus avoiding enhanced gastric emptying and steatorrhea.

This study is a proof of concept study to demonstrate that EMP16-02, an FDC of orlistat and acarbose in an oral multiple-unit MR formulation leads to a clinically relevant decrease in body weight. The study aims to evaluate the efficacy, safety and tolerability of treatment with two different doses of EMP16-02 (120 mg orlistat/40 mg acarbose and 150 mg orlistat/50 mg acarbose) for 26-weeks on reducing body weight in obese patients. In order to collect long-term data, all patients completing the 26-week treatment period will be asked to participate at an additional visit 6 months later. Weight, HbA1c and blood pressure will be assessed at this visit. It is a well-known fact that many patients gain weight after a completion of a weight loss program, a so called a rebound effect. It is of interest to understand if patients treated with EMP16-02 differs from placebo patients and to compare this rebound effect by literature data from patients treated by other medications.

6.3 Risk/benefit assessment

The mechanism of action for EMP16-02 is to delay the normal food digestion and absorption of FFAs and hexoses to the distal part of the small intestine. The drug exerts its effect locally in the intestines. Given the low plasma exposure of both of its two components orlistat and acarbose observed during the previous phase IIa study (EP-001, [28]) as well as in other studies [13,24,25,26,27], the risk of systemic effects is extremely low. Both orlistat and acarbose have been used for decades with excellent patient safety data. Because of the poor absorption together with the fact that acarbose is not a Cytochrome P450 substrate, it seems highly unlikely that any drug-drug interaction will occur during intestinal absorption and first-pass through the liver. In accordance with this, no drug-drug interactions have been reported for acarbose and orlistat. However, as orlistat decreases uptake of dietary fats, it might negatively affect the bioavailability of lipophilic drugs.

The side-effects experienced by both orlistat and acarbose are various gastrointestinal symptoms (such as flatulence, stomach rumblings, abdominal pain, increased defaecation, liquid and/or oily stools) as well as headache and nausea. Upper respiratory infections have also been reported to be more frequent with orlistat [15]. However, these side-effects are transient and will quickly resolve if patients stop taking the drugs. In rare cases, effects on the liver after taking acarbose have been reported [29]. For that reason, blood samples are taken at every visit to analyse liver function parameters.

Besides the risks related to the IMP as described above, there may also be risks related to the medical devices used in the study, for *e.g.*, venepuncture. However, these are devices that are

used in routine medical care and the risk associated with their use is considered low and ethically justifiable. Study specific evaluations and sampling procedures, like blood pressure measurements using a blood pressure cuff and frequent blood sampling, may cause transient discomfort but the risk is deemed to be low and ethically justifiable.

Overall, the combined safety data from the previous phase IIa trial [28], and other pre-clinical and clinical studies, have not revealed any safety issues that would outweigh the expected benefits of the study. While keeping the above-mentioned risk factors at a minimum level in order to not expose the patients participating in the study for risks that would not be ethically justifiable, it is concluded that the planned study assessments are considered sufficient to meet the scientific and medical goals for the study. With regard to the substantial medical need for treatment of obesity, it is concluded that the potential benefits from the study will outweigh the potential risks for the treated patients.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of EMP16-02 is found in current version of the IB.

6.3.1 *Risk assessment with regards to the COVID-19 pandemic*

Current recommendations from the authorities will be considered on a day-to-day basis. Ongoing risk evaluation, assessment sessions with Sponsors, Investigators, CRO/vendor representative members to align on local restrictions, impact assessment, contingency plans and study-specific risk mitigation strategies will be made to safeguard the study conduct and the safety of the study subjects.

Obesity as well as older age, diabetes mellitus and hypertension increases the risk for hospitalisation and death in COVID-19 patients [30] and special attention will hence be paid to the patients included in the study. Logistical measures, such as reduction in group size, as well as hygiene measures and social distancing during visits, will be taken in order to reduce interaction between patients and between patients and study personnel. Visits to the clinic will be rescheduled in case a patient has any signs of influenza-like symptoms.

The number of visits to the clinic is minimized (6 visits during approximately 32 weeks). In addition, several questionnaires will be answered at home by the patients using an electronic patient reported outcomes (ePRO) system (ViedocMe™) linked to the electronic case report form (eCRF), which will reduce the time spent at the clinic at each visit. Investigational medicinal product (IMP) will be dispensed at 3 occasions only (in association with scheduled study visits).

Administration of EMP16-02 is not expected to increase the risk of contracting a COVID-19 infection or to increase the risk for severe complications in case of an infection. Since patients on active treatment are expected to lose weight, the risk for severe complications associated with COVID-19 infection may be reduced over the course of the study as a consequence of potential improvements in blood sugar levels and blood pressure associated with weight loss.

7 STUDY OBJECTIVES AND ENDPOINTS

All primary, secondary and exploratory objectives and endpoints are summarised in Table 7.4-1.

7.1 Primary objective

To evaluate the effect of the study drug EMP16-02 (120 mg orlistat [O]/40 mg acarbose [A]) on relative body weight loss after a 26-week period of oral treatment as compared to placebo.

7.1.1 *Primary endpoint*

Relative (%) change from baseline in body weight after 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A) as compared to placebo.

The primary objective and endpoint are also summarised in Table 7.4-1.

7.2 Secondary objectives

- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on relative and absolute body weight loss during a 26-week period of oral treatment as compared to placebo.
- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on other anthropometric characteristics during a 26-week period of oral treatment as compared to placebo.
- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on satiety and meal pattern during a 26-week period of oral treatment as compared to placebo.
- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on fasting insulin, glucose metabolism markers, lipid metabolism markers and inflammation markers during a 26-week period of oral treatment as compared to placebo.
- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on blood pressure during a 26-week period of oral treatment as compared to placebo.
- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on quality of life during a 26-week period of oral treatment as compared to placebo.
- To assess the relationship between drop-out(s) and tolerability for two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) during a 26-week period of oral treatment as compared to placebo.
- To assess the safety and GI tolerability of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) during a 26-week period of oral treatment as compared to placebo.

7.2.1 *Secondary endpoints*

The secondary endpoints are summarised in Table 7.4-1.

7.3 Exploratory objectives

- To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on fasting plasma/serum levels of apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB) during a 26-week period of oral treatment as compared to placebo.
- To assess the pre-dose plasma level of orlistat and acarbose at steady state.
- To evaluate the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O /50 mg A) on relative and absolute body weight loss 6 months after completion of a 26-week period of oral treatment as compared to placebo.
- To evaluate the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O /50 mg A) on HbA1c concentration 6 months after completion of a 26-week period of oral treatment as compared to placebo.
- To evaluate the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O /50 mg A) on blood pressure 6 months after completion of a 26-week period of oral treatment as compared to placebo.

7.3.1 *Exploratory endpoints*

The exploratory endpoints are summarised in Table 7.4-1. The exploratory analyses may not be reported in the clinical study report (CSR). 6-month data will be reported in an addendum to the CSR.

7.4 Summary of objectives, endpoints and assessments

A summary of all objectives and endpoints, including the pertaining assessments, is given in Table 7.4-1.

Table 7.4-1 Summary of objectives, endpoints and assessments

	Objective	**Endpoint**	**Assessment(s)**
Primary	To evaluate the effect of the study drug EMP16-02 (120 mg O/40 mg A on relative body weight loss after a 26-week period of oral treatment as compared to placebo.	Relative (%) change from baseline in body weight after 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A) as compared to placebo.	Body weight measurement (Section 11.4.1)
Secondary	To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on relative and absolute body weight loss during a 26-week period of oral treatment as compared to placebo.	Absolute change from baseline in body weight after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A) as compared to placebo.	Body weight measurement (Section 11.4.1)
		Relative (%) and absolute change from baseline in body weight after 14 and 26 weeks of treatment with EMP16-02 (150 mg O/50 mg A) as compared to placebo.	Body weight measurement (Section 11.4.1)
		Proportion of patients with ≥5% and ≥10% decrease in body weight compared to baseline after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	Body weight measurement (Section 11.4.1)
	To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on other anthropometric characteristics during a 26-week period of oral treatment as compared to placebo.	Relative (%) and absolute change from baseline in BMI after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	Body weight measurement (Section 11.4.1) Height measurement (screening and last visit) (Section 11.5.1.1)
		Absolute change from baseline in waist circumference after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	Waist circumference measurements (Section 11.5.1.2)
		Absolute change from baseline in sagittal diameter after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	Sagittal measurement (Section 11.5.1.3)
		Relative (%) and absolute change from baseline in percentage body fat after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	Body composition via bio-impedance measurement (Section 11.5.1.4)

	Objective	**Endpoint**	**Assessment(s)**
	To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on satiety and meal pattern during a 26-week period of oral treatment as compared to placebo.	Satiety and craving after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo, corrected for satiety and craving after standardised breakfast at baseline.	Standardised breakfast at week 26 – weight/kcal correlated Satiety and craving questionnaire and meal pattern questionnaire (Section 11.5.4.3 and Section 11.5.4.1, respectively)
	To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on fasting insulin, glucose metabolism markers, lipid metabolism markers and inflammation markers during a 26-week period of oral treatment as compared to placebo.	Relative (%) and absolute change from baseline in fasting haemoglobin A1C (HbA1c), glucose, insulin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, liver enzymes, albumin and high-sensitivity C-reactive protein (hs-CRP) after 7, 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	Fasting lipid metabolism, glucose metabolism and inflammation markers (Section 11.5.2) Liver enzymes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) (Section 11.6.5)
		Change from baseline in the proportion of diabetic (fasting glucose ≥ 7.0 mmol/L) and prediabetic patients (fasting glucose ≥ 6.1 mmol/L and < 7.0 mmol/L) after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	Fasting lipid metabolism, glucose metabolism and inflammation markers (Section 11.5.2)
	To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on blood pressure during a 26-week period of oral treatment as compared to placebo.	Relative (%) and absolute change from baseline in blood pressure after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	Blood pressure measurement (Section 11.5.3)
	To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on quality of life during a 26-week period of oral treatment as compared to placebo.	Change from baseline in quality of life after 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	Health and life quality questionnaire RAND-36 (Section 11.5.4.5) Activity and sleep questionnaire (Section 11.5.4.4)
	To assess the relationship between drop-out(s) and tolerability for two different doses of EMP16-02 (120 mg O/40 mg A	Dropout rate (overall and GI-related) following treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	Careful collection of reason for early discontinuation

	Objective	Endpoint	Assessment(s)
	and 150 mg O/50 mg A) during a 26-week period of oral treatment as compared to placebo.		
	To assess the safety and GI tolerability of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) during a 26-week period of oral treatment as compared to placebo.	Frequency and severity of AEs during 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	AE questioning (Section 11.6.1)
		Clinically significant relative (%) and absolute changes from baseline in safety laboratory parameters and electrocardiogram (ECG) after 26 weeks of treatment, and in vital signs after 7, 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	Vital signs (Section 11.6.3) 12-lead ECG (Section 11.6.4) Blood sampling for assessment of safety laboratory parameters (Section 11.6.5)
		GI tolerability after 2, 4, 6, 8, 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	GSRS (gastrointestinal symptom rating scale, Section 11.5.4.2)
		Compliance after 7, 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	Measurement of compliance: count number of capsules (Section 11.2 and 10.7)
Exploratory	To assess the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) on fasting plasma/serum levels of ApoA1 and ApoB during a 26-week period of oral treatment as compared to placebo.	The absolute difference in fasting plasma/serum levels of ApoA1 and ApoB from baseline after 7, 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo.	Exploratory blood sampling (Section 11.7.1)
	To assess the pre-dose plasma level of orlistat and acarbose at steady state.	Pre-dose plasma concentrations of orlistat and acarbose after 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/ 50 mg A).	Pre-dose blood sampling for bioanalysis (11.7.2)

	Objective	**Endpoint**	**Assessment(s)**
	To evaluate the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O /50 mg A) on relative and absolute body weight loss 6 months after completion of a 26-week period of oral treatment as compared to placebo.	Relative (%) and absolute change in body weight from baseline, and from end of treatment at 26 weeks, to 6 months after end of treatment with EMP16-02 (120 mg O/ 40 mg A and 150 mg O/50 mg A) as compared to placebo.	Body weight measurement (Section 11.4.1)
	To evaluate the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O /50 mg A) on HbA1c concentration 6 months after completion of a 26-week period of oral treatment as compared to placebo.	Relative (%) and absolute change in HbA1c from baseline, and from end of treatment at 26 weeks, to 6 months after end of treatment with EMP16-02 (120 mg O/ 40 mg A and 150 mg O/50 mg A) as compared to placebo.	Fasting lipid metabolism, glucose metabolism and inflammation markers (Section 11.5.2)
	To evaluate the effect of two different doses of EMP16-02 (120 mg O/40 mg A and 150 mg O /50 mg A) on blood pressure 6 months after completion of a 26-week period of oral treatment as compared to placebo.	Relative (%) and absolute change in blood pressure from baseline, and from end of treatment at 26 weeks, to 6 months after end of treatment with EMP16-02 (120 mg O/ 40 mg A and 150 mg O/50 mg A) as compared to placebo.	Vital signs (Section 11.6.3)

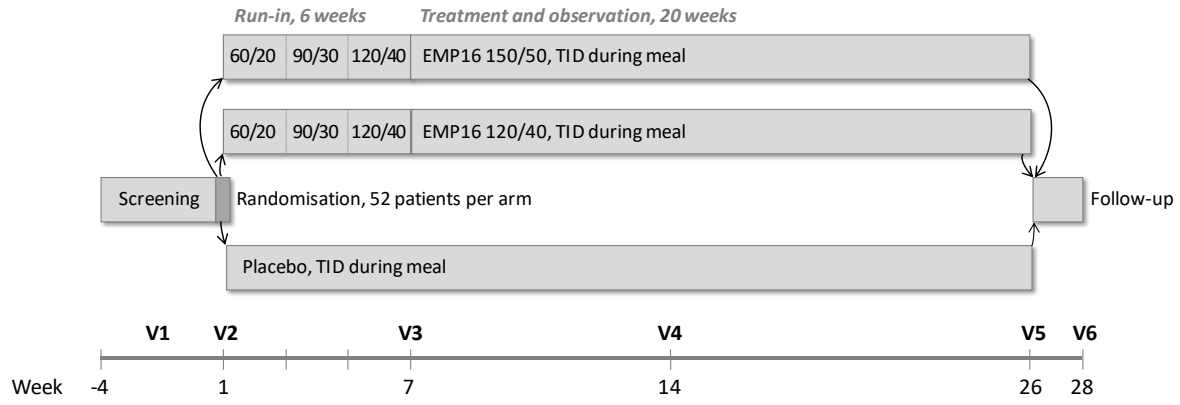
8 STUDY DESIGN

8.1 Overall study design and schedule of events

This is an exploratory, randomised, double-blind, placebo-controlled study to evaluate the effect of two different doses of EMP16-02 on body weight loss in overweight and obese patients. EMP16-02 will be taken orally three times daily (TID) together with three daily meals for a period of 26 weeks. For detailed information about treatment administration, see Section 10.5.

