PROTOCOL FOR A PROSPECTIVE STUDY

Naltrexone/bupropion with or without very low calorie ketogenic diet for weight regain after bariatric surgery

RELAY

Version number: v 1.3 – **Date** 19/11/2024

Internal ref. nbr: **S68952**

Sponsor

University Hospitals Leuven (UZ Leuven)

Herestraat 49, B-3000 Leuven

Coordinating Investigator

Fien Van der Borght

LIST OF PARTICIPATING SITES

List Of Participating Sites	Principal Investigator
UZ Leuven Herestraat 49, 3000 Leuven	Prof. dr. R. Vangoitsenhoven
AZ Sint-Jan Brugge Ruddershove 10, 8000 Brugge	Dr. B. Dillemans

Confidentiality Statement

The information in this document is strictly confidential and is available for review to Investigators, potential Investigators and appropriate Ethics Committees, Institutional Review Boards or Competent Authorities. No disclosure should take place without written authorization from the Sponsor

SIGNATURES

Title: Naltrexone/bupropion with or without very low calorie ketogenic diet for weight regain after bariatric surgery

Protocol: RELAY

The undersigned confirm that the above referenced protocol has been acknowledged and accepted, and agree to conduct the Study in compliance with the approved protocol, and will adhere to: the ICH guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on the human person (as amended), the EU General Data Protection Regulation 2016/679 (GDPR), relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights, and any other regulatory requirements and Standard Operating Procedures (SOPs), as applicable.

The undersigned agree not to disclose the confidential information contained in this document for any purpose other than the evaluation or conduct of the Study, without prior written consent of the Sponsor.

The undersigned also commit to make the findings of the Study publicly available through publication and/or other dissemination tools, in accordance with this protocol and applicable regulations, without any unnecessary delay and to provide an honest, accurate and transparent account of the Study; and to explain any discrepancies or deviations from the approved Study protocol.

Coordinating Investigator

Prof. dr. R. Vangoitsenhoven

.....	.....	.....
Name & Title	Signature	Date

Principal Investigator (UZ Leuven)

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Prof. dr. R. Vangoitsenhoven

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Coordinating Investigator

Prof. dr. R. Vangoitsenhoven

.....	.....	.....
Name & Title	Signature	Date

Principal Investigator (AZ Sint-Jan Brugge)

Dr. B. Dillemans

.....	.....	.....
Name & Title	Signature	Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	(electronic) Case Report Form
CI	Coordinating Investigator
DPA	Data Processing Annex
DTA	Data Transfer Agreement
EC	Ethics Committee
EU	European Union
GCP	Good Clinical Practice (latest version of ICH E6)
GDPR	General Data Protection Regulation
ICH	International Conference on Harmonisation
JCI	Joint Commission International
PI	Principal Investigator (Participating Site)
SOP	Standard Operating Procedure
VLCKD	Very Low Calorie Ketogenic Diet
NB	Naltrexone/bupropion

FUNDING AND SUPPORT

Funder	Type of Financial or Non-Financial Support
Pro Well	• VLCKD (Appendix 2) • Lifestyle program (Appendix 3)
Goodlife Pharma	• Mysimba tablets

This is an investigator driven trial in which trial staff is funded through KULeuven. Patients are not reimbursed for participation in this study.

A PhD student will be part-time (50%) appointed for this trial. He/she will be accountable for both sites (AZ Sint-Jan Brugge & UZ Leuven). The financial remuneration will be split between Goodlife Pharma and Pro Well. The PhD student will assist with

- Recruitment of patients: The PhD student will have access to the medical records of the patients of UZ Leuven and to the pseudomized data of AZ Sint-Jan Brugge by using Redcap.
- Data collection and monitoring
- Planning and monitoring
- Adverse event reporting
- Scientific report writing and dissemination

Goodlife Pharma

The pharmaceutical company (Goodlife Pharma) will provide the "Study drugs" (MYSIMBA) free of charge. For this multicenter study, Goodlife Pharma will supply the coordinating site (UZ Leuven) as well as the participating site (AZ Sint-Jan Brugge).

Pro Well

The study diet (VLCKD) and lifestyle program will be provided by the Company (Pro Well). For this multicenter study, Pro Well will supply the coordinating site (UZ Leuven) as well as the participating site (AZ Sint-Jan Brugge).

Both Goodlife Pharma as Pro Well

No payments other than those explicitly foreseen shall be made by Company to Institution with respect to the Study, unless agreed in writing. Such agreement must be executed by authorised personnel, must include a specific statement of any fees or costs to be paid and the reasons for payment, and must be attached as an annex to this Agreement.

An overview of the budget is displayed on the next page.

Budget

Items/Staff	Per unit Cost	Quantity	Total
VLCKD	-	-	Provided by Pro Well
Lifestyle program	-	-	Provided by Pro Well
Mysimba tablets	-	-	Provided by Goodlife Pharma
PhD student (50%)	-	-	Split between Pro Well and Goodlife Pharma
Pregnancy test	€ 10.00	20 tests	€ 200.00 by Internal fund (KUL/UZ Leuven krediet)
UZ Leuven			
Study specific lab tests (fasting glucose, lipids)	€ 10.86	62 samples	€ 673.32 by Internal fund (KUL/UZ Leuven krediet)
Pharmacy transit	€ 2,426.40	1 site	€ 2,426.40 by Internal fund (KUL/UZ Leuven krediet)
AZ Sint-Jan Brugge			
Study specific lab tests (fasting glucose, lipids)	€ 21.54	62 samples	€ 1,335.48 by Internal fund (KUL/UZ Leuven krediet)
Start-up fee	€ 250.00	1	€ 250.00 by Internal fund (KUL/UZ Leuven krediet)
Annual fee	€ 100.00	2 years	€ 200.00 by Internal fund (KUL/UZ Leuven krediet)
Pharmacy transit	€ 340.00	1 site	€ 340.00 by Internal fund (KUL/UZ Leuven krediet)
Total			**€ 5,425.20**

ROLES AND RESPONSIBILITIES

The Principal Investigator (PI) is responsible for the conduct of the Study at his/her Participating Site, and for protecting the rights, safety and well-being of Study participants. As such the PI must ensure adequate supervision of the Study conduct at the Participating Site. If any tasks are delegated, the PI will maintain a log of appropriately qualified persons to whom he/she has delegated specified Study-related duties. The PI will ensure that adequate training is provided and documented for all Study staff, prior to conducting assigned Study-related activities. Even when certain activities are delegated, the PI will ultimately remain responsible for the conduct of the Study at his/her Participating Site.

It is the Coordinating Investigator's (CI's) responsibility to supervise the general conduct (e.g. Study progress, communication, protocol training and support of the participating sites, annual reporting to the Ethics Committee (EC), end of Study notification(s) and results reporting…) of the Study. The CI fulfils

both Investigator and Sponsor responsibilities, as outlined in International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) E6(R2) and applicable regulations.

PI and CI shall each be referred to as «Investigator(s)».

STUDY SYNOPSIS

Title of clinical Study («Study»)	Naltrexone/bupropion with or without very low calorie ketogenic diet for weight regain after bariatric surgery
Protocol Short Title Acronym	RELAY
Sponsor name	University Hospitals Leuven (UZ Leuven)
Coordinating Investigator	Fien Van der Borght
Contact Address CI	Herestraat 49 – bus 7003, 3000 Leuven
Contact Email CI	roman.vangoitsenhoven@uzleuven.be
Contact Phone CI	016/34 47 75
Public database nbr	Clinicaltrials.gov
Principal Investigators and Participating Sites	Prof. Dr. R. Vangoitsenhoven UZ Leuven – Herestraat 49, 3000 Leuven Dr. B. Dillemans AZ Sint-Jan Brugge – Ruddershove 10, 8000 Brugge
Medical condition or disease under investigation	Obesity
Study rationale	Bariatric surgery induces substantial weight loss and reduction in obesity-related comorbidities. Despite the major benefits of bariatric, some patients still regain weight post-operatively. This is the reason why we want to investigate the influence of a pharmacotherapeutic treatment (naltrexone/bupropion) on weight regain after bariatric surgery. This multicenter, randomized clinical trial will compare the outcomes of two different groups: all participants will receive intensive lifestyle management and naltrexone/bupropion, and one experimental group will in addition follow a very low calorie ketogenic diet (VLCKD).
Primary objective	To evaluate the superiority of combined VLCKD, intensive lifestyle intervention and naltrexone/bupropion versus standard of care with naltrexone/bupropion on weight loss.
Secondary objective(s)	To describe changes in metabolic health parameters and health-related quality of life during combined treatment of VLCKD, intensive lifestyle program and naltrexone/bupropion versus standard of care alone with naltrexone/bupropion.
Study design	Prospective Multicentric Longitudinal Randomized Controlled Study
Endpoints	<u>Primary endpoints</u> • The percentage of weight loss at 26 weeks <u>Secondary endpoints</u> • A weight loss percentage at 10 weeks, 16 weeks and at end of trial (= 52 weeks from start)

