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Effect of liraglutide on body weight and pain in overweight or obese patients with knee osteoarthritis: Protocol for a randomised, double blind, placebo-controlled, parallel group, single-centre trial

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Complete List of Authors:	Gudbergsen, Henrik; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Henriksen, Marius; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute; Copenhagen University Hospital Bispebjerg-Frederiksberg, Department of Physio- and Occupational Therapy Wæhrens, Eva ; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Overgaard, Anders; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Bliddal, Henning; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Christensen, Robin; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute; Odense Universitetshospital, Department of Rheumatology Boesen, Mikael; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute; Copenhagen University Hospital Bispebjerg-Frederiksberg, Department of Radiology Knop, Filip K; Steno Diabetes Center Copenhagen, Gentofte Hospital, Clinical Metabolic Physiology; University of Copenhagen, Faculty of Health and Medical Sciences, Department of Clinical Medicine Astrup, Arne; Univesity of Copenhagen, Department of Nutrition, Exercise and Sports, Rasmussen, Marianne; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Bartholdy, Cecilie; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Daugaard, Cecilie; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Bartels, Else; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Ellegaard, Karen; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Heitmann, Berit; Copenhagen University Hospital Bispebjerg-Frederiksberg, Research Unit for Dietary Studies at The Parker Institute Kristensen, Lars Erik; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute

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TITLE

Effect of liraglutide on body weight and pain in overweight or obese patients with knee osteoarthritis: Protocol for a randomised, double blind, placebo-controlled, parallel group, single-centre trial

SHORT TITLE

Liraglutide 3 mg/day for knee osteoarthritis

ACRONYM

LOSEIT

BASED ON PROTOCOL VERSION

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KEYWORDS

Obesity, overweight, osteoarthritis, knee, weight loss, liraglutide, diet, dietary intervention.

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AUTHORS

Henrik Gudbergsen, MD, PhD, [1 **],
Marius Henriksen, PT, MSc, PhD [1, 2],
Eva Ejlersen Wæhrens, OT, MSc, PhD [1],
Anders Overgaard, MD [1],
Henning Bliddal, MD, DMSc [1 **],
Robin Christensen, BSc, MSc, PhD [1, 3],
Mikael Boesen, MD, PhD [1, 4],
Filip K. Knop, MD, PhD [5, 6],
Arne Astrup, MD, DMSc [7],
Marianne Uggen Rasmussen, MPH, PhD [1],
Cecilie Bartholdy, PT, MSc, [1, 2],
Cecilie Daugaard, MD, [1, 3],
Else Marie Bartels, PhD, DSc, [1],
Karen Ellegaard, PT, MSc, PhD [1],
Berit Lilienthal Heitmann, DMD, PhD [8], and
Lars Erik Kristensen, MD, PhD, DMSc [1]

[1] The Parker Institute, Copenhagen University Hospital Bispebjerg-Frederiksberg, Denmark
[2] Department of Physio- and Occupational Therapy, Copenhagen University Hospital Bispebjerg-Frederiksberg, Denmark
[3] Department of Rheumatology, Odense University Hospital, Denmark
[4] Department of Radiology, Copenhagen University Hospital Bispebjerg-Frederiksberg, Denmark
[5] Steno Diabetes Center Copenhagen, Clinical Metabolic Physiology, Copenhagen University Hospital Gentofte, Denmark
[6] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
[7] Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Copenhagen, Denmark
[8] Research Unit for Dietary Studies at The Parker Institute, Copenhagen University Hospital Bispebjerg-Frederiksberg, Denmark

* Corresponding author, telephone +45 29 84 28 88, mail: rindelgudbergsen@gmail.com
** Sponsor-investigator, telephone +45 38 16 41 51, mail: henning.bliddal@regionh.dk

ABSTRACT

Introduction: With an increasing prevalence of older and obese citizens, the health issues related to knee osteoarthritis (OA) will intensify. Weight loss is considered a primary management strategy in patients with concomitant obesity and knee OA. However, there are no widely available and feasible methods to sustain weight loss in overweight knee OA patients. The present protocol describes a randomised controlled trial evaluating the efficacy and safety of the glucagon-like peptide-1 receptor agonist liraglutide in a 3 mg/day dosing in obese patients with knee OA.

Methods and analysis: 150 volunteer overweight or obese patients above 18 years of age with knee OA will participate in a randomised, double blind, placebo-controlled, parallel group, and single-centre trial. The participants will partake in a run-in diet intervention phase (week -8 to 0) including a low-calorie diet and dietetic counselling. At week 0 patients will be randomised to either liraglutide 3 mg/day or liraglutide placebo 3 mg/day for 52 weeks as an add-on to dietetic guidance on re-introducing regular foods and a focus on continued motivation to engage in a healthy lifestyle.

Ethics and dissemination: The trial has been approved by the regional ethics committee in the Capital Region of Denmark, the Danish Medicines Agency, and the Danish Data Protection Agency. An external monitoring committee (The Good Clinical Practice Unit at Copenhagen University Hospitals) will oversee the trial. The results will be presented at international scientific meetings and through publications in peer-reviewed journals.

Trial registrations: ClinicalTrials.gov Identifier: NCT02905864, UTN: U1111-1171-4970, EudraCT: 2015-005163-16

ARTICLE SUMMARY

Strengths and limitations of this study

- Weight loss is recommended as a primary management strategy in patients with concomitant obesity and knee osteoarthritis (OA), however, there is no widely available and feasible method to sustain weight loss in overweight or obese knee OA patients
- This will be the first randomised controlled trial examining the efficacy and safety of daily liraglutide 3 mg/day in patients with knee OA
- We hypothesise that treatment with liraglutide 3 mg/day, compared to liraglutide placebo 3 mg/day, will further induce and maintain long-term weight loss and improve knee joint symptoms in overweight or obese patients with knee OA who have undergone an initial intensive dietary intervention weight loss programme
- The successful planning and conduction of the current trial may provide a breakthrough in the successful treatment of the many overweight or obese patients with knee OA
- This trial has a strict focus on a knee OA population who can successfully go through an intensive weight loss programme (losing at least 5% of their initial body weight)

INTRODUCTION

Obesity is a serious medical condition with increasing incidence and prevalence worldwide. The achievement and maintenance of a healthy body weight is the main strategy for prevention and management of obesity-related diseases [1 2]. The majority of subjects with a successful weight loss regain over the subsequent years and the maintenance of a clinically significant weight loss over time remains a challenge for healthcare professionals, patients, and societies [1].

Osteoarthritis (OA) is the most common type of arthritis, characterised by pain and physical disability [3]. In addition, more than 10% of those aged more than 55 years have symptomatic OA, primarily involving the knees [4]. Due to the pivotal role of the knee in basic mobility and locomotion, knee OA is associated with significant impairments and limitations to basic activities of daily living, such as walking and moving around, self-care, and housekeeping activities, as well as participation in community life and recreational activities – all contributing to reduced quality of life and needs for assistance. Epidemiological data link obesity to the development of knee OA [5], obesity and knee OA share pathogenic phenotypes, and the development of one disease increases the risk of the other, potentially triggering the onset of a vicious cycle [6].