An overview of the study design is shown in Figure 8.1-1.

Figure 8.1-1 Overview of the study design



The study will be conducted at two study centres in Sweden. A total of 156 randomised patients are expected to participate in the main part of the study for approximately 32 weeks, including a screening period of up to 4 weeks, a 26-weeks treatment period and a safety follow-up visit 2 weeks after the last dose. Patients giving their consent to participate in a 6 month follow-up evaluation will participate in the study for 58 weeks including a screening period of up to 4 weeks, 26 weeks of treatment, a safety follow-up visit 2 weeks after the last treatment and a follow-up visit 26 weeks after the last treatment.

EMP16-02 will be given to obese patients with an initial BMI $\geq$ 30 kg/m² or $\geq$ 28 kg/m² in the presence of other risk factors (e.g., hypertension, glucose dysregulation such as impaired glucose tolerance and T2DM, and/or dyslipidaemia). Prior to any study assessments, patients will be asked to provide signed informed consent to participate in the study. The main part of the study consists of 6 visits to the research clinic, including screening and a safety follow-up visit. Visit 7 will be a long-term follow-up visit scheduled 6 months after completion of the 26-weeks treatment. All patients completing the treatment period will be asked to participate in the long-term follow-up and a separate consent will be collected. There will be no overnight stays at the clinic. Screening (Visit 1) will take place from Day -28 to Day -1. An electronic diary will be used to provide the patients with questionnaires to be filled in during or shortly before/after the visits. At two extra occasions between Visit 4 and 5, the electronic diary will be used for collecting information on IMP compliance, AEs and use of concomitant medication

Eligible and consenting patients will arrive at the research clinic in the morning of the first dosing day (Day 1, Visit 2) after at least 8 hours overnight fasting. A re-check of eligibility including a brief physical examination, vital signs and assessment of body weight will be conducted.

The patients will be randomised to either of two doses of EMP16-02 or placebo:

1. EMP16-02 120 mg O/40 mg A
2. EMP16-02 150 mg O/50 mg A
3. Placebo (identical capsules)

Blood sampling (fasting), and anthropometric measurements will be performed. Patients will receive electronic diary instructions and will be asked to fill in a satiety and craving questionnaire before breakfast (at the clinic), and then once every hour for 4 hours until before lunch (at home). A standardised breakfast will be served at the clinic. Halfway through breakfast at Visit 2, all patients will receive a placebo capsule independent of the treatment arm to which the patients have been randomised, to provide the patients with the opportunity to train on self-administering the IMP under supervision of clinic staff. The patients will also receive instructions for filling in more questionnaires regarding health and quality of life, meal pattern, activity and sleep, and gastrointestinal symptoms (gastrointestinal rating scale [GSRS], as outlined in Section 11.5.4.

The patients will be instructed to take EMP16-02 or placebo halfway through each meal, together with approximately 100-200 mL water (or other drink) on all subsequent treatment days. Once IMP has been handed out, the patients are free to leave the clinic. The first randomised IMP dose will be taken during lunch (or the next meal) at home. See Table 8.1-4 for a detailed schedule of events for Visit 2.

Patients randomised to EMP16-02 will start with a run-in period of 6 weeks during which the dose is sequentially increased. From week 7, all patients will have reached their final intended dose and a 20-week treatment and observation period will start. The run-in phase will start at a dose of 60 mg O and 20 mg A TID, which will sequentially be increased with 30 mg O/10 mg A every two weeks until the target doses of 120 mg O/40 mg A TID (for the lower dose group) and 150 mg O/50 mg A TID (for the higher dose group) are reached. The dosing regimen is summarised in Table 8.1-1.

Table 8.1-1 Increasing dosing regimen

Target dose	Week 1 and 2	Week 3 and 4	Week 5 and 6	Week 7 to 26
EMP16-02 120 mg O/40 mg A	60 mg O/20 mg A	90 mg O/30 mg A	120 mg O/40 mg A	120 mg O/40 mg A
EMP16-02 150 mg O/50 mg A	60 mg O/20 mg A	90 mg O/30 mg A	120 mg O/40 mg A	150 mg O/50 mg A

EMP16-02 is formulated in capsules available in two strengths:

- EMP16-02-90/30, containing 90 mg O/30 mg A
- EMP16-02-60/20, containing 60 mg O/20 mg A

Placebo treatment consists of matching, oral capsules. Placebo and EMP16-02 capsules need to be taken TID together with the three main daily meals according to the schedule displayed in Table 8.1-2.

Table 8.1-2 Number and type of capsules to be taken

Target dose	Week 1 and 2	Week 3 and 4	Week 5 and 6	Week 7 to 26
EMP16-02 120 mg O/40 mg A	1x EMP16-02-60/20	1x EMP16-02-90/30	2x EMP16-02-60/20	2x EMP16-02-60/20
EMP16-02 150 mg O/50 mg A	1x EMP16-02-60/20	1x EMP16-02-90/30	2x EMP16-02-60/20	1x EMP16-02-60/20 1x EMP16-02-90/30
Placebo	1x placebo capsule	1x placebo capsule	2x placebo capsule	2x placebo capsule

During the run-in phase, after 2, 4, (6) and 8 weeks, patients will fill in the GSRS questionnaire using the electronic diary.

Patients will come to the clinic at Visit 3 (week 7), Visit 4 (week 14) and Visit 5 (week 26) for safety assessments and assessments of weight and anthropometric measurements, as outlined in Table 8.1-3 and detailed in Table 8.1-4. Patients will arrive in the morning after at least 8 hours overnight fasting. All visits will start with a brief physical examination followed by blood sampling (fasting) and assessment of body weight and body composition. A standardised breakfast will be served during which the patient will take the IMP. All or a selection of the questionnaires, including the satiety and craving questionnaire, will be filled in in a similar way as during Visit 2, see Table 11.5-2 scheduling of the questionnaires.

After 18 and 22 weeks of treatment (Day 123 ± 3 days and Day 151 ± 3 days respectively), patients will be asked to answer questions about IMP compliance, occurrence of AEs and use of concomitant medication using an electronic diary.

New IMP will be handed out to the patients at Visit 2, 3 and 4.

At Visit 5 (week 26), the patients will take the last dose during breakfast. Visit 6 is a safety follow-up visit. Visit 7 is a 6 month follow-up visit for consenting patients who has completed the 26-week treatment period with active EMP16-02 treatment (120 mg O/ 40 mg A and 150 mg O/50 mg A) or placebo.

Efficacy assessments include:

- Weight (Section 11.4.1)
- Other anthropometric measurements: BMI, waist circumference, sagittal diameter, bio-impedance (Section 11.5.1)
- Blood sampling for fasting lipid metabolism, glucose metabolism and inflammation markers (Section 11.5.2)

- Blood pressure (Section 11.5.3)
- Questionnaires (Section 11.5.4): meal pattern (Section 11.5.4.1), GSRS (Section 11.5.4.2), satiety and craving (Section 11.5.4.3), activity and sleep (Section 11.5.4.4) and health and quality of life (RAND-36, Section 11.5.4.5)
- Drop-out rate (Section11.5.5, assessed both in terms of safety and efficacy)

Safety assessments include:

- AE recording (Section 11.6.1)
- Vital signs (Section11.6.3, blood pressure assessed both in terms of safety and efficacy)
- ECG (Section 11.6.4)
- Fasting safety laboratory blood sampling (Section 11.6.5)
- Physical examination (Section 11.6.2)
- GSRS (Section11.5.4.2, assessed both in terms of safety and efficacy)

Exploratory assessments include:

- Fasting blood sampling for ApoA1 and ApoB (Section 11.7.1)
- Pre-dose blood sampling for orlistat and acarbose plasma concentrations at steady state (Section 11.7.2)
- Weight 6 months after end of treatment (Section 11.4.1)
- HbA1c 6 months after end of treatment (Section 11.5.2)
- Blood pressure 6 months after end of treatment (Section11.6.3)

For timing of assessments, refer to the schedule of events in Table 8.1-3. Details for Visit 2 to Visit 5 are provided in Table 8.1-4.

Table 8.1-3 Schedule of events

Category	**Visit**	**Refer to CSP Section**	**Main part**						**Follow-up part**
			Screening	**Outpatient**				**Safety follow-up**	**6 month follow-up**
			Visit 1	**Visit 2[1]**	**Visit 3[1]**	**Visit 4[1]**	**Visit 5[1]**	**Visit 6**	**Visit 7[13]**
			Morning visit	**Morning visit**	**Morning visit**	**Morning visit**	**Morning visit**	**Morning visit**	**Morning visit**
	Assessment		Day -28 to Day -1	Week 1	Week 7	Week 14	Week 26	Week 28[2]	Week 52 (±2 weeks)
				Day 1 Baseline	Day 46 (±3 days)	Day 95 (±3 days)	Day 179 (±3 days)	Day 193 (±3 days)	
Screening and demographics assessments	Informed consent	11.3.1	X						X[14]
	Inclusion/exclusion criteria	11.3.2	X	X					
	Demographics	11.3.3	X						
	Medical/obesity history	11.3.4	X						
	Full physical examination	11.6.2.1	X						
	Brief physical examination	11.6.2.2		X	X	X	X	X	
	HIV, hepatitis B and C	11.3.6	X						
	Alcohol breath test	11.3.7	X	X	X	X	X	X	
	Pregnancy test[3]	11.3.8	X	X	X	X	X	X	
	Urine drug screen[4]	11.3.9	X					X	
Weight-related assessments	Weight	11.4.1	X	X	X	X	X		X
	Height	11.5.1.1	X						
	BMI	11.5.1.1	X	X		X	X		X
	Waist circumference	11.5.1.2	X	X	X	X	X		
	Sagittal diameter	11.5.1.3	X	X	X	X	X		
	Bio-impedance	11.5.1.4		X	X	X	X		

Category	Visit	Refer to CSP Section	Main part						Follow-up part
			Screening	Outpatient				Safety follow-up	6 month follow-up
			Visit 1	Visit 2[1]	Visit 3[1]	Visit 4[1]	Visit 5[1]	Visit 6	Visit 7[13]
			Morning visit	Morning visit	Morning visit	Morning visit	Morning visit	Morning visit	Morning visit
	Assessment		Day -28 to Day -1	Week 1	Week 7	Week 14	Week 26	Week 28[2]	Week 52 (±2 weeks)
				Day 1 Baseline	Day 46 (±3 days)	Day 95 (±3 days)	Day 179 (±3 days)	Day 193 (±3 days)	
Blood and urine sampling (fasting)	Full safety laboratory profile[5]	11.6.5	X					X	
	Liver function[6]	11.6.5		X	X	X	X		
	HbA1c, glucose, insulin, triglycerides, total cholesterol, LDL, HDL, Hs-CRP, albumin	11.5.2		X	X	X	X		X[15]
	Exploratory: ApoA1, ApoB	11.7.1		X	X	X	X		
	Exploratory: Blood sampling for orlistat and acarbose plasma levels[7]	11.7.2					X		
Vital signs and ECG	Vital Signs	11.6.3	X	X	X	X	X	X	X[16]
	12-lead ECG	11.6.4	X					X	
Questionnaires	Meal pattern	11.5.4.1		X	X	X	X		
	GI tolerability (GSRS)[8]	11.5.4.2		X	X	X	X		
	Satiety and craving[9]	11.5.4.3		X	X	X	X		
	Activity and sleep	11.5.4.4		X	X	X	X		
	Health and quality of life RAND-36[10]	11.5.4.5		X			X		

Category	Visit	Refer to CSP Section	Main part						Follow-up part
			Screening	Outpatient				Safety follow-up	6 month follow-up
			Visit 1	Visit 2[1]	Visit 3[1]	Visit 4[1]	Visit 5[1]	Visit 6	Visit 7[13]
			Morning visit	Morning visit	Morning visit	Morning visit	Morning visit	Morning visit	Morning visit
	Assessment		Day -28 to Day -1	Week 1	Week 7	Week 14	Week 26	Week 28[2]	Week 52 (±2 weeks)
				Day 1 Baseline	Day 46 (±3 days)	Day 95 (±3 days)	Day 179 (±3 days)	Day 193 (±3 days)	
IMP	Randomisation	9.9		X					
	Dispense IMP			X	X	X			
	IMP administration at clinic[11]	10.5		X	X	X	X		
	IMP compliance	10.7			X	X	X		
Food	Standardised breakfast[12]			X	X	X	X		
Patient instructions	Diary instruction	11.2		X					
	Diet recommendations	9.6.1.2		X					
AEs and medication	Baseline symptoms	11.3.10	X	X					
	AEs	11.6.1		---------- X ----------					
	Prior and concomitant med.	11.3.5	---------- X ----------						

CSP=Clinical study protocol, HIV=Human immunodeficiency virus.