	• A proportion of patients with a weight loss percentage of 5% or more at 10, 16, 26 and 52 weeks • A proportion of patients with a weight loss percentage of 10% or more at 10, 16, 26 and 52 weeks • The time to reach a weight loss percentage of 5% and 10% • The dose of naltrexone/bupropion used at 10, 16, 26 and 52 weeks and at the end of the trial • The tolerability of VLCKD and NB • The adherence to VLCKD and NB • The Patient-Reported Outcome Measures (PROMs) of hunger and cravings at 0, 4, 10, 16, 26 and 52 weeks • The change in fasting glucose, lipids and blood pressure at 10, 16, 26 and 52 weeks
Sample Size	• Experimental/treatment arm: 31 patients • Comparator arm: 31 patients • Total: 62 patients

Third parties	• Pro Well
	  ○ Provide VLCKD
	  ○ Provide Lifestyle program
	• Goodlife Pharma
	  ○ Provide Mysimba tablets

STUDY FLOWCHART

Procedures/assessments	Phase 0: Screening and randomization		Phase 1: Lifestyle + NB with vs without VLCKD							Phase 2: Lifestyle + NB (all participants)					Follow-up (all participa nts)	
	Screening (In-clinic)	Randomization (in-clinic)	Remote	Remote	Remote	Remote	Remote	Remote	In-clinic (study specific)	Remote	Remote	In-clinic (Routine)	Remote	Remote	In-clinic (study specific)	In-clinic (routine)
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**
Timing of visits (weeks)		**Start**	**Start**	**W3**	**W4**	**W6**	**W8**	**W10**	**W10**	**W12**	**W16**	**W16**	**W20**	**W26**	**W26**	**W52**
Visit window (days)									**±30**			**±30**			**±30**	**±30**
Lifestyle program			X		X		X			X	X		X	X		
Naltrexone/bupropion (NB)		X							X			X			X	X
VLCKD			(X)[1]	(X)[1]	(X)[1]	(X)[1]	(X)[1]	(X)[1]								
Screening assessments and randomization																
Informed consent	X[2]															
Inclusion/exclusion criteria	X	X														
Randomization		X														
Anthropometric data (height, weight, waist circumference)		X							X			X			X	X

Clinical examination (Blood pressure, heart and lung auscultation, abdominal palpitation and percussion)		X							X			X			X	X
Laboratory tests																
Fasting glucose		X							X			X			X	X
Hemoglobin A1c		X										X				X
Lipids: LDL-cholesterol, HDL-cholesterol, triglycerides		X							X			X			X	X
Liver test: AST, ALT, gamma-GT, alkaline phosphatase, total bilirubin, albumin		X										X				X
Kidney function: creatinine, eGFR		X										X				X
Thyroid function: TSH, free T4		X										X				X
Uric acid		X										X				X
Questionnaires																
The PsyEndoAUDIT questionnaire[3]		X							X			X			X	X
The PsyEndoCIDI questionnaire[3]		X							X			X			X	X
The PsyEndoEDE questionnaire[3]		X							X			X			X	X
The PsyEndoHADS questionnaire[3]		X							X			X			X	X
Nederlandse vragenlijst voor eetgedrag[3]		X							X			X			X	X
The ObesitasIPAQ questionnaire [3]		X							X			X			X	X

The quality of life (SF-36) questionnaire [3]		X							X			X			X	X
The outtake questionnaire														X		
Reason for discontinuation		X							X			X			X	X
(Serious) Adverse event (S)(AE) assessment		X							X			X			X	X

- Depending on randomization in eiter intervention (with VLCKD) or comparator group (without VLCKD).
- Informed Consent must be obtained prior to performing any other Trial-related procedures as part of the standard of care.
- See appendix 4 for the respective questionnaires.

1 Background and Rationale

The world-wide prevalence of obesity has increased to the extent where it is considered as an epidemic. According to the World Health Organization (WHO) the population of people with obesity almost tripled in a time period of 40 years. Obesity is a medical condition in which excessive fat accumulation causes secondary health issues. This corresponds clinically to a body mass index (BMI) greater or equal to 30 kg/m^2.(1)

Initially, the patient will be advised to change his/her lifestyle. This includes increasing physical activity as well as being on a diet and behaviour modification. A tailored lifestyle program usually consists out of 2-3 hours of exercise per week. Here, it is especially important to engage in aerobic sports such as walking at a higher than usual pace, cycling or swimming. This ensures that patients use their fat storage as source of energy instead of carbohydrates. Unfortunately, lifestyle modification alone in terms of physical activity will result in only limited short-term weight loss. Therefore, a diet containing of a calorie restriction is an important additional part of the new lifestyle.(2)

Calorie restriction is an important part of the very low-calorie ketogenic diet (VLCKD). This diet typically consists out of a limited intake of carbohydrates and a daily energy restriction of 800 kcal. Also an increase in protein percentages is favourable in these patients.(3) A dietitian is usually appointed for this intervention because VLCKD is an important factor in the possible eligibility for surgery as well as weight loss results after bariatric surgery.(4) Studies also showed that VLCKD given prior to pharmacotherapy can have an additional benefit. It will help to reset the metabolic state and impose nutritional structure. (5) (6)

Pharmacotherapy is the last resort for patients before bariatric surgery. The medication used in this trial is naltrexone/bupropion (NB) with extended release. Naltrexone is an opioid antagonist that is currently used in the treatment of dependency, like alcoholism an drug addiction. Bupropion on the other hand is an antidepressant used not only in the treatment of depression but also to reduce cigarette cravings with the ultimate goal of inducing a smoking cessation. A common side effect of bupropion is weight loss. The use of both drugs separately has almost no effect on the patients' weight, but the combination of naltrexone and bupropion has showed a synergistic effect.(7) NB has promising results in terms of weight loss prior to or post-bariatry with an influence on food intake, cravings and a high sense of satiety.(8)

Conservative therapy may already make a difference, but the majority of patients experience a lack of beneficial effect from this. For these patients, bariatric surgery (BS) may be the solution. Bariatric surgery is considered as the best treatment for morbid obesity (BMI > 40 kg/m2 or BMI > 35 kg/m2 with one or more weight related comorbidities) in maintaining weight loss.(9) The biggest weight loss occurs the first year after surgery. Unfortunately, from then on weight stabilization or even weight regain can occur post-bariatry.(10)

Despite the fact these patients already tried conservative therapy prior to bariatric surgery, they still benefit to monitor their lifestyle in terms of physical activity, behaviour and dieting. Recent studies show a beneficial role for pharmacotherapy for post-bariatric weight regain.(11) Given the mechanism of action of NB, specific benefit can be expected in patients with insufficient reduction or relapse of food cravings and snacking after bariatric surgery. (8) Although these possible desirable effects may occur, yet patients may suffer from some side effects of the study drug. The most common adverse events are gastrointestinal disorders (nausea, vomiting, constipation), anxiety, insomnia, agitation and a headache.(12)

Generally, there is a lack of published data on the effectiveness of pharmacotherapies for post-bariatric weight regain. Therefore, this trial aims to investigate a structured follow-up with lifestyle intervention combined whether or not with a VLCKD and supported by naltrexone/bupropion on the evolution of bodyweight in patients with weight regain post-bariatry. This multi-center, randomized clinical trial will compare the outcomes of two different groups. The patients in both groups need to undergo lifestyle changes in combination with the intake of naltrexone/bupropion, but the experimental group needs to follow a VLCKD on top of it for a period of 10 weeks.

2 Study Design and Objectives

2.1 Study objectives

The aim of this trial is to evaluate the superiority of combined VLCKD, intensive lifestyle intervention and naltrexone/bupropion versus standard of care with naltrexone/bupropion on weight loss.