Glucagon-like peptide 1 (GLP-1) is an incretin hormone that stimulates endogenous insulin secretion in a glucose-dependent manner. GLP-1 also lowers blood glucagon levels, reduces gastric emptying by decreasing gastric motility, and increases satiety. These mechanisms have been exploited therapeutically in the treatment of type 2 diabetes (T2D) for more than a decade, and recently the satiety promoting and body-weight lowering effects of the GLP-1 analogue liraglutide prompted the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to approve liraglutide in a once daily dose of 3 mg for the treatment of overweight or obesity. Recently published data, investigating the use of liraglutide 3 mg/day in an obese population with dyslipidaemia and/or hypertension, revealed a long-term positive impact on both body weight and related health benefits [7].

Scientific gap

The present trial has been designed to further investigate the potential of liraglutide 3 mg/day to safely induce and maintain long-term weight loss in overweight or obese individuals with knee OA. Weight loss is strongly recommended as a management strategy of patients with concomitant obesity and knee OA, and improves both pain and function [8-11]. However, no widely available and feasible means to sustain weight loss in overweight or obese knee OA patients has been presented.

Hypotheses

A diet intervention combined with liraglutide 3 mg/day, for 52 weeks, is sufficient to induce and maintain weight loss and to improve knee OA related pain symptoms. As such, the primary hypotheses to be tested are:

- In overweight or obese individuals with knee OA a diet intervention combined with liraglutide 3 mg/day will induce and maintain a significantly greater weight loss compared to a diet intervention combined with an identically appearing liraglutide placebo treatment

- In overweight or obese individuals with knee OA a diet intervention combined with liraglutide 3 mg/day will induce and maintain a significantly greater reduction in knee OA pain compared to a diet intervention combined with an identically appearing liraglutide placebo treatment

Objectives

The primary objectives are to establish the efficacy and safety of a diet intervention combined with liraglutide 3 mg/day, or placebo, in inducing and maintaining weight loss over 52 weeks and in improving symptomatic knee pain.

METHODS AND ANALYSIS

Trial design

The trial is designed as a single-centre, randomised, placebo-controlled, participant, investigator, and outcome assessor blinded, parallel-group trial. It contains three periods. Participants will initially be enrolled in an 8-week intensive dietary intervention (IDI) period. If successfully achieving a weight loss of minimum 5 % during this period participants will continue with a tapering dietary intervention (TDI) for 8 weeks (week 0 to 8) and be randomised to receive either liraglutide 3 mg/day or identically appearing placebo throughout the 52-week main trial period (week 0 to 52). The trial will be completed by a 12-week post-interventional observation period (PIOP) (figure 1).

Figure 1 Trial design

Trial conduct

Participants will be recruited within 12 months from the osteoarthritis outpatients' clinic at the Parker Institute at Copenhagen University Hospital, Bispebjerg and Frederiksberg. General practitioners and collaborating clinical hospital departments in the Capital Region will be informed about the possibility to refer patients to the project. In addition, the trial will be advertised in newspapers and on the Parker Institutes website (*www.parkerinst.dk*).

Before enrolment takes place, potential participants will be provided with written and verbal information about the trial and the procedures involved, in accordance with local requirements. Potential participants will have the opportunity to ask questions and have ample time to consider their participation. Following the signature of the informed consent form participants will be enrolled in the 8-week IDI period.

The IDI period is comprised of a supervised dietary weight loss programme in which participants receive a hypo-caloric formula diet containing 800 to 1.000 kcal/day. The formula diet consists of ready-to-use meal bars and powders to mix with water to make shakes, soups, or porridge. The weight loss programme consists of an 8-week period with full meal replacement according to a standard liquid energy intake protocol. To facilitate adherence to the programme, patients will be scheduled for weekly facility-based group sessions with 6-8 patients led by a dietician. The recommendations for daily nutrient intake will be met during this period.

Participants achieving a weight loss ≥5% during the IDI will be randomised to daily receive either liraglutide 3 mg/day or an identical placebo throughout the subsequent 52-week main trial period.
The initial 8 weeks of the main trial period consist of an 8-week TDI period (week 0 to 8) focusing on a partial re-introduction of regular meals in combination with formula diet products. In this period, all participants (irrespective of randomisation) will be scheduled to meet for group sessions led by a dietician every 2 weeks. No dietary consultancies will be offered from the trial after week 8, but to prevent attrition patients will be offered one to two daily meal replacements with a formula diet from week 8 to 52 to be administered by themselves. Participants will be instructed to aim for an intake of 1.200 kcal/day from week 0 to 8 and for an intake of 1.500 kcal/day from week 8 and onwards.

For the main trial period (drug intervention period running from week 0 to 52), participants will be randomised at week 0 to one of the two experimental arms described below:

- Liraglutide, 3 mg/day
    - *Arm description:* Subjects will be up titrated to liraglutide 3 mg once daily and stay on that dose for the remainder of the 52-week drug intervention period
    - *Drug:* Liraglutide 3 mg once daily administered in a 6 mg/mL, 3 mL pen for subcutaneous injection
    - *Dose escalation/titration scheme:* Initial dosage of 0.6 mg per day, escalated bi-weekly by 0.6 mg to 3 mg per day over a total of 8 weeks. Visits will be conducted at weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52

- *Liraglutide placebo, 3 mg/day*
    - *Arm description:* Subjects will be up-titrated to liraglutide 3 mg placebo once daily and stay on that dose for the remainder of the 52-week drug intervention period.
    - *Drug:* Liraglutide 3 mg placebo once daily administered in a 6 mg/mL drug equivalent volumes, 3 mL pen for subcutaneous injection
    - *Dose escalation scheme:* Initial dosage of a 0.6 mg drug equivalent volume per day, escalated bi-weekly by a 0.6 mg drug equivalent volume per day to a 3 mg drug equivalent volume per day over a total of 8 weeks. Visits will be conducted at weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52

The trial will end when the last patient has i) completed the last visit as well as the 12-week post-interventional observation period, ii) prematurely discontinued the intervention, or iii) withdrawn from the trial, whichever comes last.

For all potential trial participants, the following will be recorded: number of individuals initially assessed for eligibility, number excluded before enrolment (including reasons for non-eligibility), number enrolled, number randomised, and number withdrawn/dropped out during the trial (including reasons for withdrawal or exclusion). From allocation and onwards study personnel will assess the use of study medication to evaluate adherence.

Prior to the start of the study, the sponsor-investigator will ensure that the other investigators are familiar with the protocol, eCRFs and other study documents and procedures. The sponsor-investigator will be visited by the monitor prior to trial commencement and thereafter on a regular basis. The monitor will check trial procedures, including safety assessments, drug handling, data recording and complete source data verification (SDV) procedures.

Visits, assessments and procedures will take place as visualized in table 1.

Trial site

The trial will be conducted at the Parker Institute at Copenhagen University Hospital, Bispebjerg and Frederiksberg. The Parker Institute is a well-established research institute and clinical department with secretariat, data managers, and GCP (Good Clinical Practice) educated healthcare professionals such as physicians, trained specialists in rheumatology and radiology, nurses, and laboratory

technicians. Moreover, access to other departments and specialities within the hospital is available upon request if deemed necessary.