1. For detailed schedule of events, see Table 8.1-4.
2. At Visit 6 or after early withdrawal.
3. Women of child-bearing potential (WOCBP) only, urine test.
4. Drug tests may also be performed at additional random occasions during the study.
5. Full safety laboratory profile: Clinical chemistry, haematology, coagulation, urinalysis (dip stick). Fasting is not required prior to Visit 1 and Visit 6.
6. Liver enzymes: ALT, AST, ALP, GGT.

7. Visit 5: steady-state sample pre-dose.
8. To be filled in by the patient during, before or after the visits, and at the end of week 2, week 4, and week 8 to follow GI symptoms during the run-in phase.
9. To be filled in by the patient before breakfast (at the clinic), then once every hour until lunch (at home).
10. To be filled in by the patient at any hour on the day of Visit 2, and at Visit 5 at approximately the same hour (± 1h) as was done at Visit 2.
11. IMP administration at the clinic as follows:
    Visit 2: Placebo capsule during breakfast at the clinic, first randomised IMP dose during lunch at home.
    Visit 3 and Visit 4: IMP dose during breakfast at the clinic.
    Visit 5: Last IMP dose during breakfast at the clinic.
12. Breakfast at the clinic after weight-related assessments and blood sampling. IMP taken during breakfast.
13. Visit 7 applicable for patients giving their separate consent to participate in the follow-up visit.
14. New Informed consent required before 6 months follow-up visit. Consent may be collected at any time point prior to any study assessments at Visit 7.
15. Visit 7: HbA1c only
16. Visit 7: blood pressure only

Table 8.1-4 Detailed schedule of events for Visit 2 to 5

Category	Visit	Refer to CSP Section	Visit 2						Visit 3 to 5					
			At the clinic			At home			At the clinic			At home		
	Assessment		Before breakfast	00:00	01.00	02:00	03:00	04:00	Before breakfast	00:00	01.00	02:00	03:00	04:00
Screening and demographics assessments	Incl./excl. criteria	11.3.2	X											
	Brief physical examination	11.6.2.2	X						X					
	Alcohol breath test	11.3.7	X						X					
	Pregnancy test[1]	11.3.8	X						X					
Weight-related assessments	Weight	11.4.1	X						X					
	Waist circumference	11.5.1.2	X						X					
	Sagittal diameter	11.5.1.3	X						X					
	Bio-impedance	11.5.1.4	X						X					
Blood and urine sampling (fasting)	Liver function[2]	11.6.5	X						X					
	HbA1c, glucose, insulin, triglycerides, total cholesterol, LDL, HDL, Hs-CRP, albumin	11.5.2	X						X					
	Exploratory: ApoA1, ApoB	11.7.1	X						X					
	Exploratory: orlistat and acarbose plasma levels[3]	11.7.2							X					
Vital signs	Vital Signs	11.6.3	X						X					

Category	Visit	Refer to CSP Section	Visit 2						Visit 3 to 5					
			At the clinic			At home			At the clinic			At home		
	Assessment		Before breakfast	00:00	01.00	02:00	03:00	04:00	Before breakfast	00:00	01.00	02:00	03:00	04:00
Questionnaires	Meal pattern	11.5.4.1	(X)[4]						(X)[4]					
	GSRS	11.5.4.2	(X)[4]						(X)[4]					
	Satiety and craving	11.5.4.3	X		X	X	X	X	X		X	X	X	X
	Activity and sleep	11.5.4.4	(X)[4]						(X)[4]					
	Health and quality of life RAND-36	11.5.4.5	(X)[4]						(X)[4]					
IMP	Randomisation	9.9	X											
	Dispense IMP		(X)[5]						(X)[5]					
	IMP administration halfway into meal	10.5		X[6]				X[6]		X[7]				X[7]
	IMP compliance	10.7							(X)[4]					
Food	Standardised breakfast			X						X				
Patient instructions	Diary instruction	11.2	X											
	Diet recommendations	9.6.1.2	(X)[4]											
AEs and medication	Baseline symptoms	11.3.10	X											
	AEs	11.6.1		---------- X ----------					---------- X ----------					
	Prior and concomitant medication	11.3.5	---------- X ----------						---------- X ----------					

1. WOCBP only, urine test.
2. Liver enzymes: ALT, AST, ALP, GGT.
3. Orlistat and acarbose plasma levels: steady-state sample pre-dose at Visit 5, no sampling at Visit 3 or 4.
4. Does not have to be performed before breakfast. For further details on timing of questionnaires, refer to Table 11.5-2.

5. IMP will be handed out at Visit 2, 3, and 4.
6. Visit 2: all patients will receive a placebo capsule during breakfast at the clinic. First randomised IMP dose in association with lunch at home.
7. Visit 3 and 4: IMP dose during breakfast (at clinic). Second and third IMP dose during subsequent meals at home. Visit 5: last dose at the clinic during breakfast, no other dose that day.

8.2 Rationale for study design

This study will provide a comprehensive analysis of the efficacy of EMP16-02 in reducing body weight and evaluates the effect on various anthropometric characteristics, satiety and craving, fasting metabolism markers, blood pressure and quality of life. In addition, this study will also provide insight in the safety and GI tolerability of EMP16-02. The design involves careful monitoring of the patient's well-being.

A placebo control will be used to establish the frequency and magnitude of changes in endpoints that may occur in the absence of active treatment.

Randomisation will be used to minimise bias in the assignment of patients to dose groups and to increase the likelihood that known and unknown patient attributes (*e.g.*, demographic and baseline characteristics) are balanced across the treatment groups.

Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

8.3 Selection of dose

The following doses will be used in the study:

- 120 mg orlistat/40 mg acarbose
- 150 mg orlistat/50 mg acarbose

Because both orlistat and acarbose are associated with GI side effects and intolerability, and because the severity of these side effects is less when the dose is slowly increased, a 6-week run-in phase will be employed. In this phase, patients start at a low dose of 60 mg O/20 mg A, and sequentially increase the dose with 30 mg O/10 mg A every 2 weeks. From week 7, all patients have reached their target dose. For more information on dosing scheduling, see Section 8.1.

In the previous phase IIa study (EP-001), the primary comparison made was that between a dose of 90 mg O /30 mg A and a dose of conventional orlistat (Xenical, 120 mg). The rationale behind the lower dose of orlistat was that by optimising drug delivery, a lower dose of both orlistat and acarbose could still achieve a good efficacy. The highest orlistat dose used in the previous phase IIa study was 120 mg. No untoward effects on safety and tolerability were observed and there were no drop-outs in the treatment arm receiving 120 mg O / 40 mg A [28]. Since efficacy was highest in the group receiving 120 mg O / 40 mg A, it is now planned to test a dose that is slightly higher than conventional orlistat (conventional acarbose is given in dose strengths 50 mg or 100 mg TID). Dose levels of up to 240-400 mg orlistat have been studied for up to 6 months and did not result in any safety issues [31,32,33].

9 STUDY POPULATION

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

9.1 Recruitment

The patients will be competitively recruited to both sites from CTC's database of healthy volunteers and patients, and from advertising in media (including social media).

9.2 Screening and enrolment log

Investigators must keep a record of all screened patients even if they were not subsequently included in the study. This information is necessary to verify that patients were selected without bias. The reason for screen failure should be stated for all patients screened but not included. The reason for withdrawal should be stated for all patients included but not completed.

A screening number will be allocated to each patient in connection to the informed consent process at the screening visit (Visit 1). The screening number is generated automatically in the eCRF. The screening number will allow identification of patients irrespective of their possible eligibility for the study. The screening number will have the following format: S0001 for the first patient screened, S0002 for the second, etc.

Patients included and randomised will be assigned a randomisation number from 101 to 256.

If a patient cannot receive the planned dose of IMP within 28 days after screening (*i.e.*, the time interval between signing informed consent until dose administration) the patient should be rescreened before proceeding in the study (see Section 9.7).

9.3 Number of patients

A total of 156 patients will be randomised in the main part of the study. Assuming a drop-out rate of 20%, a total of 52 patients will be randomised to each treatment arm to achieve at least 41 evaluable patients per arm. An evaluable patient is defined as a patient who has completed 26 weeks of treatment with IMP. An evaluable patient in the follow-up part is defined as a patient who has completed 26 weeks of treatment with IMP and the 6 months follow-up visit.

For replacements of patients who discontinue from the study, see Section 9.8.

9.4 Inclusion criteria

For inclusion in the study, patients must fulfil the following criteria:

1. Willing and able to give written informed consent for participation in the study.
2. Aged ≥ 18 and ≤ 75 years.
3. Maximum weight of 150 kg and BMI ≥ 30 or ≥ 28 kg/m² in the presence of other risk factors based on patient interview, *e.g.*, hypertension (either or not treated with antihypertensive agents), glucose dysregulation such as impaired glucose tolerance (defined as elevated fasting glucose or HbA1c as judged by the Investigator) and T2DM that is treated with life style changes (no medication allowed), and/or dyslipidaemia (either or not treated with antihyperlipidemic agents). If indicated, plasma/serum total cholesterol, LDL, HDL, and triglycerides can be measured to verify eligibility as judged by the Investigator.
4. Acceptable medical history, physical findings, vital signs, ECG and laboratory values at the time of screening, as judged by the Investigator.
5. Adequate renal and hepatic function as judged by the Investigator in accordance with the expected disease profile
6. Weight stable (<5% reported change during the three months preceding screening), based on patient interview and weight assessments at screening (Visit 1) and randomisation (Visit 2).
7. Willing to eat three meals per day, and willing to eat breakfast during the visits to the clinic.
8. Males and females may be included in the study. WOCBP must agree to use a highly effective method of contraception with a failure rate of < 1% to prevent pregnancy (combined [oestrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen-only hormonal contraception associated with inhibition of ovulation [oral, injectable, implantable], intrauterine device [IUD]or intrauterine hormone-releasing system [IUS]) OR practice abstinence from heterosexual intercourse (only allowed when this is the preferred and usual lifestyle of the patient) from at least 4 weeks prior to first dose to 4 weeks after last dose.

   Women of non-childbearing potential are defined as pre-menopausal females who are sterilised (tubal ligation or permanent bilateral occlusion of fallopian tubes); or post-menopausal defined as 12 months of amenorrhea (in questionable cases a blood sample with simultaneous detection of follicle stimulating hormone [FSH] 25-140 IE/L).

9.5 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. T2DM treated with medication.
2. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or influence the results or the patient's ability to participate in the study.
3. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks prior to the first administration of IMP, at the discretion of the Investigator.
4. Any planned major surgery within the duration of the study.
5. Untreated high blood pressure (systolic blood pressure [SBP] > 160 mmHg and diastolic blood pressure [DBP] >100 mmHg at screening).
6. Use of any of the prohibited medication listed in Table 9.6-1 within 2 weeks prior to the first administration of IMP. Recently started use of anti-depressants (*e.g.,* selective serotonin re-uptake inhibitors [SSRI]) within 2 weeks prior to the first IMP administration or planned start of anti-depressant treatment during the study period is not allowed, yet patients that are on stable treatment with anti-depressants for at least two months can be included.
7. Known hypersensitivity to any of the test substances. History of hypersensitivity to drugs with a similar chemical structure or class to orlistat and acarbose.
8. Gastrointestinal problems/diseases, *e.g.*, inflammatory bowel diseases and Irritable Bowel Syndrome (IBS). Untreated gastroesophageal reflux disease (GERD) or GERD that is treated occasionally is allowed as judged by the Investigator.
9. Cholestasis.
10. Previous gastrointestinal surgery that might influence gastrointestinal function significantly, previous bariatric surgery, and previous gallbladder surgery as judged by the investigator.
11. Known vitamin B12 deficiency or other signs of achlorhydria.
12. Chronical malabsorption syndrome.
13. Clinically significant abnormal laboratory values at screening as judged by the investigator.
14. History of severe allergic, cardiac or hepatic disease. History of significant cardiovascular disease such as myocardial infarction, congestive heart failure, stroke, serious cardiac arrhythmias. History of angina within 6 months prior to screening.
15. A personal or family history of Medullary Thyroid Carcinoma (MTC).
16. A personal or family history of Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
17. Current or history of alcohol abuse and/or use of anabolic steroids or drugs of abuse, as judged by the Investigator.

18. Positive screen for drugs of abuse at screening or admission to the clinic or positive screen for alcohol at screening or admission to the clinic prior to administration of the IMP.
19. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and HIV.
20. Plasma donation within one month of screening or any blood donation (or corresponding blood loss) during the three months prior to screening.
21. Administration of another new chemical entity (defined as a compound which has not been approved for marketing) or participation in any other clinical study that included drug treatment within three months of the first administration of IMP in this study. Patients consented and screened but not dosed in previous studies are not excluded.
22. Investigator considers the patient unlikely to comply with study procedures, restrictions and requirements.
23. Malignancy within the past 5 years with the exception of in situ removal of basal cell carcinoma.
24. Prolonged QTcF (>450 ms for males, >470 for females), cardiac arrhythmias or any clinically significant abnormalities in the resting ECG at the time of screening, as judged by the Investigator.
25. Patients with swallowing disorders, which may affect the patient's capability to swallow the IMP.