2.2 Primary Endpoints

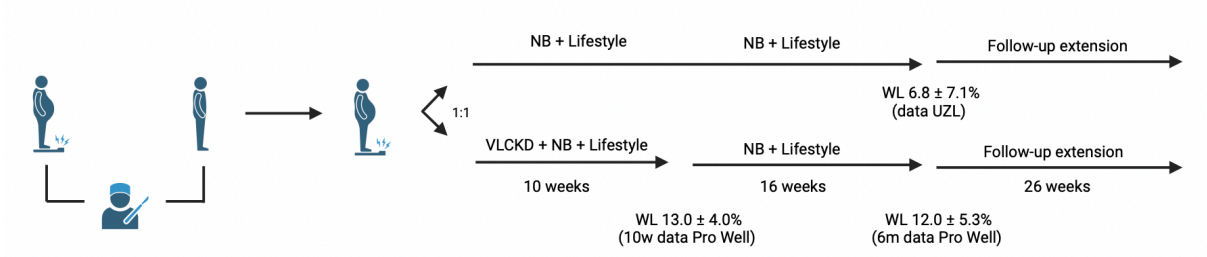
Weight loss percentage at 26 weeks; calculated as: (weight at 26 weeks – baseline weight)/baseline weight.

2.3 Secondary Endpoints

- A weight loss percentage at 10 weeks, 16 weeks and at end of trial (= 52 weeks from start)
- A proportion of patients with a weight loss percentage of 5% or more at 10, 16, 26 and 52 weeks
- A proportion of patients with a weight loss percentage of 10% or more at 10, 16, 26 and 52 weeks
- The time to reach a weight loss percentage of 5% and 10%
- The dose of naltrexone/bupropion used at 10, 16, 26 and 52 weeks and at the end of the trial
- The tolerability of VLCKD and NB
- Adherence to VLCKD and NB
- The Patient-Reported Outcome Measures (PROMs) of hunger and cravings at 0, 4, 10, 16, 26 and 52 weeks
- The change in fasting glucose, lipids and blood pressure at 10, 16, 26 and 52 weeks

2.4 Study design

This is a parallel multicentric longitudinal randomized controlled trial in which prospective data will be collected from the electronic health record. The inclusion and exclusion criteria will be checked and afterwards patients will be randomized to (unblinded) medication only or combination with VLCKD. Both groups include NB and lifestyle changes for 26 weeks but the patients belonging to the experimental group must follow a VLCKD in the first 10 weeks on top of it. Like the other group, the remaining 16 weeks will consist of NB combined with lifestyle interventions. Afterwards there is a follow-up extension of 26 weeks. See appendix 4 for detailed overview of clinical and biochemical parameters to be collected during the trial.



2.5 Expected duration of the Study

This trial will have a duration of 2 years in total. 1 year is taken into account to include the patients into the study according to the inclusion and exclusion criteria. Afterwards patients will be randomly inserted into the comparator arm (NB + lifestyle interventions) or experimental arm (NB + Lifestyle interventions + VLCKD). Both arms of the study design will be evaluated for 52 weeks. 26 weeks will consist of the treatment after which another 26 weeks will be used as a follow-up extension.

The End of Study is defined as Last Patient Last Visit (LPLV). The CI shall notify the EC of the end of the Study. The CI will submit a final report with the results of the study, including any publications/abstracts, to the EC within 1 year of study termination.

The Sponsor or EC can decide to halt or prematurely terminate the Study when new information becomes available whereby the rights, safety and well-being of Study participants can no longer be assured, when the integrity of the Study has been compromised, or when the scientific value of the Study becomes obsolete and/or unjustifiable.

3 Study Population / Eligibility Criteria

3.1 Inclusion criteria

Participants eligible for inclusion in this Trial must meet **all** of the following criteria:

1. Voluntary written informed consent of the participant or their legally authorized representative has been obtained prior to any screening procedures
2. Use of highly effective methods of birth control; defined as those that, alone or in combination, result in low failure rate (i.e., less than 1% per year) when used consistently and correctly; such as implants, injectables, combined oral contraceptives, some IUDs, true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the Trial treatment(s)) or commitment to a vasectomised partner.
3. Miminum 18 years of age at the time of Informed Consent signature
4. Underwent bariatric surgery (RYGB or SG) with weight regain ≥10% of nadir weight
5. People without Type 2 diabetes (T2D)
    - No history, no drugs, HbA1c < 6,5% and FPG <126 mg/dl)

All participants that are considered for Trial participation, per the above criteria will be documented on the Screening Log, including Screen Failures.

3.2 Exclusion criteria

Participants eligible for this Trial must **not** meet any of the following criteria:

1. Participant has a history of type 2 diabetes mellitus (also drugs, HbA1c > 6,5% and FPG >126 mg/dl)
2. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate, highly effective contraceptive
3. Participation in an interventional Trial with an investigational medicinal product (IMP) or device
4. Not willing to sign informed consent
5. Younger than 18 years of age at the time of Informed Consent signature
6. Other types of bariatric surgery other than RYGB or SG (including LAGB, BPD)
7. Underwent bariatric surgery (RYGB or SG) with weight regain <10% of nadir weight
8. Contraindication for VLCKD, including CKD stage 4-5, liver cirrhosis, type 1 diabetes mellitus, active gout
9. Contraindication for NB including the use of opioids, history of CNS tumor or seizures, severe psychiatric disorder or > 2 psychotropic medications, uncontrolled hypertension
10. Use of other drugs for weight management (e.g. GLP1Ra) in the last 3 months prior to trial intervention
11. Any disorder, which in the Investigator's opinion might jeopardise the participant's safety or compliance with the protocol

Participants who meet one or more of the above exclusion criteria **must not proceed** to be enrolled/randomized in the Trial and will be identified on the Screening Log as Screen Failure.

4 Study Procedures

4.1 Participant consent and withdrawal of consent

The Study will be conducted only on the basis of prior informed consent by the Study participants and/or their legally authorized representative(s). As such, no Study-related procedures will be conducted prior to obtaining written informed consent from potential Study participants.

The process for obtaining and documenting initial and continued informed consent from potential Study participants will be conducted in accordance with ICH-GCP E6(R2), applicable regulatory requirements and internal Standard Operating Procedures (SOPs).

All originally signed obtained Informed Consent Forms (ICFs) must be retained/archived in the Investigator Site File (ISF) at the Participating Site and must not be destroyed (even when a scanned copy is available) before expiration of the legal archiving term as defined in the protocol section entitled "Archiving".

Participants may voluntarily withdraw consent to participate in the Study for any reason at any time. The participant's request to withdraw from the Study must always be respected without prejudice or consequence to further treatment. Consent withdrawal will be documented in the participant's medical record.

Study data and samples collected before withdrawal can be used in the study. No new study data or samples will be collected after withdrawal of the participant.

4.2 Selection of Participants / Recruitment

Potential participants will be identified and recruited during patient consultations in one of the participating sites. No additional recruitment material (such as for example flyers, social media advertising, audio/video recordings) will be used.

4.3 Randomization Procedure

To ensure the integrity of the Study, the following randomization procedures have been established:

During the initial study visit, participants will be randomized in a 1:1 ratio to either the experimental arm (with VLCKD) or the comparator arm (without VLCKD), while receiving naltrexone/bupropion and lifestyle intervention. Allocation to one of these two groups will be conducted using a central randomization procedure accessible in the eCRF (RedCap). A computer-generated block randomization schedule will be created using the PLAN procedure in SAS software.

A randomization list will be prepared by the Sponsor's designated staff, not involved in recruiting Study participants, medical care, drug administration or follow-up.

4.4 Premature discontinuation

Participants may voluntarily discontinue from Study treatment and/or prematurely end their participation in the Study for any reason at any time. In such case the Investigator must make a reasonable effort to contact the participant (e.g. via telephone, e-mail, letter) in order to document the primary reason for this decision.

The Investigator may also decide at any time during the course of the Study, to temporarily interrupt or permanently discontinue the Study treatment if it is deemed that continuation would be detrimental to, or not in the best interest of the participant.

For participants whose status is unclear because they fail to appear for Study visits without stating an intention to discontinue or withdraw, the Investigator must make every effort to demonstrate "due diligence" by documenting in the source documents which steps have been taken to contact the participant to clarify their willingness and ability to continue their participation in the Study (e.g. dates of telephone calls, registered letters, etc.).

A participant should not be considered lost to follow-up until due diligence has been completed.

4.5 By visit

There are five scheduled in-clinic visits, each involving a blood draw. Among these, three visits are routine for naltrexone/bupropion, which include the initial intake and visits after 16 and 52 weeks. The study-specific visits occur at 10 weeks and 26 weeks. During the routine visits, only fasting glucose and lipid levels (LDL-cholesterol, HDL-cholesterol, triglycerides) will be assessed in the blood. However, during the study-specific visits, in addition to fasting glucose and lipids, the following parameters will also be examined in the blood: Hemoglobin A1c, liver function (AST, ALT, gamma-GT, alkaline phosphatase, total bilirubin, albumin), kidney function (creatinine, eGFR), thyroid function (TSH, free T4), and uric acid. For a detailed overview of the visit schedule, please refer to the Study Flowchart.