Trial population

To be enrolled in this trial, the following eligibility criteria must be met:

Inclusion criteria

- Informed consent obtained
- Clinical diagnosis of knee OA (American College of Rheumatology (ACR) criteria) with early to moderate radiographic changes (Kellgren-Lawrence (KL) grades 1, 2, or 3)
- Age ≥ 18 years and < 75 years
- Body mass index (BMI) ≥ 27 kg/m^2
- Stable body weight during the previous 3 months (< 5 kg self-reported weight change)
- Motivated for weight loss

Exclusion criteria

- On-going participation, or participation within the last 3 months, in an organised weight loss programme (or within the last 3 months)
- Current or history of treatment with medications that may cause significant weight gain for at least 3 months before this trial
- Current use or use within 3 months before this trial of GLP-1 receptor agonist, pramlintide, sibutramine, orlistat, zonisamide, topiramate, or phentermine
- Type 1 diabetes
- Type 2 diabetes treated with glucose-lowering drugs other than metformin
- Alloplasty in target knee joint (most symptomatic knee at screening)
- End stage disease in target knee joint (Kellgren-Lawrence grade 4)
- Immuno-inflammatory disease
- Chronic wide-spread pain
- Pregnancy or insufficient anti-conception therapy for female fertile patients
- Breast-feeding
- Estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x above upper normal range (UNR)
- Elective surgery scheduled during the trial duration period, except for minor surgical procedures

- Surgical procedures such as arthroscopy or injections into a knee within 3 months prior to enrolment
- Previous surgical treatment for obesity (excluding liposuction >1 year before trial entry)
- Thyroid stimulating hormone (TSH) outside of the range of 0.4-6.0 mIU/L
- Obesity secondary to endocrinologic or eating disorders, or to treatment with medicinal products that may cause weight gain
- Family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2
- Inflammatory bowel disease
- Congestive heart failure, New York Heart Association (NYHA) class III-IV
- Diabetic gastroparesis
- History of or current diagnosis of pancreatitis (acute and/or chronic) or pancreatic cancer
- History of cancer with the exception of in-situ malignancies of the skin or cervix uteri
- History of major depressive disorder, a PHQ-9 (Patient Health Questionnaire-9) score of more than 15, or a history of other severe psychiatric disorders or diagnosis of an eating disorder
- Subjects with a lifetime history of a suicide attempt or history of any suicidal behaviour within the past month before entry into the trial
- Inability to speak Danish fluently
- A mental state impeding compliance with the programme
- Use of opioids or similar strong analgesics
- Allergic reactions to the active ingredients of Saxenda, such as hypotension, palpitations, dyspnoea and oedema

Outcomes

Knee injury and Osteoarthritis Outcome Score (KOOS)

The KOOS is designed to assess health related quality of life (QoL) in patients with knee injuries and knee OA [12]. The KOOS consists of 42 items covering five domains, namely, Pain, Symptoms, Activities of Daily Living, Sports and Recreation, and knee-related QoL. A normalized score is calculated for each domain with 100 indicating no symptoms and functional impairment and zero indicating extreme symptoms and functional impairment.

Western Ontario and McMaster Universities Arthritis Index (WOMAC)

WOMAC is a disease-specific questionnaire designed to assess pain, stiffness, and physical function in patients with hip and/or knee OA [13]. It consists of 24 items divided into three subscales concerning

Pain, Stiffness, and Physical Function. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

Outcome Measures in Rheumatoid Arthritis Clinical Trials/Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria

The OMERACT-OARSI responder criteria include a composite index based on pain, function, and patient global [14]. These criteria are defined as improvement of 50% and absolute change of 20 points in pain or function or at least 2 of the following: (1) improvement of 20% and absolute change in function of 10 points, (2) improvement of 20% and absolute change in pain of 10 points, and (3) improvement of 20% as defined by a global rating of change score.

Intermittent and Constant Osteoarthritis Pain questionnaire (ICOAP)

The ICOAP is a diagnosis-specific 11-item questionnaire designed to assess the pain experience within the last week among people suffering from knee and hip OA [15]. The questionnaire is divided into two domains, a 5-item scale for constant pain and a 6-item scale for intermittent pain. Normalized scores, for the two subscales and for the total pain score, ranges from zero (no pain) to 100 (extreme pain).

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation. Four constructs are assessed [16]. The first is the *severity of ideation*, rated on a 5-point ordinal scale. The second is the *intensity of ideation* subscale comprising 5 items each rated on a 5-point ordinal scale. The third is *the behaviour subscale*, which is rated on a nominal scale. And the fourth is the *lethality subscale*, which is rated on a 6-point ordinal scale, and if actual lethality is zero, potential lethality of attempts is rated on a 3-point ordinal scale. The Baseline-Screening version will be employed to assess inclusion/exclusion criteria and to provide a pre-treatment assessment at Baseline. On all subsequent visits, the Since Last Visit version will be used.

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a diagnostic tool for mental health disorders [17]. The PHQ-9 is the depression subscale of the PHQ and contains nine questions related to depression disorder symptoms during the past 14 days. The answer categories are based on a 4-point response scale and the summed PHQ-9 score can range from zero to 27. A score of ≥15 is considered an indication of moderately severe or severe depression.

Binge Eating Scale (BES)

The BES is a self-report instrument that assesses the behavioural and emotional/cognitive symptoms associated with binge eating [18]. The BES is comprised of 16 items assessing key behavioural (e.g., rapid eating, eating large amounts of food), and affective/cognitive symptoms (e.g., guilt, feeling out of control or unable to stop eating) that precede or follow a binge. Each item contains three to four statements that are weighted response options, which reflect a range of severity for each characteristic. Participants are asked to select the statement that best describes their experience. The scale's possible total scores range from zero to 46, with higher scores indicating more severe binge eating symptoms.

Impact of Weight on Quality of Life-Lite (IWQoL-Lite)

The IWQoL-Lite is a 31-item, self-report, obesity-specific measure of health-related quality of life that consists of a total score and scores on each of five scales: physical function, self-esteem, sexual life, public distress, and work [19]. Scores range from zero to 100, where 100 represent the best HRQOL and zero represents the worst.

Treatment Related Impact Measure-Weight (TRIM-Weight)

The TRIM-Weight is an obesity treatment-specific patient reported outcomes measure designed to assess the key impacts of prescription anti-obesity medication and be applicable to the wide range of prescription medications currently available [20]. The TRIM-Weight is based on 22 items within seven thematic domains. All items are scored on anchored rating scales with five levels of response (1–5) in which higher scores indicate better quality of life.

Short form 36 (SF-36)

The SF-36 is a generic, short-form health status questionnaire composed of 36 questions within eight multi-item domains assessing physical function, social function, role-emotional, role-physical, bodily pain, general health, mental health and vitality [21]. These can be combined into two summary scores (physical and mental health summary scores). For each summary score, the ordinal scores are transformed to a linear zero to 100 scale; zero indicating the least favourable health state and 100 indicating the best state of health.

Waist and hip circumferences

Waist circumference will be measured mid-way between the lower rib margin and the iliac crest, while hip circumference will be measured at the point over the buttocks yielding the maximum circumference. Waist and hip circumferences will be measured to the nearest 1 cm. All anthropometric measurements will be taken in accordance with the WHO report on measuring obesity.