9.6 Restrictions during the study

The patients must be willing to comply to the restrictions outlined in Section 9.6.1 during the entire main study duration *i.e.*, from screening to the safety follow-up visit (Visit 6) if not otherwise specified.

9.6.1 *General restrictions and recommendations*

9.6.1.1 General restrictions

- Contraception Requirements: All WOCBP must use effective contraception (defined in inclusion criterion #8) or practice abstinence from at least four weeks prior to first dose to four weeks after last dose. No contraception requirement for male subjects.
- Meals and Dietary Restrictions:

  ***At the clinic*:**
  Visit 2 (Day 1): Standardised breakfast at the clinic. Administration of a test placebo capsule (all treatment arms) during breakfast. Satiety and craving questionnaire before breakfast and then once every hour for 4 hours until just before lunch (at home).

  Visit 3, 4 and 5 (Week 7, 14 and 26): Standardised breakfast at the clinic. IMP administration during breakfast. Satiety and craving questionnaire before breakfast (at the clinic) and then once every hour for 4 hours until just before lunch (at home).

For details on IMP administration, refer to Section 10.5.

Standardised breakfast: A menu option (decided by CTC) will be offered while the patients are at the research clinic. The meal selection is standardised in the sense that the nutritional content of the meals should be similar at each time point of each treatment day.

At home:
The patients should take the IMP TID in association with the three main meals per day.

- Fasting: The patients should be fasting overnight (8 hours) before Visit 2 to Visit 5 and before Visit 7.
- Alcohol: Consumption of alcohol is not allowed from 24 hours prior to and during all visits to the clinic including Visit 7.
- Nicotine: A stable habit of smoking or use of nicotine-containing products is allowed, yet patients should not change their smoking pattern during the study from screening until Visit 6.
- Exercise: The patients must refrain from strenuous exercise (defined as greater than 70% of the maximal pulse rate for one hour or more) from 48 hours prior to and during all visits.
- Blood donation: The patients must not donate blood or plasma during the study until three months after the final medical examination at Visit 6.
- Participation in other clinical studies: Study patients are not allowed to participate in any other interventional clinical study within three months prior to the first administration of IMP in this study, and during the study until Visit 7.
- Accessibility: patients have access to a mobile phone or other electronic device for electronic diary assessments (ViedocMe).

9.6.1.2 Diet recommendations

The patient will be recommended to adhere to the Nordic Nutrition recommendations, so as to minimise risk for GI-related symptoms during treatment with EMP16-02.

Several study-specific clarifications will be made in relation to the Nordic Nutrition recommendations. These will also lead to a caloric deficit if followed:

- Limit meal size and eat slowly until sufficiently full
- Focus on vegetables that contain a high proportion of fibre, such as green peas, brussels sprouts, suede, salsify, kale, broccoli, Jerusalem artichoke and mushrooms.
- If temporarily problems with gastric distension and flatulence occur, choose “kinder” vegetables that contain a lower proportion of fibres, such as carrots, zucchini/squash, sweet potatoes, beets, parsnips.
- Choose sourdough bread, preferably baked with rye.
- Add psyllium husk to morning and evening meals, especially if you have loose stools.
- Choose muesli and porridge with a high amount of oats (must not be whole-bran oats).
- Eat fruits and berries, preferably those with a higher fibre content, such as pomegranate, physalis, pear, kiwi, raspberry, gooseberry, redcurrants, blueberry.

- If eating soup, take medication together with a piece of bread before starting to eat soup.
- Consumption of meal items containing saccharose or easily digestible starch should be minimised, such as candy, chocolate, chips, cheese doodles, cookies, cakes, ice-cream, soda, ready-made mashed potatoes, white low-fibre bread, fruit yoghurt.
- No restriction on coffee or tea. The consumption of hot non-caloric beverages is encouraged.
- Water is the preferred drink.
- Eat regular meals and avoid snacking, with the exception of fresh fruits/berries and small servings of nuts if meals are delayed.
- Choose dietary fat sources that contain a high proportion of calcium, such as hard cheese, brie, halloumi, feta cheese, pesto, sardines in oil.
- Consumption of meal items containing a high amount of dietary fat should be minimised, such as large servings of pizza, certain fast foods, chips and other fried potato products.

9.6.2 *Prior and concomitant therapy*

Regular use of medication listed in Table 9.6-1 is prohibited during the study, from 2 weeks prior to IMP administration until Visit 6.

Table 9.6-1 Prohibited medication

Type of medication	ATC code	Examples (list is not exhaustive)
Drugs that are affected by or that affect orlistat and acarbose		*Cyclosporin, amiodarone, anti-epileptic drugs, benzodiazepines, anti-psychotic drugs, anti-depressants (stable treatment for more than 2 months prior to first dose of IMP is allowed), cholestyramine, coal tar, digestive products including enzymes, digoxin, anticoagulants (warfarin)*
Drugs altering glucose metabolism and drugs used for diabetes	A10A A10B	*Insulin, metformin, glibenclamide*
Over-the-counter fat or carbohydrate uptake blockers		*Glucosanol, Liposanol, XLS Medical fat binder, Bantaxin, green coffee*
Antacids, proton pump inhibitors, Histamine (H2)-receptor antagonists, prostaglandin analogues and other drugs that enhance mucosal defence and/or control reflux	A02A	*Samarin, Novalucol and other antacids*
	A02BC	*Losec (omeprazole), Nexium (omeprazole), Nixacid (lansoprazole), pantoprazole, and other proton pump inhibitors (PPIs)*
		Tagamet (cimetidine)
	A02BX02	*Andapsin (sucralfate)*
	G02AD06	*Arthrotec (misoprostol)*

Other medications considered necessary for the patient's safety and wellbeing may be given at the discretion of the Investigator. Following consultation with the Sponsor, the Investigator will determine whether or not the patient can continue in the study.

9.7 Screen failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomised in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients. Minimal information includes documentation of signed and dated informed consent form (ICF) and reason(s) for screening failure.

Re-screening can be performed once if any of the following were reasons for screening failure or non-randomisation (as judged by the Investigator):

- Practical reasons.
- Non-significant medical conditions (e.g. influenza, nasopharyngitis).
- Plasma or blood donation outside allowed time windows.

For patients who are re-screened, a new screening number will be assigned and a new, signed ICF will be collected.

9.8 Patient withdrawal

9.8.1 *General withdrawal criteria*

Patients are free to discontinue their participation in the study at any time and for whatever reason without affecting their right to an appropriate follow-up investigation or their future care. The reason for withdrawal of consent should be documented.

Patients may be discontinued from the study at any time at the discretion of the Investigator.

Reasons for discontinuation include:

- Patient withdrawal of consent
- Severe non-compliance to study protocol procedures, as judged by the Investigator. and/or Sponsor
- Patient is lost to follow-up.
- Significant AEs posing a risk for the patient, as judged by the Investigator and/or Sponsor
- Pregnancy
- Death
- Meeting of an exclusion criterion during the study, which, in the opinion of the Investigator, may pose a risk for the patient

9.8.2 *Liver chemistry withdrawal criteria*

Liver chemistry threshold stopping criteria have been designed to assure patient safety and to evaluate liver event aetiology. Study treatment will be stopped for the individual patient if any

of the following liver chemistry stopping criteria, defined in the U.S. Food and Drug Administration (FDA) Guidance on Drug-Induced Liver Injury [34] is met:

- ALT 3 x Upper Limit of Normal (ULN) and total bilirubin ≥ 2xULN (>35% direct bilirubin); **or** ALT 3xULN and INR > 1.5)

NOTE: plasma bilirubin fractionation will be performed.

- ALT 5xULN.
- ALT 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
- Patients with ALT 3xULN **and** < 5xULN **and** bilirubin < 2xULN, who do not exhibit hepatitis symptoms or rash, will be allowed to continue study treatment as long as their liver status is monitored weekly for 4 weeks.

  If ALT is still **≥ 3xULN** after 4 weeks of continued treatment, the treatment will be stopped. Approximately 4 weeks after stop of treatment, subjects will be scheduled for an safety follow-up visit (corresponding to Visit 6) for follow-up safety assessments including safety laboratory sampling.

  In case the liver enzyme parameters have not returned to baseline levels at the safety follow-up visit (2 weeks after end of treatment), subjects will be referred to their general practitioner for continued follow-up by standard medical/clinical care.

9.8.3 *Procedures for discontinuation of a patient from the study*

A patient who prematurely discontinues participation in the study will always be asked about the reason(s) for discontinuation and the presence of any AEs. If a patient withdraws consent, the Investigator must ask the patient if he/she is willing, as soon as possible, to be assessed according to the procedures scheduled for the safety follow-up visit (Visit 6). Any ongoing AEs will be followed as described in Section 11.6.1.15.

The primary reason for discontinuation/early withdrawal must be specified in the eCRF and final drug accountability must be performed.

9.8.4 *Patient replacement*

Patients who prematurely discontinue participation in the study for reasons other than AEs may be replaced.

9.9 Randomisation

On Day 1, patients will be randomised in a 1:1:1 ratio to receive either EMP16-02 150 mg O/50 mg A (n=52), EMP16-02 120 mg O/40 mg A (n=52), or placebo (n=52). A computer-generated randomisation list will be created using SAS Proc Plan, SAS Version 9.4. The randomisation list will contain patient number and treatment and will be kept by the randomiser in a sealed envelope until database lock. A copy of the randomisation list will be delivered to Recipharm, who will pack the IMP individually based on the randomisation list.

Sealed individual treatment code envelopes will be kept at the clinic and at CTC's Pharmacovigilance department (CTC PV) in locked and restricted areas if needed for emergency unblinding.

9.10 Blinding

This is a double-blind study and the allocation of treatments will not be disclosed until clean file has been declared and the database has been locked.

Active treatment and placebo capsules are identical in appearance.

9.11 Emergency unblinding during the study

The treatment code may only be broken by the Principal Investigator or delegate in case of emergency when knowledge of the treatment received is necessary for the proper medical management of the patient. The code breaking procedure should be carefully documented.

For unblinding procedures in case of a potential suspected unexpected serious adverse reaction (SUSAR), refer to Section 11.6.1.14.

10 TREATMENTS

10.1 Identity of investigational medicinal products

The drug product, EMP16-02, is an FDC that contains two active pharmaceutical ingredients (API):

- Orlistat (CAS No. 96829-58-2)
- Acarbose (CAS No. 56180-94-0)

The IMP is supplied as oral MR capsules in two different strengths:

- 60 mg orlistat/20 mg acarbose
- 90 mg orlistat/30 mg acarbose'

EMP16-02 capsules are composed of three pharmaceutical fractions (granules denoted G1, G2 and G3) of multiple unit pellets with different release rates and amounts of orlistat and acarbose. The EMP16-02 capsules with highest strength (90 mg/30 mg) are composed of the following fractions:

1. A granule fraction (G1) with a prolonged release of 18 mg acarbose, which is designed to release acarbose with a delayed on-set of 30 minutes after oral intake in fed state, and a subsequent extended release phase of 4-5 hours.
2. An enteric-coated granule fraction (G2) containing 65 mg orlistat and 12 mg acarbose, which is designed to initiate a rapid release of orlistat and acarbose once the formulation parts have been emptied into the almost neutral luminal conditions (pH around 6.5) in the proximal small intestine [35].

3. A third fraction (G3) containing 25 mg orlistat with a delayed on-set release mechanism of 30 minutes after oral intake in the fed state, and a subsequent extended release phase of 4-5 hours.

The average size distributions of the pellet fractions G1, G2 and G3 are below 700 µm to be emptied from the stomach uniformly during the post-prandial phase [36,37].

EMP16-02 capsules are supplied in plastic bottles.

Placebo capsules are identical in appearance but contain only cellulose.

10.2 Manufacturing, packaging and labelling

The IMP, including placebo, is manufactured by Recipharm Pharmaceutical Development AB, Solna, Sweden, and Recipharm Pessac, Pessac, France.

Primary packaging and release will be performed by Recipharm Pessac, France, and labelling and secondary packaging will be performed by Recipharm, Solna, Sweden. Primary individually packed IMP contains 42 capsules per bottle. The bottle and closure are compliant to food grade requirements. The bottles for the run-in phase and bottles for final dose will be packed in one plastic bag or box per individual patient. Details will be specified in a separate Pharmacy Manual. The individually packed IMP will be labelled with randomisation number and shipped to the research clinic.

Labels will comply with applicable Good Manufacturing Practice (GMP), with Annex 13 of the European Union Good Manufacturing Practice regulations and local regulatory requirements [38].

10.3 Conditions for storage

Both EMP16-02 60/20 and EMP16-02 90/30 capsules should be stored in the fridge (2ºC to 8ºC) to prolong stability to up to 12 months. Single capsules can be stored at room temperature for a maximum of 12 h.

At temperatures above 40ºC, the G3 fraction containing orlistat can melt, which may affect the granulation of the fraction and as such the release of orlistat and the efficacy of the IMP. This may result in gastrointestinal symptoms. No toxic degradation products have been observed in stability tests.

10.4 Preparation and accountability

Each site and the Investigator will maintain a Storage and Accountability Log as well as a Drug Dispensing Log detailing the dates and quantities of study medication received and used by each patient, and study medication destroyed at the safety follow-up visit (Visit 6). Any discrepancies between prepared and returned IMP must be explained and documented. Products deliberately and/or accidentally destroyed by the site or the patient must be accounted for.

10.5 Treatment administration

The patients will be treated with IMP for a period of 26 weeks.

At the clinic, the IMP will be dispensed by site staff, *e.g.*, a study nurse, directly from the individually packed boxes. At home, the patients will self-administer the IMP. The IMP should be taken halfway into a meal, with approximately 100-200 mL water or other drink. The patient should be instructed to not take more than 200 mL water or other drink during the meal, as this can affect the efficacy of the IMP.