4.6 Very Low Calorie Ketogenic Diet (VLCKD)

Participants in the experimental arm follow the Very Low-Calorie Ketogenic Diet (VLCKD) for the first 10 weeks of the study. This entails adhering to the VLCKD for 10 weeks while also receiving support from a coach. The coach provides explanations, follow-ups, and moments for progression and reflection throughout this period. The VLCKD begins with a strict phase of 800 kcal/day (consisting of 50g of carbohydrates, >100g of proteins, and low-carb vegetables), followed by a gradual increase in daily calorie intake (1000 kcal, 1200 kcal for women/1400 kcal for men, 1500 kcal for women/1800 kcal for men) based on a Mediterranean diet. For further details on the schedule of contact moments and the content of the VLCKD, please refer to Appendix 2.

4.7 Naltrexone/bupropion

After starting the treatment, the dose should be increased over a 4-week period as follows:

- Week 1: One tablet in the morning
- Week 2: One tablet in the morning and one tablet in the evening
- Week 3: Two tablets in the morning and one tablet in the evening
- Week 4 and onward: Two tablets in the morning and two tablets in the evening

The maximum recommended daily dose of Mysimba is two tablets twice daily with a total dose of 32 mg of naltrexone hydrochloride and 360 mg of bupropion hydrochloride. Patients with too many side effects at high dose may return to the previous dose and continue with it (maximum tolerated dose).

Naltrexone/bupropion need to be taken orally. The tablets should be swallowed whole with some water. The tablets should preferably be taken with some food. The tablets must not be cut, chewed or crushed.

The formulation of naltrexone/bupropion exists of the following:

- Tablet core: cysteine hydrochloride, microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate, lactose anhydrous, lactose monohydrate, crospovidone type A, indigo carmine aluminium paint (E132), hypromellose, disodium deetate, colloidal silicon dioxide
- Film coating: titanium dioxide (E171), macrogol (3350), talc, indigo carmine aluminium paint (E132)

The package size consists of 112 tablets naltrexone/bupropion.

4.7.1 Concomitant / Prohibited Medication / Treatment

Permitted:

- Concomitantly used blood glucose-lowering agents. Assess the dose to minimize the risk of hypoglycaemia because treatment with naltrexone/bupropion may result in decreased glucose levels.
- Digoxin. Monitor digoxin levels when used concurrently because bupropion may lower the plasma level of digoxin. Upon discontinuation of naltrexone/bupropion, digoxin levels may increase; monitor patient for possible digoxin toxicity.
- Concomitant administration of a serotonergic agent (SSRI or SNRI). There have been reports of serotonin syndrome, a potentially life-threatening condition. Careful observation is therefore required, especially at initiation and after each dose increase. Watch for changes in mental status,

autonomic instability, neuromuscular dysfunction, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, consider discontinuing treatment.

Not permitted:

- Concomitant treatment with bupropion or naltrexone.
- Concomitant administration of MAO-inhibitors (MAOIs). There should be at least a 14-day period between discontinuation of irreversible MAOIs and initiation of treatment with naltrexone/bupropion. For reversible MAOIs, a 24-hour period is sufficient.
- Opioids such as codeine, loperamide and opioid analgesics, may be less effective. If (temporary) treatment with opioids is necessary, discontinue (or interrupt) treatment with naltrexone/bupropion. Use naltrexone/bupropion cautiously after chronic opioid use has been stopped for 7-10 days, to avoid occurrence of withdrawal symptoms.
- CYP2D6 substrates: Bupropion and hydroxybupropion are CYP2D6 inhibitors. Exposure to drugs metabolized by CYP2D6 may be increased; examples include certain antidepressants (SSRIs and many TCAs, including imipramine, paroxetine, venlafaxine), antipsychotics (haloperidol, risperidone), β-blockers (metoprolol) and class 1C antiarrhythmics (flecainide, propafenone). Dose reductions of these agents may be necessary, especially with narrow therapeutic breadth (such as TCAs); consider blood level guided dosing (TDM). Exposure to citalopram increases by about 40%. Tamoxifen may be less effective due to CYP2D6 inhibition.
- Influence on CYP2B6: Bupropion is converted by CYP2B6 to its major active metabolite hydroxybupropion. Use caution with concomitant use of drugs that induce CYP2B6 (e.g., carbamazepine, efavirenz, phenytoin, ritonavir) because the efficacy of bupropion is affected. Use caution with concomitant use of drugs that may inhibit CYP2B6 (e.g., clopidogrel, cyclophosphamide, ifosfamide); the clinical consequences of this interaction are unknown but may decrease the efficacy of bupropion.
- Avoid or minimize the use of alcohol, as neuropsychiatric side effects and decreased alcohol tolerance have rarely been reported with the use of alcohol during bupropion treatment.
- concomitant use of drugs that lower the insult threshold, such as antidepressants, antipsychotics, sedative antihistamines, antimalarial drugs, tramadol, quinolones, theophylline and systemic corticosteroids.
- Concomitant use of levodopa or amantadine, there is evidence of a higher incidence of adverse events (e.g., nausea, vomiting, and neuropsychiatric side effects).

4.8 Lifestyle

Lifestyle support, excluding the VLCKD, is offered to both the experimental and comparator arms and is regarded as part of the standard care protocol. Consequently, both groups will both have a total of 11 contact sessions, during which 30 minutes will be allocated for individual coaching and routine personal follow-up via telephone. Additionally, there are three modules comprising 12 educational presentations and 12 practical tasks designed for application in everyday life. For a comprehensive schedule outlining specific time points, please refer to Appendix 3.

5 Assessment of Safety

5.1 Adverse Event Reporting

5.1.1 Definitions

5.1.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or subject during an experiment, and which does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related

to the product. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.

5.1.1.2 Adverse Reaction (AR)

An AR is any untoward and unintended responses to an investigational medicinal product or to an experiment and, when an investigational product is concerned, related to any dose administered.

5.1.1.3 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that results in any of the following:

- Death
- A life-threatening[a] experience
- In-patient hospitalisation or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Important medical events that may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the above outcomes

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

5.1.2 Adverse Events that do not require reporting

In general, the following should <u>not be reported as AEs:</u>

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

The following events are commonly observed and are therefore not considered as adverse events for the purpose of the study:

- Gastrointestinal events (constipation, nausea, vomitting, dry mouth)
- Headache
- Insomnia (especially if naltrexone/bupropion taken at night)

Although these events should not be reported to the Sponsor, these should be recorded in the patient's medical notes according to routine practice.

The following events <u>not to be considered as SAEs</u> are:

- Pre-planned hospitalisations unless the condition for which the hospitalisation was planned has worsened from the first study-related activity after the subject has signed the informed consent.
- Hospitalisation as part of a standard procedure for protocol therapy administration. However, hospitalisation or prolonged hospitalisation for a complication of therapy administration will be reported as an SAE.
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE.

5.1.3 Recording and reporting of Adverse Events

The study-specific visit does not entail any additional risk compared to the routine visit.

Investigators will seek information on AEs during each patient contact. All events, whether reported by the patient or noted by study staff, will be recorded in the patient's medical record and in the (e)CRF within a

reasonable time after becoming aware. If available, the diagnosis should be reported on the AE page, rather than the individual signs or symptoms. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs.

The following minimum information should be recorded for each AE:

- AE description
- start and stop date of the AE
- severity
- seriousness
- causality assessment to the study interventions
- outcome

5.1.3.1 Assessment

All AEs must be evaluated by an Investigator as to:

- **Seriousness:** whether the AE is an SAE. See above for the seriousness criteria.

- **Severity:**
  - Severity must be evaluated by an Investigator according to the following definitions:
    - *Mild* – no or transient symptoms, no interference with the subject's daily activities
    - *Moderate* – marked symptoms, moderate interference with the subject's daily activities
    - *Severe* – considerable interference with the subject's daily activities, unacceptable
- **Causality:**
  - *None* – An AE which is not related to the study-related interventions
  - *Unlikely* – An AE for which an alternative explanation is more likely (e.g. concomitant medication(s), concomitant disease(s)), and/or the relationship in time suggests that a causal relationship is unlikely
  - *Possible* – An AE which might be due to the study-related interventions. An alternative explanation is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be ruled out.
  - *Probable* - An AE which might be due to the study-related intervention. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely.
  - *Definitely* – An AE which is known as a possible adverse reaction and cannot be reasonably explained by an alternative explanation. The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

5.1.3.2 Timelines for reporting

- After informed consent has been obtained and after initiation of study-related interventions:
  - All AEs and SAEs will be reported in a "written diary" in between visits during the first 12 weeks after initiation of the study-related interventions.
  - After 12 weeks until the last follow-up visit, only SAEs causally related to a study-specific intervention will be reported.