Height

Height without shoes will be measured using a stadiometer and rounded to the nearest 1 cm.

Body weight

Body weight will be measured to the nearest 0.1 kg with a decimal weighing scale (TANITA BW-800, Tanita Europe BV Hoogoorddreef 56e, 1101BE Amsterdam, The Netherlands) with participants fasting and wearing underwear or light clothing, only.

BMI

The BMI (kg/m^2) will be calculated from body weight and height.

DXA scans

Body composition as well as bone mineral measurements will be assessed via whole-body dual energy X-ray absorptiometry (DXA) using a Norland XR 800 scanner. The following parameters will be assessed; fat mass (kg), lean body mass (kg), and total body weight (kg).

Blood samples

Standard biochemistry: CRP, ALT, AST, calcium, creatinine, potassium, sodium, uric acid, LDL, HDL, TG, and TC. Haematology: Haemoglobin, leucocytes, differential cell count, and thrombocytes. Glucose metabolism: HbA1c and FPG.

Radiography

Radiographic examinations include standard clinical semi-flexed weight bearing posterior-anterior radiographs of both knees. During the examination patients will be facing the plate of the radiography equipment with the knees touching the cassette holder or a reclining table top. The radiography plate or cassette holder is placed so that the centre of the film will be at the level of the patient's tibiofemoral joint line. The radiography beam is centred between the knees with a 10 degrees cranio-caudal angle and the body weight will be distributed equally between the two legs.

The radiographs will be assessed by use of the Kellgren & Lawrence (KL) grading system; a categorical grading scale of knee OA going from 0 to 4 by means of an evaluation of osteophytes, joint space narrowing, sclerosis, and altered bone shapes.

Endpoints

Co-primary endpoints

To demonstrate that liraglutide 3 mg/day not only lowers body weight, but also reduces pain, the co-primary endpoints are changes in body weight and the KOOS pain subscale from baseline (week 0) to the last visit in the main trial period (week 52).

Confirmatory secondary endpoints

The confirmatory secondary endpoints are changes in the KOOS symptom, ADL, sport and recreation, and health related QoL subscales, the WOMAC pain, stiffness, and function subscales, the total score and subscales in the ICOAP questionnaire, BMI, waist circumference, or the waist/hip ratio from baseline (week 0) to the last visit in the main trial period (week 52). Moreover, the proportion of patients with ≥5 or ≥10 % weight loss at the last visit in the main trial period (week 52).

Visit schedule

Table 1 Visit schedule

	Information	Screening	Enrolment	Pre-allocation	-	-	-	-	-	-	-	Allocation	Post-allocation	-	-	-	-	-	-	-	-	-	-	-	-	-	End of trial	-	Off-treatment follow-up
VISIT NAME	-Ty	-Tz	-Tx	-T8	-T7	-T6	-T5	-T4	-T3	-T2	-T1	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	Tx	Tz
WEEK NO.	x	x	x	-8	-7	-6	-5	-4	-3	-2	-1	0	2	4	6	8	12	16	20	24	28	32	36	40	44	48	52	x	64
INFORMATION & SCREENING																													
Motivation appraisal	X																												
Exchange of information	X																												
Eligibility screening & consent		X																											
X-ray & physical examination		X																											
Blood testing & urine stix		X																											
Medical & medication history		X																											
KOOS pain, WOMAC pain, C-SSRS & PHQ-9		X																											
Vital signs, height, body weight & ECG		X																											
INTERVENTION																													
IDI				X	X	X	X	X	X	X	X																		
TDI												X	X	X	X	X													
Lira 3 mg OR Lira 3 mg pbo												X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ASSESSMENTS																													
Physical examination			X									X															X	X	
Dietician (group session)				X	X	X	X	X	X	X	X	X	X	X	X	X													
Titration visit (MD)												X	X	X	X	X	(X)	(X)											
Medical history			X																										
Update of medical history												X															X	X	
Medication history			X									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
KOOS, WOMAC, SF-36, IWQoL-lite & O-O resp. crit.			X									X															X	X	
ICOAP			X									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
KOOS pain & WOMAC pain													X	X	X	X	X	X	X	X	X	X	X	X	X	X			
C-SSRS			X									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHQ-9 & BES			X									X															X	X	X
TRIM-weight													X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events report form				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs & waist and hip circumferences			X									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body weight			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood testing, height & DXA			X									X															X	X	
X-ray			X																								X	X	
ECG												X					X										X	X	X
Medicine hand-out												X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adherence assessment													X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

**Lira: Liraglutide; pbo: placebo, O-O resp.crit: OMERACT-OARSI responder criteria*

Data management

The collection, preservation and dissemination of the clinical data is specified in this clinical trial protocol and abide to the standard requirements for GCP-compliant data management in clinical trials. The source data and documents, eCRF, protocol and amendments, drug accountability forms, correspondence, patient identification list, informed consent forms, and other essential GCP documents will be retained for at least 10 years after the study is completed at the study site. Data entries are quality ensured by double data entry, classification of data type (i.e. text and numbers) and/or range checks for data values.

All data collected during this project will be managed and quality certified by the Parker Institutes data management team, composed by the primary investigator, a data manager and a chief administrator. This team is responsible for ensuring data completeness and accuracy as well as source data verification. The latter will be performed by the monitor and the relevant investigators. The team is also responsible for ensuring operations of a secure database established for the collection of clinical data collected via the electronic case report form (eCRF) platform through a secure connection. All data obtained during the study will be documented in the individual eCRFs. reasons for any missing data will be noted in the database, and logging and tracking of data changes will be documented.

Randomisation

Participants will be randomised to treatment daily with liraglutide 3 mg/day or liraglutide placebo 3 mg at week 0, i.e. after the initial 8-week IDI period. Patients will be randomised in a 1:1 manner to receive either 3 mg/day liraglutide or identically appearing placebo; stratified randomisation will be based on gender (male vs. female), age (<60 years vs. ≥60 years), and obesity class (BMI; < 40 vs. ≥ 40 [kg/m^2]) status at trial enrolment (week -8). A computer-generated randomisation sequence will be produced using SAS PROC PLAN to generate the eight randomisation schedules before any participant is enrolled, allocating participants in permuted blocks of 2 to 6 to the daily liraglutide 3 mg/day or placebo group (1:1). The randomisation sequence is entered into the eCRF by a data manager.

Allocation concealment and blinding

The trial utilizes a computer-generated allocation process in which the patient identifier is coupled to one of the experimental arms when the physician clicks on the 'randomisation button', appearing at visit T0 in the eCRF system. Upon allocation to one of the two experimental arms the patient identifier is automatically coupled to specific pens, each of them labelled by a single and unique Dispensing Unit Number (DUN). The entire process is blinded for all investigators, clinical, academic, and administrative trial personnel.

Unblinding will only take place in exceptional circumstances when knowledge of the actual treatment is essential for further management of the patient. If unblinding is deemed necessary, the investigator will activate a data solution, within the eCRF, build for this specific purpose and controlled by an independent data manager and the chief administrator. The actual allocation will not be disclosed to the patient and/or other study personnel including other site personnel, monitors, corporate sponsors or project office staff.