The IMP should preferably be taken halfway through each of the three main meals during the day, but can be taken up to 1 hour after the meal. If a dose of EMP16-02 is missed more than 1 hour from the start of the meal, the dose should not be taken. The IMP should not be taken on an empty stomach. If the patient is not eating three main meals on a day, the IMP can be taken with a lighter snack as well. The patients will be recommended to leave 3-4 h between each meal/IMP dose.

The first IMP dose will be taken at home in association with lunch (or other main meal following breakfast) on Day 1 (after Visit 2). One placebo capsule will be given to all patients in association with breakfast at the clinic on Day 1 (Visit 2).

The last dose will be taken at the clinic in association with breakfast on Day 179±3 days (Visit 5, week 26; in total one dose on Day 179).

At Visit 3 and Visit 4 IMP will be taken at the clinic in association with breakfast. All other doses will be taken at home.

IMP will be handed out to the patients at Visit 2 (for week 1-8), Visit 3 (for week 9-14) and Visit 4 (for week 15-26).

10.6 Continuation of treatment with Investigational Medicinal Product

There will be no treatment with EMP16-02 after Visit 5.

10.7 Treatment compliance

The compliance will be calculated by counting the number of capsules, as follows:

$$compliance = \frac{number\ of\ delivered\ capsules - number\ of\ returned\ capsules}{number\ of\ delivered\ capsules}$$

Based on timing of Visit 5, the total length of the treatment period may vary per patient. Compliance calculations should be based on the individual treatment period. IMP administration is planned as follows:

- Day 1: 2 doses of IMP (and one dose of placebo in association with breakfast)
- Day 2 to Day 178 ± 3: 3 doses
- Day 179 ± 3: 1 dose

10.8 Return and destruction of investigational medicinal products

Any unused study medication will be destructed at each site following confirmation by the Sponsor. Empty containers will be destroyed at the study sites. The Monitor will perform final IMP accountability reconciliation at the study end to verify that all unused IMP is adequately destroyed and documented.

11 STUDY ASSESSMENTS

The study assessments are described in the sections below and the timing of these assessments are detailed in the overall schedule of events (Table 8.1-3) and in the detailed schedule of events for Visit 2 to 5 (Table 8.1-4).

11.1 Recording of data

The Principal Investigator will provide the Sponsor with all data produced during the study from the scheduled study assessments. He/she ensures the accuracy, completeness, legibility, and timeliness of the data reported to Sponsor in the eCRF and in all required reports.

11.2 Electronic diary

An electronic diary (ViedocMe™) will be used to collect the following information:

- Questionnaires at visits outlined in Table 11.5-2:
    - Meal pattern, see Section 11.5.4.1.
    - Gastrointestinal tolerability (GSRS), see Section 11.5.4.2.
    - Satiety and craving, see Section 11.5.4.3.
    - Activity and sleep, see Section 11.5.4.4.
    - Health and quality of life RAND-36, see Section 11.5.4.5.
- IMP compliance, AEs and concomitant medication (at week 18 and 22, i.e. between Visit 4 and Visit 5).

11.3 Demographics and other baseline characteristics

11.3.1 *Informed consent*

Signed informed consent must be obtained before any screening procedures in the main part of the study are initiated. A separate informed consent must be obtained before the 6 months

follow-up part (Visit 7) is initiated. The informed consent procedure is further described in Section 14.3.

11.3.2 *Eligibility criteria*

Eligibility criteria should be checked during screening and verified before randomisation/IMP administration. The criteria are specified in Sections 9.4 and 9.5.

11.3.3 *Demographic information*

The following demographic data will be recorded: gender, age, ethnicity and race.

11.3.4 *Medical history and obesity history*

Medical and obesity history will be obtained by patient interview in order to verify that the eligibility criteria are met.

The medical history should include all relevant diseases and operations as judged by the Investigator.

11.3.5 *Prior and concomitant medication*

Prior medications taken within two weeks will be obtained by patient interview in order to verify that the eligibility criteria are met (see also Section 9.6.2).

Medications are classified as prior if the stop date was before or on the day of the first dose administration (pre-dose) and as concomitant if ongoing on the day of the first dose administration, stopped after the first dose administration or started after the first dose administration. To distinguish between prior and concomitant medications on Day 1 (*i.e.*, the first dosing day), the start time of any newly introduced medication or the stop time of any previously ongoing medication must be recorded in the eCRF.

Any use of concomitant medication from screening until the safety follow-up visit (Visit 6) must be documented appropriately in the patient's eCRF. Relevant information (*i.e.* name of medication, dose, unit, frequency, dose form, route of administration, start and stop dates, reason for use) must be recorded. All changes in medication should be noted in the eCRF.

11.3.6 *HIV and Hepatitis B/C*

Patients will be tested for HIV and hepatitis B/C prior to inclusion into the study. Any positive result will exclude the patient from participating in the study.

11.3.7 *Alcohol breath test*

An alcohol breath test will be performed at all visits to the clinic (Table 8.1-3).

11.3.8 *Pregnancy test*

All WOCBP will do a pregnancy test (urine dipstick) at all visits to the clinic (Table 8.1-3).

11.3.9 *Urine drug screen*

Urine will be screened for drugs of abuse at time points outlined in the schedule of events (Table 8.1-3) using the Alere™ Drug Screen Test Panel. Additional random tests can be performed during the study period.

11.3.10 *Baseline symptoms*

A baseline symptom is defined as an event that occurs between the patient's signing of the ICF until the first administration of IMP (i.e. an event that occurs during the screening period). Such events are not AEs and will be recorded as baseline symptoms in the Medical History Log in the eCRF.

11.4 Assessments related to primary endpoints

11.4.1 *Weight*

Weight will be measured in kg (one decimal) without shoes and without thick clothes such as jumpers at visits specified in Table 8.1-3.

Weight at Visit 2 will be compared with weight at Visit 1 prior to randomisation, to ensure that the patient is fulfilling inclusion criterion #6.

All patients completing the treatment period in the main part of the study will be asked to participate in the follow-up part where weight will be measured 6 months after end of treatment (Visit 7). Weight at Visit 7 will be compared with the weight at Visit 2 (baseline) and the weight at Visit 5 (end of 26-weeks treatment).

11.5 Assessments related to secondary endpoints – efficacy

11.5.1 *Anthropometric measurements*

11.5.1.1 Height and BMI

Height will be measured in cm (no decimals) without shoes at visits specified in Table 8.1-3. BMI will be calculated with height measured at Visit 1 for all timepoints where BMI is assessed (Section 11.4.1).

11.5.1.2 Waist circumference

Waist circumference will be measured in cm (one decimal) at visits specified in Table 8.1-3.

11.5.1.3 Sagittal diameter

Sagittal diameter will be measured in cm (one decimal) at visits specified in Table 8.1-3.

For measurement of the sagittal diameter, the patient will need to lie down on his/her back while having knees bent, so that even the lower back is in contact with the surface he/she is

lying on. The distance from the back to the highest point of the abdomen will be measured in cm while the patient exhales.

11.5.1.4 Bio-impedance

Body composition (% body fat) will be measured using a bio-impedance measuring device, according to the manufacturer's instructions, at visits specified in Table 8.1-3.

11.5.2 *Lipid metabolism, glucose metabolism and inflammation markers*

Venous blood samples (4 mL) will be collected to analyse the fasting profile of lipid metabolism markers, glucose metabolism markers, and inflammation markers, as detailed in Table 11.5-1. All parameters will be analysed in immediate association with sampling.

If indicated, total cholesterol, LDL, HDL and triglycerides can be measured at screening to verify if the patient fulfils inclusion criterion #3.

Timing of the assessments is outlined in the overall schedule of events (Table 8.1-3) and in the detailed schedule of events for Visit 2 to 5 (Table 8.1-4).

Table 11.5-1 Glucose metabolism, lipid metabolism and inflammation markers

Patient state	Parameter
Fasting	Hb1Ac
	Total cholesterol
	LDL
	HDL
	Hs-CRP
	Albumin
	Glucose
	Insulin
	Triglycerides

11.5.3 *Blood pressure*

Systolic and diastolic blood pressure and pulse will be measured in supine position after 10 minutes of rest. Blood pressure is both an efficacy assessment and a safety assessment (Section 11.6.3) and should be registered in the vital signs form of the eCRF.

For timing of assessments refer to Table 8.1-3.

11.5.4 *Questionnaires*

A summary of the questionnaires and when they are scheduled to be answered is given in Table 11.5-2. Timing of the questionnaires is also outlined in the overall schedule of events (Table 8.1-3) and in the detailed schedule of events for Visit 2 to 5 (Table 8.1-4).

All questionnaires will be included in the electronic diary.

Table 11.5-2 Summary of questionnaires

Questionnaire	CSP section	Timing
Meal pattern	11.5.4.1	Visit 2 at the clinic or at home the same day as Visit 2 Visit 3 (±2 days) at the clinic or at home Visit 4 (±2 days) at the clinic or at home Visit 5 at the clinic
Gastrointestinal tolerability (GSRS)	11.5.4.2	Visit 2 at the clinic End of Week 2 (-2 days) at home End of Week 4 (-2 days) at home Visit 3 (±2 days) at the clinic or at home End of Week 8 (-2 days) at home Visit 4 (±2 days) at the clinic or at home Visit 5 at the clinic
Satiety and craving	11.5.4.3	Before breakfast, then every hour for 4 hours until lunch (total 5 times): Visit 2 at the clinic and at home Visit 3 at the clinic and at home Visit 4 at the clinic and at home Visit 5 at the clinic and at home
Activity and sleep	11.5.4.4	Visit 2 at the clinic or at home the same day as Visit 2 Visit 3 (±2 days) at the clinic or at home Visit 4 (±2 days) at the clinic or at home Visit 5 at the clinic
Health and quality of life (RAND-36)	11.5.4.5	Visit 2 at the clinic Visit 5 at the clinic at the same hour (± 1 h) as done on Visit 2

11.5.4.1 Meal pattern questionnaire

The questionnaire for intake of meals consists of five multiple choice questions about dietary habits, in which each question contains 4 options to select from. For each question, a score (0-3 points) is obtained.

11.5.4.2 Gastrointestinal tolerability questionnaire

The GSRS consists of 15 questions about gastrointestinal symptoms such as abdominal discomfort, heart burn, acid reflux, stomach rumbling, flatulence, constipation and diarrhoea. The questions need to be answered on the following scale: no discomfort at all, minor discomfort, mild discomfort, moderate discomfort, moderately severe discomfort, severe discomfort, very severe discomfort.

11.5.4.3 Satiety and craving questionnaire

The satiety and craving questionnaire consists of 7 questions about sense of hunger, sense of satiety and craving for certain types of food that need to be answered on a scale from 0 (not at all) to 9 (extremely much).

11.5.4.4 Activity and sleep questionnaire

The activity and sleep questionnaire consists of 2 questions about physical activity and sleep during the previous day/night.

11.5.4.5 Health and quality of life (RAND-36) questionnaire

The health and quality of life questionnaire consists of 36 questions about how the patient experiences his/her own physical and mental health.

11.5.5 ***Drop-out rate***

Early discontinuations should be handled as described in Section 9.8.3.

11.6 **Assessments related to secondary endpoints - safety**

11.6.1 ***Adverse events***

The Principal Investigator is responsible for ensuring that all medical staff involved in the study is familiar with the content of this section and the content of CTC's standard operating procedures (SOPs) regarding emergencies.

11.6.1.1 Definition of adverse event

An AE is defined as any untoward medical occurrence in a patient 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 medicinal product, whether or not considered related to the medicinal product.

Since GI symptoms are collected using the GSRS gastrointestinal intolerance questionnaire, the following symptoms, expected for acarbose and orlistat according to the summary of product characteristics (SmPC), will only be reported as AE in case the symptoms are of severe intensity. If severe or very severe discomfort is reported by a patient via GSRS, clinical staff will be notified and the intensity assessed by Investigator at next scheduled visit as part of normal AE assessment. If severe intensity is confirmed after Investigator judgement the GI symptom included in list below, will be reported as AE:

- Abdominal distension
- Abdominal pain
- Belching
- Bloating
- Constipation
- Diarrhoea
- Dyspepsia
- Faecal incontinence
- Flatulence
- Gastrointestinal pain
- Nausea
- Vomiting
- Oily/fatty stools
- Increased defecation
- Defecation urgency

11.6.1.2 Definition of serious adverse event

An SAE is any AE which:

- results in death
- is life-threatening (this refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might had led to death if the reaction was more severe)
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (IME) (this refers to a reaction that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent any of the other outcomes defined above)

Examples of IMEs are intensive treatment in an emergency room for allergic bronchospasm or blood dyscrasias, convulsions that do not result in hospitalisation, development of drug dependency, and drug abuse.

Planned hospitalisations or surgical interventions for a condition that existed before the patient signed the ICF and that did not change in intensity are not SAEs.

If there is any doubt as to whether an AE meets the definition of an SAE, a conservative viewpoint must be taken, and the AE must be reported as an SAE.

11.6.1.3 Definition of adverse drug reaction

The term adverse drug reaction (ADR) is to be used whenever either the Investigator or Sponsor or designee assessed the AE as at least possibly related to the IMP.

11.6.1.4 Definition of serious adverse drug reaction

The term Serious Adverse Drug Reaction (SADR) is to be used whenever either the Investigator or Sponsor or designee assessed the SAE as at least possibly related to the IMP.