All SAEs as defined in the protocol must be reported to the Sponsor within 24 hours of the study staff becoming aware of the event. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by Study identification.

SAE details will be reported by the Investigator to the Sponsor:

- By completing the SAE form in the (e)CRF

If an authorised Investigator from the reporting site is unavailable, initial reports without causality and expectedness assessment should be submitted to the Sponsor by a healthcare professional within 24 hours

of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

5.1.3.3 Follow-up

The Investigator must record follow-up information by updating the medical records and the appropriate forms in the (e)CRF. The worst case severity and seriousness of an event must be kept throughout the study.

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

- All *SAEs* must be followed up until the outcome of the event is 'recovered', 'recovered with sequelae', 'not recovered' (in case of death due to another cause) or 'death' (due to the SAE) and until all related queries have been resolved, or until end of study (whichever occurs first).
- *Non-serious AEs* must be followed up until the patient's last study visit, and until all related queries have been resolved.

SAEs after the end of the study: If the Investigator becomes aware of an SAE with suspected causal relationship to the study-related interventions after the subject has ended the study, the Investigator should report this SAE within the same timelines as for SAEs during the study.

5.1.3.4 Pregnancy

Female subjects must be instructed to notify the Investigator immediately if they become pregnant during the study. The Investigator must report any pregnancy in subjects during the study to the Sponsor.

5.1.3.5 Death

All deaths will be reported without delay to the Sponsor (irrespective of whether the death is related to disease progression, study procedure or is an unrelated event). The sponsor will notify all deaths, as soon as possible after becoming aware, to the Central EC and the EC of the concerned site and provide additional information if requested.

5.1.4 Reporting requirements to Ethics Committee's (EC's)

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided below.

The Sponsor will promptly evaluate all SAEs against medical experience to identify and expeditiously communicate possible new safety findings to Investigators and to EC('s) based on applicable legislation.

5.1.4.1 Annual reporting

The sponsor has the obligation to, once a year throughout the study (or on request), submit a progress report to the EC's containing an overview of all SARs occurred during the reporting period and taking into account all new available safety information received during the reporting period.

5.1.4.2 Overview reporting requirements

	WHAT	HOW	TO	TIMELINES
Investigator	AE	AE form	sponsor	Within 7 calendar days
	SAE	SAE form	sponsor	Immediately (within 24 hours of becoming aware of the event) Exceptions: as defined in protocol
	death	SAE form	sponsor	asap
Sponsor	death	SAE form + narrative	Ethics Committees	asap
	Annual Progress Report	APR template	Ethics Committees	annually

5.1.5 Pharmacovigilance

Any adverse reactions related to the medicinal products used by the participants in the study, can be reported to the Marketing Authoridation Holder and/or the Compentent Authorities according to the pharmacovigilance guidelines.

6 Statistics and Data Analysis

Statistical analysis will be performed in accordance with ICH E9; a detailed description of the analysis is provided in the Trial-specific Statistical Analysis Plan (SAP). ICH E3 and E8 will guide the structure and content of the clinical trial report.

The hypothesis for this trial is that the percentage of weight loss will be greater for the experimental arm than the comparator arm.

6.1 Sample Size Determination

The sample size was determined for a two-sided two-sample t-test to test the difference in mean weight loss percentage between both treatment arms, assuming a mean weight loss of 6.75% (SD 7.12%) [unpublished, own retrospective data] in the control arm and a mean weight loss of 12% (SD 5.3) [unpublished, data provided by Pro Well] in the intervention arm. Assuming a 20% drop-out rate, a 5% significance level and 80% of power, a total sample size of 62 patients is indicated, or 31 patients per study arm

6.2 Statistical Analysis

The primary analysis will be performed using a two-sample two-sided t-test to test the difference in mean weight loss percentage between both treatment arms. Mean weight loss percentages and the mean difference in weight loss percentage wil be estimated and presented with 95% confidence intervals. A 5% significance level will be adopted for the primary analysis. Given the pragmatic nature of the trial, the primary analysis will be performed following the intention-to-treat (ITT) principle, in that all randomized patients will be analyzed in the study arm in which they were randomized, regardless of adherence to the therapy assigned to the patient. In presence of missing outcome data due to drop-out of patients for whom

no follow-up data were collected, the method of multiple imputation will be used. Fully conditional specification will be used to create 10 complete data sets, of which each will be analyzed and analysis results combined according to multiple imputation principles. Treatment arm and previous weight loss measures will be used as predictors in the imputation model.

A per protocol (PP) analysis will be performed as a secondary analysis, including patients adherent to the randomized treatment. Missing data will be dealt with as described above, using multiple imputation.

Linear mixed models for longitudinal data will be used for the analysis of a treatment effect on weight loss percentage at other time points. The explanatory model will contain treatment arm, time point and the interaction thereof. A random effect for patient will be modelled to deal with data clustering. Results will be presented as mean differences per time point with 95% confidence intervals.

The treatment effect on the proportion of patients with weight loss at various time points will be analyzed using logistic regression analysis, with generalized estimating equations (GEE) to account for data clustering. The explanatory model will contain treatment arm, time point and the interaction thereof. Results will be presented as odds ratios per time point with 95% confidence intervals

The treatment effect on the time to reach a pre-defined weight loss percentage will be analyzed using a log-rank test for time-to-event outcomes. Additionally, a Cox model will be used for the estimation of the hazard ratio with 95% confidence interval.

Descriptive analyses will be used for tolerability or adherence to treatment.

6.2.1 Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary	Two-sided two sample t-test, with analysis following the intention-to-treat principle and multiple imputation to deal with missing data.
Secondary (if applicable)	Linear mixed models for continuous and longitudinal data. Logistic regression for binary and longitudinal data. Log-rank test and Cox model for time-to-event data. Descriptive statistics for adherence and tolerability.

6.3 Other Analysis

Pharmacokinetic, pharmacodynamic, and biomarker exploratory analysis/analyses will be described in the statistical analysis plan and finalized before database lock. The population for pharmacokinetic analysis and pharmacodynamic analysis will be presented separately from the main clinical Trial report.

7 Data handling

The investigator shall ensure that all procedures defined in this Protocol and in the Agreement are complied with, so that all cata coming from the Participating site are reliable and have been processed correctly (especially the randomization lists) and shall ensure that the contentof the case report form (CRF) shall accurately reflect source documents. Findings of the Study will be reported by the Participating Site through Investigator to Sponsor in the form of case reports. The collected data will be pseudonymized.

7.1 Data Collection Tools and Source Document Identification

7.1.1 Operational aspects

Data collection, handling, processing and transfer for the purpose of this Trial will be performed in compliance with applicable regulations, guidelines for clinical trials and internal procedures.

7.1.1.2 Data collection

Source Data will be collected and recorded in the Trial participant's files/medical records.

Patient-related socio-demographic and health-related data will be gathered in the (e)CRF.

RedCAP will be used to capture study related data.

If applicable, worksheets may be used for capturing some specific data in order to facilitate completion of the (e)CRF. Any such worksheets will become part of the Trial participant's source documentation and will be filed together with or as part of the medical records (during but also following completion of the Trial).

It remains the responsibility of the Investigator to check that all data relating to the Trial, as specified in the Trial protocol, are entered into the (e)CRF in accordance with the instructions provided and that the forms are filled out accurately, completely and in a timely manner.

(e)CRFs are provided by the Sponsor for each participant. The Trial data will be transcribed from the source records (i.e. participant's medical file or Trial-specific source data worksheets) into an (e)CRF by Trial Staff. Transcription to the (e)CRF will be done as soon as possible after a participant visit and in a pseudonymized manner using a unique identifier assigned by the Sponsor.

The (e)CRFs will be available for review at the next scheduled monitoring visit (as applicable) and shall under no circumstances capture personal data such as but not limited to the participant or their relative(s) name, home address, contact details, full date of birth medical record number (e.g. UZ Leuven EAD number), social security number etc.

7.1.1.3 Data Validation

All data relating to the Trial must be prepared and validated by the Investigator. Any (e)CRF entries, corrections and alterations must be made by the Investigator or other authorized Trial staff.

Proper audit trails must be available to demonstrate the validity of the Trial data collected. This includes historical records of original data entries, by whom and when the data was entered, as well as detailed records of any corrections or additions made to the original data entry (i.e. who made the correction/addition, when and why), without obliterating the original data entry information.

***7.1.1.4** Data Management*

The Trial Data Manager will perform extensive consistency checks on the received data. Queries will be issued in case of inconsistencies in accordance with internal procedures.