Sample size and power considerations

The co-primary outcomes are changes in body weight and KOOS-Pain from randomisation to the end of the trial, 52 weeks after randomisation. The sample size of 150 is designed to provide a reasonable power (>80%) to detect a 5-kg difference in body weight change between the groups, AND an 8-units difference in the KOOS-Pain. All power and sample size analyses were conducted using 'SAS Power and Sample Size', version 3.1 (SAS Institute Inc., Cary, North Carolina):

- Body weight: For a two-sample pooled t-test of a normal mean difference with a two-sided significance level of 0.05 (P<0.05), assuming a common standard deviation of 10 kg, a sample size of 75 per group, has a power of 92% to detect a mean difference of 5.5 kg.
- KOOS-Pain: For a two-sample pooled t test of a normal mean difference with a two-sided significance level of 0.05 (P<0.05), assuming a common standard deviation of 15 KOOS-points, a sample size of 75 patients per group has a power of 90% to detect a mean difference of 8 KOOS-Points (corresponding to a moderate Cohen's effect size of 0.5).

The combined power for the two endpoints is 83%.

Statistical methods

The prespecified efficacy analyses will be based on the data from the full-analysis set; i.e. the intention-to-treat (ITT) population - including all participants who are randomised and assessed at baseline. In case of missing data at week 52, a simple non-responder imputation technique will be applied. The baseline observation carried forward approach will be used for patients who do not complete the trial. The safety analysis set includes all patients who are randomly assigned to a trial group and have had exposure to a trial drug (i.e., liraglutide 3 mg/day or placebo). This trial does not plan for any interim analyses.

The primary analysis will be the comparison between liraglutide and placebo using an Analysis of Covariance (ANCOVA) model with treatment, gender, age-, and obesity-stratification as fixed effects and with adjustment for the level at baseline as a covariate. From this model, the observed differences in weight change and KOOS pain change between liraglutide treatment and placebo will be estimated

together with the associated 95% confidence interval and the *p*-value corresponding to the test of the hypothesis of no difference between treatments (i.e., the null hypothesis).

To establish the efficacy of liraglutide 3 mg/day compared to placebo in overweight/ obese participants with knee OA, inducing and maintaining weight loss and pain relief over 52 weeks, endpoints are tested in a hierarchical manner in the order in which the endpoints are presented. Liraglutide 3 mg/day will be considered statistically significantly better than liraglutide placebo 3 mg/day placebo with respect to change in body weight if the null hypothesis is rejected ($p<0.05$). But, overall, liraglutide 3 mg/day will only be *confirmed* as statistically significantly better than placebo with respect to change in KOOS pain subscale, if it is ALSO statistically significantly better with respect to change in body weight.

Categorical changes for dichotomous end-points will be analysed with the use of logistic regression with the same fixed effects and covariates as the respective ANCOVA. Sensitivity analyses will be performed to assess the robustness of the primary analyses, including 'per protocol' scenarios, repeated-measures linear mixed models, and multiple-imputation techniques.

Management

The project management team consists of the Primary Investigator, Dr. Henrik Rindel Gudbergsen who is responsible for the execution of the project, the Sponsor-Investigator Professor Henning Bliddal who is responsible for the overall scientific planning of the project, and Chief Administrator Claus Bomhoff who is responsible for administrative and financial tasks. The steering committee (SC), led by the Primary Investigator, is the principal management body with respect to the operational and scientific facets of this trial. Members of the SC are the investigators involved in the development of this protocol and include HRG (chairman), HB (sponsor), MH, EW, HB, RC, MK, FK, AA, MUR, and LEK. The SC will ensure trial resources, schedule all trial related activities, and ensure execution of the trial.

The independent ethics committee (ICE) monitors any safety and/or ethical concerns arising during the project and to advise the SC. The members of the ICE are Lennart Jacobsson, Professor in Rheumatology, Department of Rheumatology, Sahlgrenska University Hospital, Gothenburg, Sweden and Karl Agner Kristensen MD, PhD, Specialist in Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, Lund University Hospital, Lund, Sweden.

Patient and public engagement

Via a formal review process the authors ensured that the development of this trials hypotheses, interventions and outcomes were discussed with an appointed knee OA patient advisor.

The engagement of patients will also include recruitment and enrolment in the trial and through the dialogue around the informed consent patients will be engaged to assess the burden of the interventions and assessments.

Patients will be informed, via dialogue and a briefing document, that they may access results on an individual basis throughout the trial and that the study personnel will engage in presenting the overall results for each individual patient once the trial is complete. Upon trial completion patients will be invited to a meeting where the project results are presented in a manner that is understandable by layman.

ETHICS AND DISSEMINATION

The investigator will monitor each participant for clinical and laboratory evidence of adverse events (AEs) on a routine basis throughout the trial. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the participant, will be recorded. The investigator will assess and record any AE in detail, including the date of onset, description, severity, duration and outcome, relationship of the AE to trial drug, and any action(s) taken.

The treatment and investigations in this trial are associated with minimal discomfort for the participants. The injection is practically pain-free but may leave a small haemorrhage, resolving spontaneously within a few days in the vast majority of patients. Less commonly, the patients may experience abdominal pain, insomnia, reflux, gastritis, and dizziness. Uncommon AEs comprise dehydration, tachycardia, pancreatitis, cholecystitis, urticarial, and malaise.

When collecting blood samples some participants may experience minor discomfort when the needle penetrates the skin, and rarely a small bleeding occurs. The planned radiographs will be identical and obtained at the same frequency as recommended in the current care model at the involved outpatient clinics.

The participants included in the planned clinical trial will not receive any financial compensation. Neither the sponsor-investigator nor any of the other members of the project group has financial interest in neither the conduct nor the results of the trial.

All participants will be covered by a patient-insurance, according to national requirements and common conduct, during the conduction of the clinical trials.

The trial is approved by the regional ethics committee in the Capital Region of Denmark; approval ID H-16019969.

The successful planning and conduction of the LOSEIT trial may provide the basis for a significant improvement in the disease management of the many overweight citizens impacted by knee OA.

At the end of the trial, one or more manuscripts will be prepared for publication in peer-reviewed journals. The manuscripts will be written in accordance with the CONSORT Statement. The

manuscripts will include positive, negative, as well as inconclusive results. In addition, the results from the trial will be presented as posters or oral presentations at national and/or international conferences.

Novo Nordisk A/S and The Cambridge Weight Plan had no influence on the study design, nor will they have any influence on the analyses and interpretation of data or the writing of manuscripts/abstracts based on trial data. Novo Nordisk A/S and The Cambridge Weight Plan will be given 4 weeks to review any manuscript/abstract or other means intended for publication or presentation of the data. All authors will qualify for authorship according to International Committee of Medical Journal Editors, 1997, and must have participated sufficiently in the work to take public responsibility for the content.