11.6.1.5 Definition of suspected unexpected serious adverse reaction

A SUSAR is any SADR whose nature or intensity is not consistent with the current Reference Safety Information (RSI) in the IB and therefore is assessed as unexpected.

11.6.1.6 Time period and frequency for collecting adverse events

All AEs (including SAEs) will be collected from the start of IMP administration (i.e. from the first placebo capsule given in association with breakfast to all patients at Visit 2) until the safety follow-up visit (Visit 6).

Any AE with start date of the day IMP administration must be recorded with start time.

At the safety follow-up visit (Visit 6), information on new AEs or SAEs, if any, and stop dates for ongoing events must be recorded as applicable.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

11.6.1.7 Assessment of intensity

The grading of the intensity of AEs will follow the common terminology criteria for adverse events (CTCAE) v5.0 [39]. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

The Investigator must assess the intensity of an AE using the following definitions, and record it on the AE Log in the eCRF:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

11.6.1.8 Assessment of causal relationship

The Investigator must assess the causal relationship between an AE and the IMP using the definitions below and record it the AE Log of the eCRF:

Probable	The event has a strong temporal relationship to the IMP or recurs on re-challenge, and another aetiology is unlikely or significantly less likely.
Possible	The event has a suggestive temporal relationship to the IMP, and an alternative aetiology is equally or less likely.
Unlikely	The event has no temporal relationship to the IMP or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the IMP and the event).

An AE is considered causally related to the use of the IMP when the causality assessment is probable or possible.

11.6.1.9 Assessment of outcome

The Investigator must assess the outcome of an AE using the definitions below and record it on the AE Log of the eCRF:

Recovered/resolved	The patient has recovered completely, and no symptoms remain.
Recovering/resolving	The patient's condition is improving, but symptoms still remain.
Recovered/resolved with sequelae	The patient has recovered, but some symptoms remain (for example, the patient had a stroke and is functioning normally but has some motor impairment).
Not recovered/not resolved	The patient's condition has not improved and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
Fatal	
Unknown	

11.6.1.10 Reporting of action taken with study treatment

The Investigator must report the action taken with study treatment using the definitions below and record it on the AE Log of the eCRF:

Dose increased

Dose not changed

Dose rate reduced

Dose reduced

Drug interrupted

Drug withdrawn

Not applicable

Unknown

11.6.1.11 Collecting adverse events

AEs identified using any of the following methods will be recorded:

- AEs spontaneously reported by the patient
- AEs observed by the Investigator or medical personnel
- AEs elicited based on non-leading questions from the Investigator or medical personnel

11.6.1.12 Recording adverse events

AEs must be recorded in the AE Log of the eCRF. The Investigator must provide information on the AE, preferably with a diagnosis or at least with signs and symptoms;

start and stop dates, start and stop time; intensity; causal relationship to IMP; action taken, and outcome.

If the AE is serious, this must be indicated in the eCRF.

AEs, including out-of-range clinically significant clinical safety laboratory values, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

11.6.1.13 Reporting of serious adverse events

SAE reporting should be performed by the Investigator within 24 hours of awareness via the eCRF. All available information regarding the SAE should be entered in the AE Log for the specific patient. By saving the event as "serious" in the eCRF and once the Investigator has signed-off of the event, an e-mail alert is automatically sent to predefined recipients to highlight that an SAE has been registered. The same information is automatically sent to sae@ctc-ab.se.

The SAE report is reviewed by a designated person at the CTC PV department to ensure that the report is valid and correct. For fatal or life-threatening SAEs where important or relevant information is missing, immediate follow-up is undertaken and queries to the site are raised. Investigators or other site personnel should inform CTC PV of any follow-up information on a previously reported SAE immediately but no later than within 24 hours of awareness.

If the SAE report in the eCRF is updated, a new e-mail alert will be sent.

If any additional documentation is required (e.g. autopsy report), CTC PV will request this information from the study site.

In case the eCRF cannot be accessed, the SAE should be reported by manual completion of the paper SAE Form, provided in the Investigator Site File (ISF). The completed, signed and dated paper SAE Form should, within 24 hours, be scanned and e-mailed to:

Medical Monitor: Cornelia Lif- Tiberg

Telephone: +46 (0)73 978 94 45

E-mail: cornelia-lif-tiberg@ctc-ab.se

Sponsor's medical representative: Anders Forslund
Telephone: +46 (0)73 509 06 6
E-mail: anders.forslund@akademiska.se

A copy of the paper SAE form must also be e-mailed to CTC at: sae@ctc-ab.se, and to arvid.soderhall@emprospharma.com.

The study site should notify the site Monitor via phone or e-mail about the submission of the SAE report. As soon as the site personnel have access to the eCRF, the SAE should be reported electronically as well.

The Sponsor or delegate will assume responsibility for reporting SAEs to the competent authority (CA) and independent ethics committee (IEC) in accordance with local regulations.

11.6.1.14 Reporting of SUSARs to EudraVigilance, local CA and IEC

The term SADR is used whenever either the Investigator or Medical Monitor deems a blinded SAE as possibly or probably related to IMP. If an SADR is assessed as unexpected by the Medical Monitor, it is a potential SUSAR and under such circumstances an EudraVigilance reporter will be unblinded. In case the event is regarded as a SUSAR, the certified EudraVigilance reporter will report the SUSAR to the CA, via the EudraVigilance database, and to the IEC in accordance with local regulations and CTC SOPs within the following timelines:

- 7 calendar days if fatal or life-threatening (follow-up information within an additional 8 days)
- 15 calendar days if non-fatal and non-life-threatening (follow-up information as soon as possible)

The clock for expedited initial reporting (Day 0) starts as soon as the Sponsor becomes aware of an SAE. The date should be documented in an acknowledgement receipt.

The Medical Monitor is responsible for medical review of the SAE narrative in the Council for International Organisations of Medical Sciences (CIOMS) for (or equivalent) prior to expedited reporting.

The Sponsor or delegate is responsible for informing the Investigators concerned of relevant information about SUSARs that could adversely affect the safety of patients.

The Sponsor or delegate is responsible for once a year throughout the clinical study (or on request) submitting a safety report to the CA and the IEC taking into account all new available safety information received during the reporting period.

11.6.1.15 Treatment and follow-up of adverse events

Patients with AEs that occur during the study must be treated according to daily clinical practice at the discretion of the Investigator.

AEs must be followed up until resolution or to the safety follow-up visit (Visit 6), whichever comes first. At the safety follow-up visit, information on new AEs, if any, and stop dates for previously reported AEs must be recorded (if known). AEs assessed as stable by the Investigator at the safety follow-up visit will not have to be followed up until resolution.

It is the responsibility of the Investigator to follow up on all SAEs until the patient has recovered, stabilised, or recovered with sequelae, and to report to the Sponsor all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultation.

11.6.1.16 Procedures in case of pregnancy

In case of pregnancy or suspicion of possible pregnancy of any female patients, the study treatment must be stopped immediately, and the patient discontinued from participation in the study. Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of the contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital

abnormality) must be followed up and documented even after the patient was discontinued from the study.

All events of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as AEs. All outcomes of pregnancy must be reported to the Sponsor and the Principal Investigator on the pregnancy outcomes report form.

11.6.1.17 Treatment of overdose

An overdose is a dose in excess of the dose specified for each treatment arm in this CSP.

In cases of accidental overdose, the patient should contact the clinic and standard supportive measures should be adopted as required.

An overdose should be documented as follows:

- An overdose with associated AE is recorded as the AE diagnosis/symptoms in the AE Log of the eCRF.
- An overdose without associated symptoms is only reported in the patient's medical records.

No known antidote is available.

11.6.2 ***Physical examination***

11.6.2.1 Full physical examination

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities.

Physical examination will be judged as normal, abnormal, not clinically significant or abnormal, clinically significant. The assessment will be recorded in the eCRF. Post-dose findings judged as abnormal, clinically significant will be reported as AEs.

Timing of the assessment is outlined in the overall schedule of events (Table 8.1-3) and in the detailed schedule of events for Visit 2 to 5 (Table 8.1-4).

11.6.2.2 Brief physical examination

A brief physical examination will include assessment of general health condition, skin, lungs and cardiovascular (auscultation), abdomen (palpation).

Physical examination will be judged as normal, abnormal, not clinically significant or abnormal, clinically significant. The assessment will be recorded in the eCRF. Post-dose findings judged as abnormal, clinically significant will be reported as AEs.

Timing of the assessment is outlined in the overall schedule of events (Table 8.1-3) and in the detailed schedule of events for Visit 2 to 5 (Table 8.1-4).

11.6.3 *Vital signs*

Systolic and diastolic blood pressure and pulse will be measured in supine position after 10 minutes of rest. Blood pressure is both an efficacy assessment (Section 11.5.3) and a safety assessment and should be registered in the vital signs form of the eCRF.

Vital signs will be judged as normal, abnormal, not clinically significant or abnormal, clinically significant. The assessment will be recorded in the eCRF. Post-dose vital signs judged as abnormal, clinically significant will be reported as AEs.

Timing of the assessment is outlined in the overall schedule of events (Table 8.1-3) and in the detailed schedule of events for Visit 2 to 5 (Table 8.1-4).

11.6.4 *Resting 12-lead ECG*

Single 12-lead ECG will be recorded in supine position after 10 minutes of rest using an ECG machine. HR and PR (or PQ if registered by ECG machine), QRS, QT and QTcF intervals will be recorded. If the ECG machine does not record QTcF, a QTcF calculator will be used.

Safety ECGs will be reviewed and interpreted on-site by the Investigator.

Any abnormalities will be specified and documented in the eCRF as clinically significant or not clinically significant. Abnormal post-dose findings assessed by the Investigator as clinically significant will be reported as AEs.

Timing of the assessment is outlined in the overall schedule of events (Table 8.1-3) and in the detailed schedule of events for Visit 2 to 5 (Table 8.1-4).

11.6.5 *Safety laboratory assessments*

Blood samples for analysis of clinical chemistry, haematology and coagulation parameters will be collected through venepuncture and sent to the certified local laboratory at Uppsala University Hospital and/or Linköping and analysed by routine analytical methods.

Urine analysis will be performed at each research clinic using dip sticks. The assessments will be performed at visits specified in Table 8.1-3.

Urine pregnancy tests will be performed at visits specified in Table 8.1-3.

The safety laboratory parameters are defined in Table 11.6-1 (full safety laboratory) and Table 11.6-2 (liver function only), and will be assessed at time-points detailed in Table 8.1-3.

Abnormal values assessed by the Investigator as clinically significant will be reported as AEs. If an abnormal value is associated with corresponding clinical signs or symptoms, the sign/symptom should be reported as the AE.

Table 11.6-1 Safety laboratory parameters

Category	Parameter
Clinical chemistry	ALT
	Albumin
	ALP
	AST
	Bilirubin (total and conjugated)
	Calcium
	Creatinine
	GGT
	Glucose
	Hb1Ac[1]
	Phosphate
	Potassium
	Sodium
	Urea
Haematology	Haematocrit
	Haemoglobin (Hb)
	Platelet count
	Red blood cell (RBC) count
	White blood cell (WBC) count with differential count
Coagulation	Activated Partial Thromboplastin Time (APTT)
	Prothrombin Complex International Normalised Ratio (PK[INR])
Urinalysis (dip stick)	Erythrocytes
	Glucose
	Ketones
	Leucocytes
	Nitrite
	pH
	Protein
	Specific gravity
	Urobilinogen
FSH-test	FSH[2]
Pregnancy test	Urine pregnancy test[3]

[1] HbA1c at screening only
[2] At screening, post-menopausal females only, as applicable
[3] WOCBP only

Table 11.6-2 Liver function parameters

Category	Parameter
Clinical chemistry	ALT
	ALP
	AST
	GGT

11.7 Assessments related to exploratory endpoints

11.7.1 *Exploratory blood sampling*

Venous blood samples (2 mL) for the determination of the fasting ApoA1 and ApoB will be collected. Details on sample handling will be provided in a separate laboratory manual.

Timing of the assessment is outlined in Table 8.1-4.

Table 11.7-1 Metabolism markers

Patient state	Parameter
Fasting	ApoA1
	ApoB

11.7.2 *Orlistat and acarbose plasma concentration*

Venous blood samples (approximately 4 mL) for the determination of plasma concentrations of orlistat and acarbose after administration of the IMP, will be collected pre-dose at Visit 5, as displayed in Table 8.1-4.

The date and time of collection of each sample will be recorded in the eCRF.

The collected blood samples will be centrifuged to separate plasma, which will be divided into aliquots after centrifugation for bioanalysis. Further collection and handling details will be specified in a separate laboratory manual.

Samples for determination of plasma concentrations of orlistat and acarbose will be analysed by Lablytica Life Science AB, Uppsala, Sweden, by means of a validated bioanalytical method. The details of the analytical method used will be described in a separate bioanalytical report.

11.8 Appropriateness of measurements

All methods used for safety assessments are commonly used in standard medical care and in Phase I and Phase II clinical studies. Obesity parameter assessments are in accordance with the European Medicines Agency (EMA) guideline on clinical evaluation of medicinal products used in weight management [40].

12 PROCEDURES FOR BIOLOGICAL SAMPLES

12.1 Sample collection

Safety laboratory samples and samples for lipid metabolism, glucose metabolism and inflammation markers are collected according to standard procedures as described in Section 11.6.5 and Section 11.5.2.

The sample procedure for exploratory blood samples is described in Section 11.7.

12.2 Volume of blood

The estimated volume of blood to be collected from each patient during the study will be approximately 100 mL. The anticipated volume of blood samples collected during the study from each patient will not exceed 450 mL (*i.e.*, less than the volume drawn during a regular blood donation).