***7.1.1.5** Data Transfer*

Any participant records or datasets that are transferred to the Sponsor or any partners of the Sponsor will contain the Trial-specific participant identifier only; participant names or any information which would make the participant identifiable will not be transferred. All pseudonymized data relating to the Trial must be transmitted in a secure manner to the Sponsor or any partners of the Sponsor(see 8.1.2. legal requirements).

7.1.2 Legal requirements

All source data will be kept at a secured location with restricted access at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular the EU General Data Protection Regulation 2016/679 (GDPR) and relevant national laws implementing the GDPR. Appropriate technical and organizational measures to protect the data against unauthorized disclosure or access, accidental or unlawful destruction, or accidental loss or alteration must be established. Trial staff whose responsibilities require access to personal data agree to keep the data confidential.

The Investigator and the Participating Site(s) (as applicable) shall treat all information and data relating to the Trial disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the Trial as described in this protocol. The collection, processing and disclosure of personal data, such as participant health and medical

information is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

The Investigator will maintain all source documents and completed (e)CRFs that support the data collected from each Trial participant, and will maintain a Trial Master File (TMF)/Investigator Site File (ISF) containing all Trial documents as specified in ICH-GCP E6(R2) Chapter 8 entitled "Essential Documents for the Conduct of a Clinical Trial", and as specified by applicable regulatory requirement(s). The Investigator will take appropriate measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the European General Data Protection Regulation). The receiving party will be bound by contractual agreement to keep the transferred data confidential at all times and to only process the data for the purpose of the Trial. To this end, appropriate Data Transfer Agreements (DTAs) will be established.

7.2 Audits and Inspections

The Investigator will permit direct access to Trial data and documents for the purpose of monitoring, audits and/or inspections by authorized entities such as but not limited to: the Sponsor or its designees and competent regulatory or health authorities. As such (e)CRFs, source records and other Trial related documentation (e.g. Investigator Site File, the Trial Master File, pharmacy records, etc.) must be kept current, complete and accurate at all times.

7.3 Monitoring

In accordance with GCP the Sponsor is responsible for monitoring the Trial to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the Trial procedures have been followed as shown in the approved protocol, and that relevant Trial data have been collected and reported in a manner that assures data integrity.

For those trials with UZ Leuven as Sponsor, UZ Leuven Clinical Trial Center (CTC) monitors only prospective interventional IMP/ IMD trials which are categorized as high risk trials, according to UZ/KU Leuven policy. Therefore, monitoring by CTC is not applicable for this study without IMP/IMD.

Hence, based on the above policy and as permitted by GCP, the Sponsor of the trial accepts the minimal risks associated with this trial and determines that monitoring activities (as defined by GCP) by a qualified individual, independent of the study team, is not necessary as it will provide little or no added value in protecting the safety of trial participants and assuring the integrity of collected trial data. Nonetheless, the UZ Leuven study team will take all possible measures to assure the quality and integrity of trial data and to safeguard the safety and wellbeing of trial participants, in accordance with the requirements set out in GCP.

7.4 Archiving

As specified in ICH-GCP E6(R2) section 8.1 Addendum, the Sponsor and Investigator/Participating Site will maintain a record of the location(s) of all respective Essential Trial Documents (including but not limited to Source Documents, completed and final (e)CRF and ISF/TMF). The Sponsor should ensure that the Investigator has control of and continuous access to the (e)CRF data reported to the Sponsor during the Trial.

The Investigator/Participating Site should have control of all Essential Documents and records generated by the Investigator/Participating Site before, during and following termination of the Trial.

The Sponsor is responsible for archiving Trial specific documentation (such as but not limited to the Trial protocol, any amendments thereto, the final Clinical Study Report (CSR) and the Trial database) according to ICH-GCP E6(R2). Source data and site-specific Trial documents (such as but not limited to the original signed ICFs) will be archived by the participating site(s) according to local practice, and for at least 25 years following termination of the Trial. Archived data may be held on electronic record, provided that media back-up exists, hard copies can be obtained, if required and measures are taken to prevent accidental or premature loss or destruction of data. Destruction of Essential Documents prior to, during or upon completion of the required archival period, will require written authorisation from the Sponsor.

8 Ethical and Regulatory Considerations

7.5 Ethics Committee (EC) review & reports

Before the start of the Study, this protocol and other related documents will be submitted for review to the EC for Study authorization. The Study shall not commence until such approvals have been obtained and until other relevant essential Study documents, such as duly signed contract agreements, evidence of adequate Study financing etc. are in place.

It is the responsibility of the CI to produce the Annual Progress Report (APR) and submit to the EC within 30 days of the anniversary date on which favourable opinion to start the Trial was given, and annually until the Trial is declared ended.

8.3 Regulatory Compliance

The Study will be conducted in compliance with ICH-GCP E6(R2) guidelines, other GxP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on the human person (as amended) and with the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights and all other applicable legal and regulatory requirements.

8.4 Protocol / GCP compliance

The Study must be performed in accordance with the protocol, current ICH and ICH-GCP guidelines, and applicable regulatory and country-specific requirements. ICH guidelines are an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of Study participants are protected, consistent with the principles that originated in the most recent version of the Declaration of Helsinki, and that the Study data are credible, reliable and reproducible.

The Investigator and Trial team acknowledge and agree that prospective, planned deviations or waivers to the protocol are not permitted under applicable regulations on clinical studies. However, should there be an accidental protocol deviation, such deviation shall be adequately documented in the source documents and on the relevant forms and reported to the CI and Sponsor. Deviations should also be reported to the EC as part of the EC's continued review of the Trial (e.g. through the ASR, APR, etc.). Protocol deviations which are found to frequently recur, will require (immediate) action. The Investigator acknowledges that such recurring protocol deviations could potentially be classified as a serious violation of ICH and/or the protocol.

It is understood that "a serious violation" is likely to affect to a significant degree:

- the safety or physical or mental integrity of the Trial participants; or
- the scientific validity of the Trial

The Investigator is expected to take any immediate action required to protect the safety of any participant included in the Trial, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action and the EC at the Trial site should be informed according to local procedures and regulations.

8.5 Data protection and participant confidentiality

The Study will be conducted in compliance with the requirements of the EU General Data Protection Regulation 2016/679 (GDPR), and the relevant Belgian laws implementing the GDPR including the Belgian Privacy Act of 30 July 2018 on the protection of privacy in relation to the processing of personal data. Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws (cfr. Data Processing Annex (DPA) in Appendix 1). In case personal data is transferred outside the European Economic Area, safeguards will be taken by the Sponsor to ensure that appropriate protection travels with the data in accordance with the GDPR. (https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/rules-international-data-transfers_en#documents)

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

8.6 Insurance

The Participating Site, the Investigator and Sponsor shall have and maintain in full force and effect during the term of this Trial, and for a reasonable period following termination of the Trial, adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability.

For Belgian Participating Sites

Art 29 of the Belgian Law relating to experiments on human persons dated May 7th, 2004 applies.
Prior to the start of the Trial, the Sponsor shall enter into an insurance contract in order to adequately cover Trial participants from Belgian sites in accordance with art. 29 of the said law.

8.7 Amendments

Unless for urgent reasons as specified in ICH-GCP E6(R2) section 4.5.4, amendments must not be implemented prior to EC review and/or approval.

In accordance with the Belgian law of May 7th 2004 regarding experiments on humans, the Sponsor may develop a non-substantial amendment at any time during the Trial. If a substantial amendment to the clinical Study agreement or the documents that supported the original application for the clinical Trial authorisation is needed, the Sponsor must submit a valid substantial amendment to the EC for review and approval. The EC will provide a response in accordance with timelines defined by applicable regulations. It is the Sponsor's responsibility to assess whether an amendment is substantial or non-substantial for the purpose of submission to the EC.

Amendments to the Study are regarded as 'substantial' when they are likely to have a significant impact on the safety or physical or mental integrity of the clinical Study participants, or the scientific value of the Study.

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf

8.8 Post-Trial activities

After completing the clinical trial, participants will not be provided with study medication nor VLCKD. The study drug and VLCKD programs are approved and available to patients on the Belgian market, at own expense, and after medical advice and prescription as needed.

9 Human Body Material

The investigator and study team will comply with all applicable laws and patient and privacy rights and all applicable laws regarding the use of human body material (HBM) when collecting, processing, storing and/or using samples of HBM for scientific research..