COMPETING INTERESTS STATEMENT

HG; has received speaker fees from Pfizer and MSD

MH, EEW, AO, HB, RC, MUR, CB, CD, EMB, BH and KE; none to declare

MB; has received speaker fees from Esaote, Abbvie, and UCB

FKK; has received lecture fees from, participated in advisory boards of and/or consulted for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD/Merck, Novo Nordisk, Sanofi and Zealand Pharma

AA; reports grants and personal fees from Global Dairy Platform, USA; McCain Foods, USA; McDonald's, USA; Arena Pharmaceuticals Inc, USA; Basic Research, USA; Dutch Beer Knowledge Institute, NL; Gelesis, USA; Novo Nordisk, DK; Orexigen Therapeutics Inc., USA; S-Biotek, DK, Twinlab, USA; Vivus Inc., USA; and grants from Arla Foods, DK; Danish Dairy Research Council, Nordea Foundation, DK outside the submitted work; and Royalties received for the book first published in Danish as "Verdens Bedste Kur" (Politiken, Copenhagen), and subsequently published in Dutch as "Het beste dieet ter wereld" (Kosmos Uitgevers, Utrecht/ Antwerpen), in Spanish as "Plan DIOGenes para el control del peso. La dieta personalizada inteligente" (Editorial Evergráficas, Léon), and in English as "World's Best Diet" (Penguin, Australia).

LEK; has received fees for speaking and consultancy from Pfizer, AbbVie, Amgen, Sanofi, UCB, Celgene, BMS, Biogen, Novo Nordisk, MSD, Novartis, Eli Lilly, and Janssen pharmaceuticals

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DATA SHARING STATEMENT

Once the trial has been completed data and information about the study may be accessed by contacting the corresponding author after obtaining and documenting legitimate approval from the Danish data authorities and to the extent possible according to Danish national law.

CONTRIBUTORSHIP STATEMENT

HG, EEW, MH, HB, RC, MB, FKK, MH, AA, EMB, and LEK have contributed by conceptualising, designing, writing, reviewing, and approving the protocol for this trial.

AO, MUR, CB, CD, BLH, and KE have contributed by writing, reviewing, and approving the protocol, and are all part of the acquisition of data from the trial.

Moreover, all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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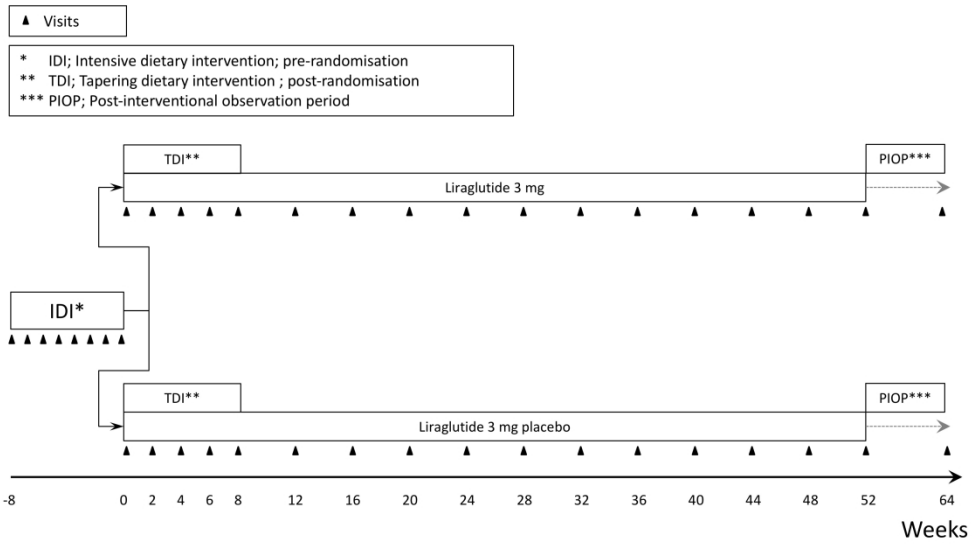

Figure 1. Trial design

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BMJ Open

Effect of liraglutide on body weight and pain in patients with overweight and knee osteoarthritis: Protocol for a randomised, double blind, placebo-controlled, parallel group, single-centre trial

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Complete List of Authors:	Gudbergsen, Henrik; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Henriksen, Marius; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute; Copenhagen University Hospital Bispebjerg-Frederiksberg, Department of Physio- and Occupational Therapy Wæhrens, Eva ; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Overgaard, Anders; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Bliddal, Henning; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Christensen, Robin; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute; Odense Universitetshospital, Department of Rheumatology Boesen, Mikael; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute; Copenhagen University Hospital Bispebjerg-Frederiksberg, Department of Radiology Knop, Filip K; Steno Diabetes Center Copenhagen, Gentofte Hospital, Clinical Metabolic Physiology; University of Copenhagen, Faculty of Health and Medical Sciences, Department of Clinical Medicine Astrup, Arne; Univesity of Copenhagen, Department of Nutrition, Exercise and Sports, Rasmussen, Marianne; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Bartholdy, Cecilie; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Daugaard, Cecilie; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Bartels, Else; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Ellegaard, Karen; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Heitmann, Berit; Copenhagen University Hospital Bispebjerg-Frederiksberg, Research Unit for Dietary Studies at The Parker Institute; Kobenhavns Universitet Det Samfundsvidenskabelige Fakultet, Department of Public Health, Section for General Medicine Kristensen, Lars Erik; Copenhagen University Hospital Bispebjerg-

	Frederiksberg, The Parker Institute
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Nutrition and metabolism, Research methods
Keywords:	overweight, osteoarthritis, Knee < ORTHOPAEDIC & TRAUMA SURGERY, weight loss, liraglutide, dietary intervention

TITLE

Effect of liraglutide on body weight and pain in patients with overweight and knee osteoarthritis: Protocol for a randomised, double blind, placebo-controlled, parallel group, single-centre trial

SHORT TITLE

Liraglutide 3 mg/day for knee osteoarthritis

ACRONYM

LOSEIT

BASED ON PROTOCOL VERSION

Version 6; the 30th of January 2017, 15:30

KEYWORDS

Obesity, overweight, osteoarthritis, knee, weight loss, liraglutide, diet, dietary intervention.

WORD COUNT

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AUTHORS

Henrik Gudbergsen, MD, PhD, [1 **],
Marius Henriksen, PT, MSc, PhD [1, 2],
Eva Ejlersen Wæhrens, OT, MSc, PhD [1],
Anders Overgaard, MD [1],
Henning Bliddal, MD, DMSc [1 **],
Robin Christensen, BSc, MSc, PhD [1, 3],
Mikael Boesen, MD, PhD [1, 4],
Filip K. Knop, MD, PhD [5, 6],
Arne Astrup, MD, DMSc [7],
Marianne Uggen Rasmussen, MPH, PhD [1],
Cecilie Bartholdy, PT, MSc, [1, 2],
Cecilie Daugaard, MD, [1, 3],
Else Marie Bartels, PhD, DSc, [1],
Karen Ellegaard, PT, MSc, PhD [1],
Berit Lilienthal Heitmann, DMD, PhD [8, 9], and
Lars Erik Kristensen, MD, PhD, DMSc [1]

[1] The Parker Institute, Copenhagen University Hospital Bispebjerg-Frederiksberg, Denmark
[2] Department of Physio- and Occupational Therapy, Copenhagen University Hospital Bispebjerg-Frederiksberg, Denmark
[3] Department of Rheumatology, Odense University Hospital, Denmark
[4] Department of Radiology, Copenhagen University Hospital Bispebjerg-Frederiksberg, Denmark
[5] Steno Diabetes Center Copenhagen, Clinical Metabolic Physiology, Copenhagen University Hospital Gentofte, Denmark
[6] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
[7] Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Copenhagen, Denmark
[8] Research Unit for Dietary Studies at The Parker Institute, Copenhagen University Hospital Bispebjerg-Frederiksberg, Denmark
[9] Department of Public Health, Section for General Medicine, University of Copenhagen, Copenhagen, Denmark

* Corresponding author, telephone +45 29 84 28 88, mail: rindelgudbergsen@gmail.com
** Sponsor-investigator, telephone +45 38 16 41 51, mail: henning.bliddal@regionh.dk

ABSTRACT

Introduction: With an increasing prevalence of citizens of older age and with overweight, the health issues related to knee osteoarthritis (OA) will intensify. Weight loss is considered a primary management strategy in patients with concomitant overweight and knee OA. However, there are no widely available and feasible methods to sustain weight loss in patients with overweight and knee OA. The present protocol describes a randomised controlled trial evaluating the efficacy and safety of the glucagon-like peptide-1 receptor agonist liraglutide in a 3 mg/day dosing in patients with overweight and knee OA.