12.3 Handling, storage and destruction of laboratory samples

All biological samples will be registered in a biobank at CTC (893).

Any remains from the safety laboratory samples will be disposed of after analyses.

The samples for analyses of orlistat and acarbose plasma concentrations parameters will be stored at <-70°C until analysed. The samples will be disposed of once the CSR has been finalised following confirmation by the Sponsor.

The samples for analysis of glucose metabolism, lipid metabolism and inflammation markers, and the exploratory blood samples will be stored at <-70°C until analysed. The samples will be disposed of once the CSR has been finalised and following confirmation by the Sponsor.

12.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

CTC keeps full traceability of collected biological samples from the patients while in storage at the research clinics until shipment and keeps documentation of receipt of arrival.

The sample receiver (the analytical laboratory) keeps full traceability of the samples while in their storage and during use until used or disposed of.

The Sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

12.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of biological samples donated, the samples will be disposed of /destroyed, if not already analysed and documented.

The Principal Investigator will ensure that:

- Patient withdrawal of informed consent is notified immediately to Sponsor.
- Biological samples from the patient, if stored at the research clinics, are immediately identified, disposed of/destroyed and the action is documented.

The Sponsor has to ensure that the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed or returned to the research clinics and the action is documented.

13 QUALITY MANAGEMENT, QUALITY ASSURANCE AND QUALITY CONTROL

13.1 Quality management: critical process, system and data identification

During CSP development, the Sponsor will identify those processes, systems (facilities, computerised systems) and data that are critical to ensure human patient protection and the reliability of trial results according to applicable SOPs and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 R2.

Identified risks, including risks associated with the COVID-19 (Coronavirus) pandemic, will be categorised separately from the CSP.

Sponsor oversight responsibilities, such as monitoring, adverse event reporting, safety monitoring, changes in Investigators and key study team staff and quality assurance activities may need to be reassessed in relation to the COVID-19 pandemic and temporary, alternative proportionate mechanisms of oversight may be required.

13.2 Quality assurance and quality control

The Sponsor is responsible for implementing and maintaining quality assurance (QA) and quality control (QC) systems with written SOPs with regards to management of identified risks, CSP compliance, good clinical practice (GCP) compliance and applicable regulatory requirements.

The Sponsor is responsible for securing agreements with involved subcontractors and to perform regular subcontractor oversight to ensure CSP compliance, GCP compliance and compliance with applicable regulatory requirements.

The Sponsor is responsible for implementing a risk-based validated electronic data capture system and maintain SOPs for the whole life cycle of the system.

QC should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

The Sponsor has delegated the responsibilities outlined above to CTC whilst maintaining overall study oversight.

14 ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [41] and are consistent with ICH/GCP E6 (R2), EU Clinical Trials Directive, and applicable local regulatory requirements.

14.2 Ethics and regulatory review

The Principal Investigator is responsible for submission of the CSP, the patient information and ICF, any other written information to be provided to the patients and any advertisements used for recruitment of patients to applicable IEC for approval.

The Sponsor has delegated to CTC the responsibility to submit study documents to the applicable CA according to local regulatory requirements.

Approval must be obtained in writing from both IEC and CA before the first patient can be recruited.

The Sponsor will provide the CA, IEC and Principal Investigators with safety updates/reports according to local requirements. Progress reports and notifications of SUSARs will be provided to the IEC according to local regulations and guidelines.

14.3 Patient information and consent

It is the responsibility of the Investigator or an authorised associate to give each potential study patient adequate verbal and written information before any study specific assessments are performed.

The information will include the objectives and the procedures of the study as well as any risks or inconvenience involved. It will be emphasised that participation in the study is voluntary and that the patient may withdraw from participation at any time and for any reason, without any prejudice. All patients will be given the opportunity to ask questions about the study and will be given sufficient time to consider participation before signing the ICF.

Before performing any study-related procedures the ICF must be signed and personally dated by the patient and by the Investigator. A copy of the patient information including the signed ICF will be provided to the patient.

Documentation of the discussion and the date of informed consent must be recorded in the source documentation and in the eCRF. The patient information sheet and the signed ICF should be filed by the Investigator for possible future audits and/or inspections.

The final approved version of the patient information and ICF must not be changed without approval from the Sponsor and the applicable IEC.

All patients completing the treatment period will be asked to participate in a long-term follow-up part and attend Visit 7, scheduled 6 months after completion of the 26-weeks

treatment period (main part of the study). A separate informed consent for participation in the long-term follow-up must be obtained before initiation of any study-specific assessments at Visit 7. Informed consent will be collected following the same procedure as explained above.

14.4 Patient information card

The patient will be provided with a Patient information card including the following information:

- That he/she is participating in a clinical study
- Patient study ID
- That he/she is treated with the IMP
- The name and phone number of the Investigator
- Name and address of the Sponsor

14.5 Patient data protection

The ICF includes information that data will be recorded, collected and processed and may be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the European Union Data Protection Directive (95/46/EC) and General Data protection Regulation (GDPR), the data will not identify any persons taking part in the study.

The potential study patient should be informed that by signing the ICF he/she approves that authorised representatives from Sponsor and CTC, the concerned IEC and CA have direct access to his/her medical records for verification of clinical study procedures. For further details on the patient information and ICF process, refer to Section 14.3.

The patient has the right to request access to his/her personal data and the right to request rectification of any data that is not correct and/or complete in accordance with the European Union Data Protection Directive (95/46/EC) and the request will be raised to the Principal Investigator.

The Investigator must file a Patient Identification List which includes sufficient information to link records, i.e. the eCRF and clinical records. This list should be preserved for possible future inspections/audits but must not be made available to the Sponsor except for monitoring or auditing purposes.

Personal data that are collected in the study such as health information and ethnicity are considered as sensitive personal data. This data will be pseudoanonymised, i.e. personally identifiable information (PII) will be removed and replaced by a unique Patient ID and will be processed by the Sponsor and other involved parties during the study. After the study end, only anonymised data, i.e. aggregated data sets, can be used.

For this study, the Sponsor Empros Pharma AB is the data controller of all data processed during the study (e.g. Trial Master File [TMF], study reports) and CTC is the data processor. Any subcontractors used in the study (see Section 5) are also data processors.

For data that are processed at the clinics (e.g. medical records and ISF), CTC is the data controller.

14.6 Changes to the approved clinical study protocol

Any proposed change to the approved final CSP (including appendices) will be documented in a written and numbered clinical protocol amendment. All substantial amendments to the protocol must be approved by the appropriate IEC and/or CA before implementation according to applicable regulations.

14.7 Audits and inspections

Authorised representatives of Sponsor, a CA, or an IEC may perform audits or inspections at the research clinics, including source data verification (SDV). The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, ICH-GCP guidelines and any applicable regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by a CA about an inspection at the centre.

14.8 Insurance

Patients will be covered under the Swedish Pharmaceutical Insurance (Läkemedelsförsäkringen). The certificate of insurance and an information leaflet containing essential information about the insurance coverage can be provided upon request. The participating patients are also protected in accordance with national regulations, as applicable. CTC has a company insurance covering services performed by CTC.

15 STUDY MANAGEMENT

15.1 Training of study site personnel

Before screening of the first study patient a Sponsor representative or delegate will perform a study initiation visit at each research clinic. The requirements of the CSP and related documents will be reviewed and discussed and the investigational staff will be trained in any study specific procedures and system(s) utilised.

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study and have a detailed knowledge of and training in the procedures that are to be executed by them. Any new information of relevance to the performance of this study must be forwarded to the staff involved in a timely manner.

The Investigator will keep a list of all personnel involved in the study together with their function and study related duties delegated. A Curriculum Vitae will be available for all staff to whom study-specific duties are delegated.

15.2 **Clinical monitoring**

The Sponsor is responsible for securing agreement from all involved parties to ensure direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities.

As defined in the risk-based monitoring (RBM) plan, approved by the Sponsor and provided separately, the responsible Monitor will periodically visit the study site at times agreed upon by the Investigator and the Monitor. The RBM plan, including a description of planned on-site visits, remote and central monitoring will take into consideration the challenges presented by COVID-19 pandemic to align on local restrictions, impact assessment, contingency plans and stud specific mitigation strategies.

Adaptations related to the on-site monitoring plan may be required, e.g. supplementation with (additional/increased) centralised monitoring and central review of data if considered possible and meaningful. Results of adjusted monitoring/review measures should be reported to the Sponsor in monitoring reports and in the CSR.

At the time of each monitoring visit, the role of the Monitor is (but not limited to) to:

- provide information and support to the investigational team.
- confirm that facilities and resources remain acceptable.
- confirm that the investigational team is adhering to the CSP, applicable SOPs, guidelines, manuals and regulatory requirements.
- verify that data are being accurately and timely recorded in the CRFs and that IMP accountability checks are being performed.
- verify that data in the eCRF are consistent with the clinical records (SDV) in accordance with the RBM plan.
- verify that the correct informed consent procedure has been adhered to for participating patients.
- ensure that withdrawal of informed consent to the use of the patient's biological samples will be reported and biological samples are identified and disposed of/destructed accordingly, and that this action is documented and reported to the patient.
- verify that AEs are recorded and reported in a timely manner and according to the CSP.
- raise and escalate any serious quality issues, serious GCP breach and any data privacy breach to the Sponsor.

Centralised monitoring will also be performed continuously by study team members at CTC in accordance with the RBM plan.

When the study has been completed and all queries have been resolved and the database has been locked, the Monitor will perform a close-out visit.

15.3 Source data documents

A separate Origin of Source Data List will be generated for each site before start of enrolment, specifying the location of the source of derived information appearing in the CRF. This document must be signed by the Principal Investigator and the Monitor to confirm agreement before start of recruitment.

Source documents are all documents used by the Investigator or hospital that relate to the patient's medical history, that verifies the existence of the patient, the inclusion and exclusion criteria, and all records covering the patient's participation in the trial. They include laboratory notes, memoranda, material dispensing records, patient files, etc. The eCRF may constitute source data if clearly defined in the Origin of Source Data List.

The Investigator should guarantee access to source documents to the Monitor, CAs and the IECs, if required.

15.4 Study agreements

The Principal Investigator must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study.

Agreements between Sponsor and CTC must be in place before any study-related procedures can take place, or patients be enrolled.

15.5 Study time table and end of study

The main part of the study (Visits 1 to 6) is expected to start in Q2 2020 and to be completed by Q2 2021. The follow-up part of the study (Visit 7) is expected to start in Q2 2020 and to be completed by Q3 2021.

A patient is considered to have completed the main part of the study if he/she has completed all visits in the study including Visit 6. The follow-up Visit 7 is a voluntarily visit and the results from this visit will be reported in an addendum to the CSR.

The end of the study is defined as the date of the last Visit 7 of the last patient in the study.

15.6 Termination of the study

The Investigator or the Sponsor may terminate this study prematurely for any reasonable cause. The IEC and CA should be informed promptly. Conditions that may warrant study termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study or potential study patients; or
- A decision by the Sponsor to suspend or discontinue development of the IMP.
- If the CA obtains information that raises doubts about the safety or scientific validity of the clinical study, the CA can suspend or prohibit the study. Before the CA reaches its decision, it shall, except where there is imminent risk, ask the Sponsor and/or the

Investigator for their opinion, to be delivered within one week (Directive 2001/20/EC, Article 12, Section 1).

If the study is prematurely terminated or suspended for any reason, the Investigator/institution should promptly inform the study patients and should assure appropriate follow-up for the patients.

15.7 Reporting and publication

15.7.1 *Clinical study report*

A summarising report must be submitted to the applicable CA and IEC within 12 months after completion of the study (in accordance with LVFS 2011:19, Chapter 9).

A CSR, in compliance with ICH-E3, describing the conduct of the study, any statistical analyses performed, and the results obtained, will be prepared by CTC. The report will be reviewed and approved by, as a minimum, the Principal Investigator, the Statistician and the Sponsor. The study results will be reported in the EudraCT database per applicable regulations within 12 months after completion of the study.

All data obtained from exploratory analyses will be reported separately.

15.7.2 *Annual safety report*

If the study duration exceeds one year, the Sponsor must submit development safety update report (DSUR) to the CA and to the IEC. The report shall summarise all pertinent safety information collected during the reporting period and contain an update of the risk-benefit evaluation if there has been any change since the approval of the clinical study.

15.7.3 *Confidentiality and ownership of study data*

Any confidential information relating to the IMP or the study, including any data and results from the study, will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the study are responsible for protecting the confidentiality of this proprietary information belonging to the Sponsor.

15.7.4 *Publication*

The results from this study may be submitted for publication at the discretion of the Sponsor.

15.8 Archiving

The Principal Investigator is responsible for maintaining essential documents, (as defined in ICH E6 GCP, Section 8) for 10 years after finalisation of the CSR. This includes any original source documents related to the study, the Patient Identification List (providing the sole link between named patient source records and anonymous eCRF data), the original signed ICFs and detailed records of disposition of IMP.

It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The Sponsor will archive the TMF in accordance with ICH E6 GCP, Section 8 and applicable regulatory requirements.

The data from the eCRFs will be sent to the Sponsor and a copy will be sent to the clinic and filed in the Investigator Study File for archiving for 10 years after finalisation of the CSR.

The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorised representatives of appropriate Health/Regulatory Authorities, without written permission from the Sponsor.

16 DATA MANAGEMENT

The data management routines include procedures for handling of the eCRF, database set-up and management, data entry and verification, data validation, QC of the database, and documentation of the performed activities including information of discrepancies in the process. The database, data entry screens, and program will be designed in accordance with the CSP.