Particularly, the investigator shall act in accordance with the Law of 19 December 2008 regarding the procurement and use of human biological material intended for human medical applications or for scientific research purposes and its royal decree. To this end, the investigator will obtain approval from the notified UZ/KU Leuven Biobank prior to the start of the research. The investigator and his team shall ensure the traceability of the HBM during the complete lifecycle of the HBM.
The investigator will use the HBM for the purposes as described in the Protocol. If the HBM is to be used for any other purposes than those stated in the Protocol, the investigator shall first obtain approval from the UZ/KU Leuven Biobank and the appropriate Ethics Committee (EC).
The Participating Site warrants that these Samples have been collected in accordance with the legislation in force in the country of origin and in accordance with the (inter)national standards on ethics and protection of privacy and personal data, and can be legitimately used for the Study. The providers of the Samples in particular warrant that the donor has consented to the use of his/her Samples for the Study and/or has not objected to it to the extent required under the legislation in force in the country of origin. Since UZ Leuven will receive coded/pseudonymized Samples from the Participating Site/Collaborating Hospital, UZ Leuven is subject to the rights and obligations as 'data controller' set forth under GDPR in relation to the processing of Personal Data. The providers of the Samples are subject to the rights and obligations as 'data processor' set forth under the GDPR in relation to the processing of Personal Data. UZ Leuven and the providers of the Samples' rights and obligations with respect to Personal Data are further detailed in the data processing agreement attached in Addendum I.

10 Research Registration, Dissemination of Results and Publication Policy

The Declaration of Helsinki (latest version) and European and Belgian regulations require that every research Study involving human participants be registered in a publicly accessible database before recruitment of the first participant. The CI is responsible for registering the Study.

In addition, the CI will fulfil their ethical obligation to disseminate and make the research results publicly available. As such the CI is accountable for the timeliness, completeness and accuracy of the reports. Researchers, authors, Sponsors, editors and publishers must adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in publication.

Publications will be coordinated by the CI. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

For multicentre Trials, it is anticipated that the primary results of the overall Trial shall be published in a multicentre publication.

Participating Sites are not allowed to publish any subset data or results from the Trial prior to such multicentre publication.

Any publication by a Participating Site must be submitted to the Sponsor for review at least thirty (30) calendar days prior to submission or disclosure. Sponsor shall have the right to delay the projected publication for a period of up to three (3) months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its intellectual property rights and know-how.

11 Intellectual Property

Any know how, inventions, methods, developments, innovations, discoveries and therapies, whether patentable or not, arising from the Trial or made in the performance of the Trial protocol ("Inventions") shall vest in the Sponsor. The Participating Site, its employees and Investigator(s) shall promptly disclose to the Sponsor any such Inventions. Parties have expressly agreed that any and all Trial data as collected and prepared in the performance of the Trial protocol shall be the sole property of Sponsor unless otherwise agreed in the clinical trial agreement.

12 References

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APPENDICES

Appendix 1: Data Processing Annex (DPA)

Definitions:

- "Protocol" means the document entitled Naltrexon/bupropion with or withour very low calorie ketogenic diet for weight regeain after bariatric surgery containing the details of the academic Study as developed by the Sponsor and approved by the relevant Ethics Committee.
- "Sponsor" means University Hospitals Leuven (UZ Leuven).
- Participating site acts as a data processor as defined under article 4, 8) of the Regulation (EU) 2016/679 ("Data Processor") for the Sponsor who acts as data controller as defined under article 4, 7) of the Regulation (EU) 2016/679 ("Data Controller").
- "Applicable Law" means any applicable data protection or privacy laws, including:
    b) the Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR");
    c) other applicable laws that are similar or equivalent to or that are intended to or implement the laws that are identified in (a) of this definition;
- "Personal Data" means any information relating to an identified or identifiable natural person ("Data Participant"), including without limitation pseudonymized information, as defined in Applicable Law and described in the Protocol.

Rights and obligations:

1. The Data Processor is instructed to process the Personal Data for the term of the Study and only for the purposes of providing the data processing tasks set out in the Protocol. The Data Processor may not process or use Personal Data for any purpose other than a Data Participant's medical records, or other than provided in the instructions of the Study protocol, including with regard to transfers of personal data to a third country or an international organization, unless the Data Processor is required to do so according to Union or Member State law.
2. Data Processor shall at all times maintain a record of processing of Personal Data in accordance with Applicable Law and if the Data Processor considers an instruction from the Data Controller to be in violation of the Applicable Law, the Data Processor shall promptly inform the Data Controller in writing about this.
3. The Data Processor must ensure that persons authorized to process the Personal Data have committed themselves to confidentiality or are under an appropriate statutory obligation of confidentiality.
4. The Data Processor shall implement appropriate technical and organizational measures to prevent that the Personal Data processed is:
    (i) accidentally or unlawfully destroyed, lost or altered,
    (ii) disclosed or made available without authorization, or
    (iii) otherwise processed in violation of Applicable Law.
5. The appropriate technical and organizational security measures must be determined with due regard for:
    (i) the current state of the art,
    (ii) the cost of their implementation, and
    (iii) the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons.

6. Taking into account the nature of the processing, the Data Processor shall assist the Data Controller, by means of appropriate technical and organizational measures, insofar as this is possible, in fulfilling its obligation to respond to requests from Data Participants pursuant to laws and regulations in the area of privacy and data protection (such as, the right of access, the right to rectification, the right to erasure, the right to restrict the processing, the right to data portability and the right to object)
7. The Data Processor shall upon request provide the Data Controller with sufficient information to enable the Data Controller to ensure that the Data Processor's obligations under this DPA are complied with, including ensuring that the appropriate technical and organizational security measures have been implemented.
8. The Data Controller is entitled to appoint at its own cost an independent expert, reasonably acceptable to the Data Processor, who shall have access to the Data Processor's data processing facilities and receive the necessary information for the sole purpose of auditing whether the Data Processor has implemented and maintained said technical and organizational security measures. The expert shall upon the Data Processor's request sign a non-disclosure agreement provided by the Data Processor, and treat all information obtained or received from the Data Processor confidentially, and may only pass on, after conferral with the Data Processor, the findings as described under 10) (ii) below to the Data Controller.
9. The Data Processor must give authorities who by Union or Member State law have a right to enter the Data Controller's or the Data Controller's processors' facilities, or representatives of the authorities, access to the Data Processor's physical facilities against proper proof of identity and mandate, during normal business hours and upon reasonable prior written notice.
10. The Data Processor must without undue delay in writing notify the Data Controller about:
    (i) any request for disclosure of Personal Data processed under the Protocol by authorities, unless expressly prohibited under Union or Member State law,
    (ii) any finding of (a) breach of security that results in accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, Personal Data transmitted, stored or otherwise processed by the Data Processor under the Protocol, or (b) other failure to comply with the Data Processor's obligations, or
    (iii) any request for access to the Personal Data (with the exception of medical records for which the Data Processor is considered data controller) received directly from the Data Participants or from third parties.
11. Such a notification from the Data Processor to the Data Controller with regard to a breach of security as meant in 10) (ii)(a) above will contain at least the following information:
    (i) the nature of the Personal Data breach, stating the categories and (by approximation) the number of Data Participants concerned, and stating the categories and (by approximation) the number of the personal data registers affected (datasets);
    (ii) the likely consequences of the Personal Data breach;
    (iii) a proposal for measures to be taken to address the Personal Data breach, including (where appropriate) measures to mitigate any possible adverse effects of such breach.
12. The Data Processor shall document (and shall keep such documentation available for the Data Controller) any Personal Data breaches, including the facts related to the Personal Data breach, its effects and the corrective measures taken. After consulting with the Data Controller, the Data Processor shall take any measures needed to limit the (possible) adverse effects of Personal Data breaches (unless such consultation cannot be awaited due to the nature of the Personal Data breach).
13. The Data Processor must promptly and reasonably assist the Data Controller (with the handling of (a) responses to any breach of security as described in 10) (ii) above and (b) any requests from Data Participants under Chapter III of the GDPR, including requests for access, rectification, blocking or deletion. The Data Processor must also reasonably assist the Data Controller by

implementing appropriate technical and organizational measures for the fulfilment of the Data Controller's obligation to respond to such requests.

14. The Data Processor must reasonably assist the Data Controller with meeting the other obligations that may be incumbent on the Data Controller according to Union or Member State law where the assistance of the Data Processor is implied, and where the assistance of the Data Processor is necessary for the Data Controller to comply with its obligations. This includes, but is not limited to, at the request to provide the Data Controller with all necessary information about an incident under 10) (ii), and all necessary information for an impact assessment in accordance with Article 35 and Article 36 of the GDPR.