Methods and analysis: 150 volunteer adult patients with overweight or obesity and knee OA will participate in a randomised, double blind, placebo-controlled, parallel group, and single-centre trial. The participants will partake in a run-in diet intervention phase (week -8 to 0) including a low-calorie diet and dietetic counselling. At week 0 patients will be randomised to either liraglutide 3 mg/day or liraglutide placebo 3 mg/day for 52 weeks as an add-on to dietetic guidance on re-introducing regular foods and a focus on continued motivation to engage in a healthy lifestyle.

Ethics and dissemination: The trial has been approved by the regional ethics committee in the Capital Region of Denmark, the Danish Medicines Agency, and the Danish Data Protection Agency. An external monitoring committee (The Good Clinical Practice Unit at Copenhagen University Hospitals) will oversee the trial. The results will be presented at international scientific meetings and through publications in peer-reviewed journals.

Trial registrations: EudraCT: 2015-005163-16, ClinicalTrials.gov Identifier: NCT02905864, UTN: U1111-1171-4970

ARTICLE SUMMARY

Strengths and limitations of this study

- Weight loss is recommended as a primary management strategy in patients with concomitant overweight or obesity and knee osteoarthritis (OA), however, there is no widely available and feasible method to sustain weight loss in patients with overweight or obesity and knee OA
- This will be the first randomised controlled trial (RCT) examining the efficacy and safety of daily liraglutide 3 mg/day in patients with knee OA
- We hypothesise that treatment with liraglutide 3 mg/day, compared to liraglutide placebo 3 mg/day, will further induce and maintain long-term weight loss and improve knee joint symptoms in adults with overweight or obesity and knee OA who have undergone an initial intensive dietary intervention weight loss programme
- The successful planning and conduction of this RCT may provide a breakthrough in long-term management of the many patients with overweight or obesity and knee OA
- This trial has a strict focus on an adult population with clinical knee OA who can successfully go through an intensive dietary programme (the target being to lose at least 5% of their initial body weight)

INTRODUCTION

Obesity is a serious medical condition with increasing incidence and prevalence worldwide. The achievement and maintenance of a healthy body weight is the main strategy for prevention and management of obesity-related diseases [1 2]. The majority of subjects with a successful weight loss regain weight over the subsequent years and the maintenance of a clinically significant weight loss over time remains a challenge for healthcare professionals, patients, and societies [1].

Osteoarthritis (OA) is the most common type of arthritis, characterised by pain and physical disability [3]. In addition, more than 10% of those aged more than 55 years have symptomatic OA, primarily involving the knees [4]. Due to the pivotal role of the knee in basic mobility and locomotion, knee OA is associated with significant impairments and limitations to basic activities of daily living, such as walking and moving around, self-care, and housekeeping activities, as well as participation in community life and recreational activities – all contributing to reduced quality of life and needs for assistance. Epidemiological data link obesity to the development of knee OA [5], obesity and knee OA share pathogenic phenotypes, and the development of one disease increases the risk of the other, potentially triggering the onset of a vicious cycle [6].

Glucagon-like peptide 1 (GLP-1) is an incretin hormone that stimulates endogenous insulin secretion in a glucose-dependent manner. GLP-1 also lowers blood glucagon levels, reduces gastric emptying by decreasing gastric motility, and increases satiety. These mechanisms have been exploited therapeutically in the treatment of type 2 diabetes for more than a decade, and recently the satiety promoting and body-weight lowering effects of the GLP-1 analogue liraglutide prompted the U.S. Food and Drug Administration and the European Medicines Agency to approve liraglutide in a once daily dose of 3 mg for the treatment of patients with overweight or obesity. Published data, investigating the use of liraglutide 3 mg/day in a population of patients with obesity as well as dyslipidaemia and/or hypertension, revealed a long-term positive impact on both body weight and related health benefits [7].

Scientific gap

The present trial has been designed to further investigate the potential of liraglutide 3 mg/day to safely induce and maintain long-term weight loss in patients with overweight or obesity and knee OA. Weight loss is strongly recommended as a management strategy of patients with concomitant overweight or obesity and knee OA, and improves both pain and function [8-11]. However, no widely available and feasible means to sustain weight loss in patients with overweight or obesity and knee OA has been presented.

Hypotheses

A diet intervention combined with liraglutide 3 mg/day, for 52 weeks, is sufficient to induce and maintain weight loss and to improve knee OA related pain symptoms. As such, the primary hypotheses to be tested are:

- In patients with overweight or obesity and knee OA a diet intervention combined with liraglutide 3 mg/day will induce and maintain a significantly greater weight loss compared to a diet intervention combined with an identically appearing liraglutide placebo treatment

- In patients with overweight or obesity and knee OA a diet intervention combined with liraglutide 3 mg/day will induce and maintain a significantly greater reduction in knee OA pain compared to a diet intervention combined with an identically appearing liraglutide placebo treatment

Objectives

The primary objectives are to establish the efficacy and safety of a diet intervention combined with liraglutide 3 mg/day, or placebo, in inducing and maintaining weight loss over 52 weeks and in improving symptomatic knee pain.

METHODS AND ANALYSIS

Trial design

The trial is designed as a single-centre, randomised, placebo-controlled, participant, investigator, and outcome assessor blinded, parallel-group trial. It contains three periods. Participants will initially be enrolled in an 8-week intensive dietary intervention (IDI) period. If successfully achieving a weight loss of minimum 5 % during this period participants will continue with a tapering dietary intervention (TDI) for 8 weeks (week 0 to 8) and be randomised to receive either liraglutide 3 mg/day or identically appearing placebo throughout the 52-week main trial period (week 0 to 52). The trial will be completed by a 12-week post-interventional observation period (PIOP) (figure 1).

Figure 1 Trial design

Trial conduct

Participants will be recruited within 12 months from the osteoarthritis outpatients' clinic at the Parker Institute at Copenhagen University Hospital, Bispebjerg and Frederiksberg. General practitioners and collaborating clinical hospital departments in the Capital Region will be informed about the possibility

to refer patients to the project. In addition, the trial will be advertised in newspapers and on the Parker Institutes website (*www.parkerinst.dk*).