Data validation/data cleaning procedures are designed to assure validity and accuracy of clinical data. These procedures consist of computerised online edit checks identifying e.g. data values that are outside the allowed range and SAS-programmed batch checks on data exports. All study-specific and standard data validation programming will be tested in a separate testing environment prior to use on production data.

Detailed information on data management will be described in a study-specific Data Management Plan (DMP).

16.1 The web-based eCRF

Clinical data will be entered into a 21 CFR Part 11-compliant eCRF (Viedoc™) provided by PCG Solutions AB. The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents or at bedside (if the eCRF data constitutes source data). Source data are to be defined at the site before inclusion of the first patient (Section 15.3).

Authorised site personnel designated by the Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all authorised trial site personnel prior to the trial being initiated and any data being entered into the system for any study patient.

16.2 The entering of data into the eCRF

All entries, corrections, and alterations are to be made by the Investigator or designee. Neither the Monitor nor any other study team member besides site staff can enter data in the eCRF. All data should be entered in English. The eCRFs should be completed as soon as possible

during or after the patient's visit. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator or assigned clinical staff should record such information in the eCRF. The Investigator will be required to electronically sign off the clinical data. This will be performed by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature.

16.3 **Electronic patient reported outcome**

The patients themselves will record data (see Section 11.2) using an ePRO system (ViedocMe™) linked to the eCRF. The ePRO system includes password protection and internal quality checks. Text reminders can be sent to the patient through the ePRO. All data registered in the ePRO are stored together with the eCRF data.

16.4 **The query process**

The Monitor will review the eCRFs and evaluate them for completeness and consistency. Data in the eCRF will be compared with the respective source documents to ensure that there are no discrepancies for critical data as described in the RBM plan. All entries, corrections, and alterations are to be made by the Investigator or designee. Neither the Monitor nor any other study team member besides site staff can enter data in the eCRF.

If corrections are needed, queries will be raised within the eCRF, either as a result of built-in edit checks or manually raised by the monitor. An appropriate member of the site staff will answer the queries in the eCRF either by correcting the data or by entering a response to the query. The monitor will either approve the answer/correction or re-issue the query.

16.5 **Audit trail**

All entries in the eCRF will be fully recorded in a protected audit trail. Once clinical data have been saved, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged.

16.6 **External data**

External data consists of data that are not recorded in the eCRF. Data may be received in electronic format or as a paper printout. Key variables are defined in order to uniquely identify each sample record. File and data formats are agreed with the external data provider.

16.7 **Medical coding**

Medical coding will be performed by trained personnel at CTC. AEs and medical/surgical history verbatim terms will be coded using the Medical Dictionary of Regulatory Activities

(MedDRA; latest version available at start of coding). Prior and concomitant medications will be coded according to the World Health Organisation (WHO) Anatomic Therapeutic Chemical (ATC) classification system. All coding will be approved by Sponsor prior to database lock.

16.8 Database lock

When all data in the main part (Visits 1 to 6) have been entered and all discrepancies are solved, clean file will be declared, the database will be locked, the code will be broken and the data will be analysed. The CSR will be written based on the main part (Visits 1 to 6).

When data from the follow-up part (Visit 7) have been entered and all discrepancies are solved, clean file for Visit 7 will be declared, the database will be locked, the data will be analysed and presented in an addendum to the CSR.

17 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The principal features of the statistical analysis to be performed are described in this section. A more technical and detailed elaboration of the principal features will be presented in a separate Statistical Analysis Plan (SAP), which will be signed and approved prior to database lock.

Analyses of the primary and secondary endpoints will be performed by CTC AB.

17.1 General

Continuous data will be presented in terms of evaluable and missing observations, arithmetic mean, standard deviation (SD), median, minimum and maximum value.

Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by treatment, and by assessment time. Individual patient data will be listed by patient number, treatment, and, where applicable, by assessment time.

All descriptive summaries and statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute, Inc., Cary, NC).

Baseline will be defined as the visit with last data collection point prior to the first administration of IMP.

Outliers will be included in summary tables and listings and will not be handled separately in any analyses. No imputation of data will be performed neither for dropouts nor for missing data. An analysis of dropouts will be performed as detailed in Section 17.6.6.

All hypothesis testing will use a significance level of 5%.

Comparisons will be made pairwise and analysed at each visit if not stated otherwise.

17.2 Determination of sample size

The hypothesis is to show that patients treated with EMP16-02 have a greater relative change (reduction) in body weight compared to placebo. The estimated treatment difference should be 5% with a standard deviation of 8%, a power of 80% and a significance level of 5% based on two-sided hypothesis testing. Using PASS V16.0 (method compare means), the number of evaluable patients needed per treatment arm is calculated to 41 patients. An evaluable patient is defined as a patient who has completed 26 weeks of treatment with IMP. Taking into account an estimated drop-out frequency of 20%, a total of 156 patients need to be randomised.

17.3 Analysis data sets

17.3.1 *Full analysis set*

The Full Analysis Set (FAS) will consist of all patients who have been randomised and received at least one dose of IMP and who have at least one post-baseline assessment of efficacy data.

17.3.2 *Safety analysis set*

The Safety Analysis Set will consist of all patients who received at least one dose of the IMP.

17.3.3 *Per protocol set*

The Per Protocol Set (PPS) will consist of all patients who have been randomised and completed the study without any major protocol deviations that are judged to compromise the analysis of the data. All protocol violations will be judged as major or minor prior to database lock.

17.4 Description of study population

17.4.1 *Demographics and baseline characteristics*

Descriptive statistics for demographics, weight and height, BMI, waist circumference, sagittal diameter and body composition will be presented by treatment.

17.4.2 *Medical/obesity history and prior/concomitant medication*

Medical/obesity history will be presented by treatment, system organ class (SOC) and preferred term (PT). Prior/concomitant medications will be presented by treatment and applicable ATC level.

All data will be listed by treatment and patient.

17.4.3 *Baseline symptoms*

Baseline symptoms will be presented by treatment, SOC and PT. All data will be listed by treatment and patient.

17.4.4 *Treatment compliance*

Compliance will be calculated by counting tablets, as follows:

$$compliance = \frac{number\ of\ delivered\ capsules - number\ of\ returned\ capsules}{number\ of\ delivered\ capsules}$$

17.5 Analysis of primary endpoints

17.5.1 *Weight*

Relative (%) change from baseline in body weight after 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A) as compared to placebo will be analysed using analysis of variance with treatment as independent variable.

17.6 Analysis of secondary endpoints – efficacy

17.6.1 *Weight*

The absolute change from baseline in body weight after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A) as compared to placebo will be analysed using analysis of covariance with treatment and body weight at baseline as covariates.

The relative (%) change from baseline in body weight after 14 and 26 weeks of treatment with EMP16-02 (150 mg O/50 mg A) as compared to placebo will be analysed using analysis of variance with treatment as independent variable.

The proportion of patients with ≥5% and ≥10% decrease in body weight compared to baseline after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using Chi-square test without continuity correction.

17.6.2 *Anthropometric measurements*

The relative change from baseline in BMI after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using analysis of variance with treatment as independent variable. Baseline is defined as BMI measured pre-dose at Visit 2. The absolute change from baseline in BMI will be analysed using analysis of covariance with treatment and body weight at baseline as covariates.

The absolute change from baseline in waist circumference after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using analysis of covariance with treatment and body weight at baseline as covariates.

The absolute change from baseline in sagittal diameter after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using analysis of covariance with treatment and body weight at baseline as covariates.

The relative (%) change from baseline in percentage body fat after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using analysis of variance with treatment as independent variable. The absolute change from base line in percentage of body fat will be analysed using analysis of covariance with treatment and body weight at baseline as covariates.

17.6.3 *Glucose metabolism markers, lipid metabolism markers and inflammation markers*

Fasting HbA1c, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, liver enzymes, albumin and hs-CRP will be assumed to be normally distributed.

The relative (%) change from baseline in fasting HbA1c, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, liver enzymes, albumin and hs-CRP after 7, 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using analysis of variance with treatment as independent variable. The absolute change from baseline in these markers will be analysed using analysis of covariance with treatment and body weight at baseline as covariates.

The proportions of diabetic patients (patients with a fasting glucose ≥ 7.0 mmol/L) and prediabetic patients (fasting glucose ≥ 6.1 and < 7.0 mmol/L) and non-diabetic patients (fasting glucose < 6.1 mmol/L) after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) will be presented using shift tables. The change from baseline in the proportion of diabetic and prediabetic patients after 14 and 26 weeks of treatment with EMP16-02 as compared to placebo will be analysed using Chi-square test without continuity correction.

17.6.4 *Blood pressure*

The relative (%) change from baseline in blood pressure after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using analysis of variance with treatment as independent variable. The absolute change from baseline in blood pressure will be analysed using analysis of covariance with treatment and body weight at baseline as covariates.

17.6.5 *Questionnaires*

17.6.5.1 Meal pattern questionnaire

For each treatment group, the absolute and percent change from baseline in total score of the Meal pattern questionnaire will be calculated and analysed using the Wilcoxon Rank Sum test at each visit. The absolute change for each question will be compared between the treatment groups by using the Wilcoxon Rank Sum test.

17.6.5.2 Gastrointestinal tolerability questionnaire

For each treatment group, the absolute and percent change from baseline in total score of the GSRS be calculated and analysed using analysis of covariance with at least treatment, weight at baseline as covariates. More covariates will be addressed in the SAP.

17.6.5.3 Satiety and craving

Satiety and craving as total score after 14 and 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo, corrected for hunger and craving after standardised breakfast at baseline will be analysed using the Wilcoxon Rank Sum test. Each individual question may be analysed, if so, will this be described in the SAP.

17.6.5.4 Activity and sleep questionnaire

The two questions included in the Activity and Sleeping questionnaire will be analysed pairwise at each visit using a Chi-square test without continuity correction and presented in frequency tables.

17.6.5.5 Health and quality of life (RAND-36)

The change from baseline in quality of life after 26 weeks of treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using the Wilcoxon Rank Sum test.

17.6.6 ***Drop-out rate***

The drop-out rate (overall and GI-related) following treatment with EMP16-02 (120 mg O/40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using Chi-square test without continuity correction.

17.7 **Analysis of secondary endpoints – safety**

17.7.1 ***Adverse events***

An overview of all AEs, including SAEs, intensity, relationship to IMP, withdrawals due to AEs and deaths will be presented by treatment, SOC and PT.

Incidence of AEs and SAEs will be summarised by SOC and PT by treatment and overall.

All AE data will be listed by treatment and patient and include the verbatim term entered by the Investigator.

17.7.2 *Physical examination*

Clinically significant and non-clinically significant abnormal findings will be specified and presented by patient and summarised by treatment.

Changes over time will be presented using shift tables if considered appropriate.

All data will be listed by treatment and patient.

17.7.3 *Vital signs*

Vital signs (systolic/diastolic BP and pulse) will be summarised by treatment. Data will be presented with absolute and percent change from baseline at each visit.

All data will be listed by treatment and patient.

17.7.4 *Resting 12-lead ECG*

All ECGs will be categorised as ”normal”, ”abnormal, not clinically significant”, or ”abnormal, clinically significant” (as judged by the Investigator) and summarised by treatment using frequency tables.

Changes over time will be presented using shift tables.

All data will be listed by treatment and patient.

17.7.5 *Laboratory safety assessments*

Safety laboratory data will be summarised by treatment with absolute and percent change from baseline at each visit.

Abnormal, clinically significant values will be summarised separately if considered appropriate.

All data will be listed by treatment and patient.

17.8 **Analysis of exploratory endpoints**

17.8.1 *Plasma/serum profile of ApoA1 and ApoB*

Details of these analyses will be given in the SAP.

17.8.2 *Orlistat and acarbose plasma values*

Details of these analyses will be given in the SAP.

17.8.3 *Weight*

The absolute change in body weight from baseline, and from end of treatment at 26 weeks, to 6 months after end of treatment with EMP16-02 (120 mg O/ 40 mg A and 150 mg O/50 mg) as compared to placebo will be analysed using analysis of covariance with treatment and body weight as covariates.

The relative (%) change in body weight from baseline, and from end of treatment at 26 weeks, to 6 months after end of treatment with EMP16-02 (120 mg O/ 40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using analysis of variance with treatment as independent variable.

17.8.4 *Glucose metabolism marker HbA1c*

The absolute change in fasting HbA1c from baseline, and from end of treatment at 26 weeks, to 6 months after end of treatment with EMP16-02 (120 mg O/ 40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using analysis of covariance with treatment and body weight as covariates.

The relative (%) change in fasting HbA1c from baseline, and from end of treatment at 26 weeks, to 6 months after end of treatment with EMP16-02 (120 mg O/ 40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using analysis of variance with treatment as independent variable.

17.8.5 *Blood pressure*

The absolute change in blood pressure from baseline, and from end of treatment at 26 weeks, to 6 months after end of treatment with EMP16-02 (120 mg O/ 40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using analysis of covariance with treatment and body weight as covariates.

The relative (%) change in blood pressure from baseline, and from end of treatment at 26 weeks, to 6 months after end of treatment with EMP16-02 (120 mg O/ 40 mg A and 150 mg O/50 mg A) as compared to placebo will be analysed using analysis of variance with treatment as independent variable.

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19 SIGNATURES

19.1 Principal Investigator statement

I have read and understood this CSP and agree to conduct the study accordingly and to comply with the Investigator obligations stated in this CSP, GCP and applicable regulatory requirements.

Principal Investigator

Name	*Signature*	*Date*

Site

19.2 Signature page (approval of the clinical study protocol)

Sponsor signatories

Arvid Söderhäll, PhD CEO Empros Pharma AB		
Name	*Signature*	*Date*

Coordinating Investigator

Helena Litorp, MD PhD		
Name	*Signature*	*Date*

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