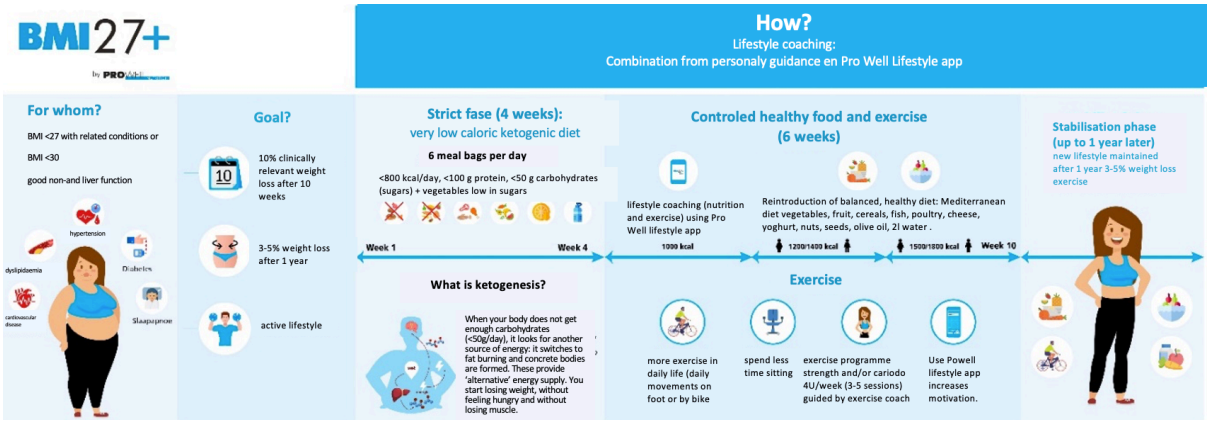
Subprocessor:

15. The Data Processor may only engage a subprocessor, with prior specific or general written consent from the Data Controller. The Data Processor undertakes to inform the Data Controller of any intended changes concerning the addition or replacement of a subprocessor by providing a reasonable prior written notice to the Data Controller. The Data Controller may reasonably and in a duly substantiated manner object to the use of a subprocessor. The Data Processor must inform the Data Controller in writing of the discontinued use of a subprocessor.
16. Prior to the engagement of a subprocessor, the Data Processor shall conclude a written agreement with the subprocessor, in which at least the same data protection obligations as set out in this DPA shall be imposed on the subprocessor, including obligations to implement appropriate technical and organizational measures and to ensure that the transfer of Personal Data is done in such a manner that the processing will meet the requirements of the Applicable Law.
17. The Data Controller has the right to receive a copy of the relevant provisions of Data Processor's agreement with the subprocessor related to data protection obligations. The Data Processor shall remain fully liable to the Data Controller for the performance of the subprocessor obligations under this DPA. The fact that the Data Controller has given consent to the Data Processor's use of a subprocessor is without prejudice for the Data Processor's duty to comply with this DPA.

Appendix 2: [Pro Well VLCKD protocol]

- BMI 27+ program: 10 weeks
  - 4 weeks VLCKD strict phase: 800 kcal/day (<50g carbs, >100g proteins, vegetables with a low carb content
  - 3 x 2 weeks of progressive increase of daily kcal: 1000 kcal, 1200 kcal (W) / 1400 kcal (M), 1500 kcal (W) / 1800 kcal (M) based on Mediterranean diet
  - Coaching minutes: 2 hours 15 minutes

Intake	30 minutes	Explanation VLCKD & App
Follow-up 1: after 3 weeks	15 minutes	Follow-up
Follow-up 2: after 4 weeks	15 minutes	Explanation 1000 kcal meal plan
Follow-up 3: after 6 weeks	15 minutes	Explanation 1200/1400 kcal meal plan
Follow-up 4: after 8 weeks	15 minutes	Explanation 1400/1800 kcal meal plan
Outtake after 10 weeks	15 minutes	Progress & Reflection



Appendix 3: [Pro Well Lifestyle protocol]

- **Lifestyle e-learning program :**

- **30 minutes 1-on-1 coaching and regular personal follow-up by telephone (if possible regular videocall Whatsapp/FaceTime)**
- **3 modules including 12 educational presentations**
- **12 practical tasks to apply in daily life**

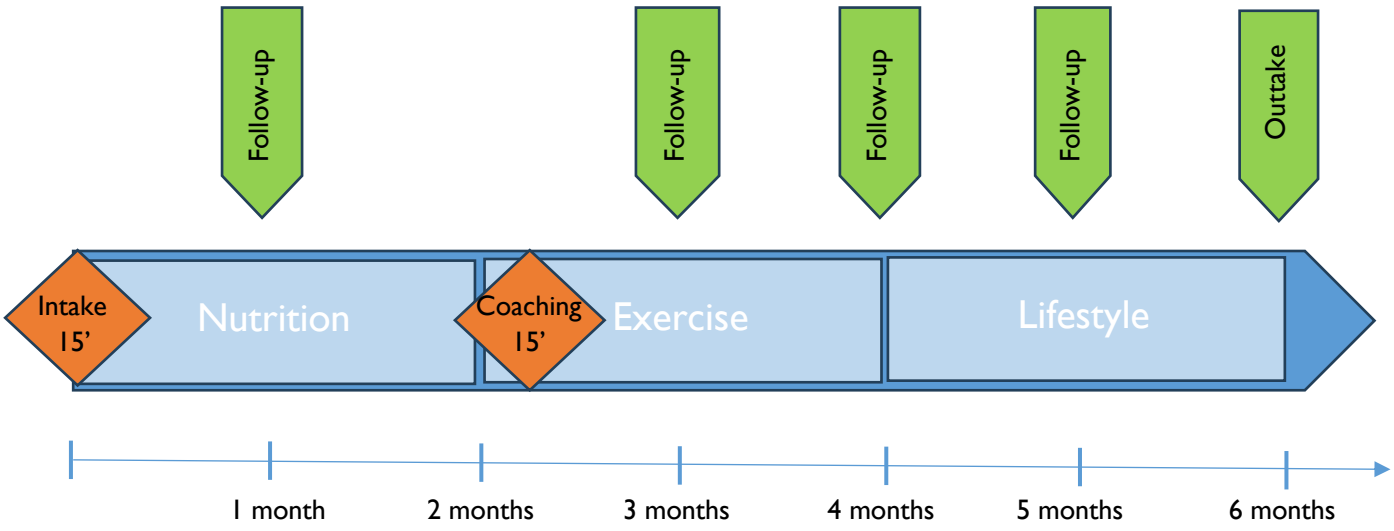
  - **Lifestyle e-learning program in addition to Naltrexon/bupropion**

Lifestyle coaching 1: at the start	15 minutes	Intake: overview e-learning modules and tasks
Lifestyle coaching 1: month 1 & 2	e-learning	Module : nutrition & 4 tasks about nutrition
Lifestyle coaching 1: after 1 month	Telephone	Follow-up
Lifestyle coaching 1: after 2 months	Telephone	Follow-up
Lifestyle coaching 1: month 3 & 4	e-learning	Module : physical exercise & 4 tasks
Lifestyle coaching 1: after starting module 2	15 minutes	Introducing a personal exercise program
Lifestyle coaching 1: after 3 months	Telephone	Follow-up
Lifestyle coaching 1: after 4 months	Telephone	Follow-up
Lifestyle coaching 1: month 5 & 6	e-learning	Module : Lifestyle topics sleep, stress management, relaxation and focus
Lifestyle coaching 1: after month 5	Telephone	Follow-up
Lifestyle coaching 1: at the end of month 6	Telephone	Outtake questionnaire: reflection & future goals

  - **Lifestyle e-learning program as a follow-up after 10 weeks BMI 27+ starting after 3 months**

Lifestyle coaching 1: after 3 months	15 minutes	Intake: overview e-learning modules and tasks
Lifestyle coaching 1: month 4	e-learning	Module : nutrition & 4 tasks about nutrition
Lifestyle coaching 1: halfway month 4	Telephone	Follow-up
Lifestyle coaching 1: at the end of month 4	Telephone	Follow-up
Lifestyle coaching 1: month 5	e-learning	Module : physical exercise & 4 tasks
Lifestyle coaching 1: after starting module 2	15 minutes	Introducing a personal exercise program
Lifestyle coaching 1: halfway month 5	Telephone	Follow-up
Lifestyle coaching 1: at the end of month 5	Telephone	Follow-up
Lifestyle coaching 1: month 6	e-learning	Module : Lifestyle topics sleep, stress management, relaxation and focus
Lifestyle coaching 1: halfway month 6	Telephone	Follow-up
Lifestyle coaching 1: at the end of month 6	Telephone	Outtake questionnaire: reflection & future goals

Lifestyle e-learning program in addition to Naltrexon/bupropion



BMI 27+ and Lifestyle Coaching