Potential study participants will initially partake in a motivational assessment including an interview in which the nature of the initial IDI is explained together with a description of the overall study, a thorough outline of the interventions and visits, and a session in which the investigator addresses any questions the potential participant may have. The study will not use any standardised scoring system to assess motivation, but during the interview the investigator will assess the individual's motivation for weight loss through both the IDI period and the subsequent participation in the randomised part of the study.

Before enrolment takes place, potential participants will be provided with written and verbal information about the trial and the procedures involved, in accordance with local requirements. Potential participants will have the opportunity to ask questions and have ample time to consider their participation. Following the signature of the informed consent form participants will be enrolled in the 8-week IDI period.

The IDI period is comprised of a supervised dietary weight loss programme in which participants receive a hypo-caloric formula diet containing 800 to 1.000 kcal/day. The formula diet consists of ready-to-use meal bars and powders to mix with water to make shakes, soups, or porridge. The weight loss programme consists of an 8-week period with full meal replacement according to a standard liquid energy intake protocol. To facilitate adherence to the programme, patients will be scheduled for weekly facility-based group sessions with 6-8 patients led by a dietician. The recommendations for daily nutrient intake will be met during this period.

Participants achieving a weight loss ≥5% during the IDI will be randomised to daily receive either liraglutide 3 mg/day or an identical placebo throughout the subsequent 52-week main trial period.
The initial 8 weeks of the main trial period consist of an 8-week TDI period (week 0 to 8) focusing on a partial re-introduction of regular meals in combination with formula diet products. In this period, all participants (irrespective of randomisation) will be scheduled to meet for group sessions led by a dietician every 2 weeks. No dietary consultancies will be offered from the trial after week 8, but to prevent attrition patients will be offered one to two daily meal replacements with a formula diet from week 8 to 52 to be administered by themselves. Participants will be instructed to aim for an intake of 1.200 kcal/day from week 0 to 8 and for an intake of 1.500 kcal/day from week 8 and onwards.

For the main trial period (drug intervention period running from week 0 to 52), participants will be randomised at week 0 to one of the two experimental arms described below:

- Liraglutide, 3 mg/day
  - *Arm description:* Subjects will be up titrated to liraglutide 3 mg once daily and stay on that dose for the remainder of the 52-week drug intervention period
  - *Drug:* Liraglutide 3 mg once daily administered in a 6 mg/mL, 3 mL pen for subcutaneous injection
  - *Dose escalation/titration scheme:* Initial dosage of 0.6 mg per day, escalated bi-weekly by 0.6 mg to 3 mg per day over a total of 8 weeks. Visits will be conducted at weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52

- *Liraglutide placebo, 3 mg/day*
  - *Arm description:* Subjects will be up-titrated to liraglutide 3 mg placebo once daily and stay on that dose for the remainder of the 52-week drug intervention period.
  - *Drug:* Liraglutide 3 mg placebo once daily administered in a 6 mg/mL drug equivalent volumes, 3 mL pen for subcutaneous injection
  - *Dose escalation scheme:* Initial dosage of a 0.6 mg drug equivalent volume per day, escalated bi-weekly by a 0.6 mg drug equivalent volume per day to a 3 mg drug equivalent volume per day over a total of 8 weeks. Visits will be conducted at weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52

Research nurses with experience in trials involving self-administered injections will instruct participants in the use of pens, and the materials used to support the verbal instructions will be the publicly available materials produced by Novo Nordisk for Liraglutide. Dose escalation will be based on safety as well as tolerability and if dose escalation is not feasible, then delayed increments are allowed. Subjects will be maintained at the highest tolerated dose level and the reduction of the achieved maintenance dose will lead to patient discontinuation.

The trial will end when the last patient has i) completed the last visit as well as the 12-week post-interventional observation period, ii) prematurely discontinued the intervention, or iii) withdrawn from the trial, whichever comes last.

For all potential trial participants, the following will be recorded: number of individuals initially assessed for eligibility, number excluded before enrolment (including reasons for non-eligibility),

number enrolled, number randomised, and number withdrawn/dropped out during the trial (including reasons for withdrawal or exclusion). From allocation and onwards study personnel will assess the use of study medication to evaluate adherence.

Prior to the start of the study, the sponsor-investigator will ensure that the other investigators are familiar with the protocol, eCRFs and other study documents and procedures. The sponsor-investigator will be visited by the monitor prior to trial commencement and thereafter on a regular basis. The monitor will check trial procedures, including safety assessments, drug handling, data recording and complete source data verification (SDV) procedures.

Visits, assessments and procedures will take place as visualized in table 1.

Trial site

The trial will be conducted at the Parker Institute at Copenhagen University Hospital, Bispebjerg and Frederiksberg. The Parker Institute is a well-established research institute and clinical department with secretariat, data managers, and GCP (Good Clinical Practice) educated healthcare professionals such as physicians, trained specialists in rheumatology and radiology, nurses, and laboratory technicians. Moreover, access to other departments and specialities within the hospital is available upon request if deemed necessary.

Trial population

To be enrolled in this trial, the following eligibility criteria, assessed at screening, must be met:

Inclusion criteria

- Informed consent obtained
- Clinical diagnosis of knee OA (American College of Rheumatology (ACR) criteria) with early to moderate radiographic changes (Kellgren-Lawrence (KL) grades 1, 2, or 3)
- Age ≥ 18 years and < 75 years
- Body mass index (BMI) ≥ 27 kg/m^2
- Stable body weight during the previous 3 months (< 5 kg self-reported weight change)
- Motivated for weight loss
- Achieved at least 5% weight loss during the initial 8-week IDI (assessed at allocation visit; T0)

Exclusion criteria

- On-going participation, or participation within the last 3 months, in an organised weight loss programme (or within the last 3 months)

- Current or history of treatment with medications that may cause significant weight gain for at least 3 months before this trial
- Current use or use within 3 months before this trial of GLP-1 receptor agonist, pramlintide, sibutramine, orlistat, zonisamide, topiramate, or phentermine
- Type 1 diabetes
- Type 2 diabetes treated with glucose-lowering drugs other than metformin
- Alloplasty in target knee joint (most symptomatic knee at screening)
- End stage disease in target knee joint (Kellgren-Lawrence grade 4)
- Immuno-inflammatory disease
- Chronic wide-spread pain
- Pregnancy or insufficient anti-conception therapy for female fertile patients
- Breast-feeding
- Estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x above upper normal range (UNR)
- Elective surgery scheduled during the trial duration period, except for minor surgical procedures
- Surgical procedures such as arthroscopy or injections into a knee within 3 months prior to enrolment
- Previous surgical treatment for obesity (excluding liposuction >1 year before trial entry)
- Thyroid stimulating hormone (TSH) outside of the range of 0.4-6.0 mIU/L
- Obesity secondary to endocrinologic or eating disorders, or to treatment with medicinal products that may cause weight gain
- Family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2
- Inflammatory bowel disease
- Congestive heart failure, New York Heart Association (NYHA) class III-IV
- Diabetic gastroparesis
- History of or current diagnosis of pancreatitis (acute and/or chronic) or pancreatic cancer
- History of cancer with the exception of in-situ malignancies of the skin or cervix uteri
- History of major depressive disorder, a PHQ-9 (Patient Health Questionnaire-9) score of more than 15, or a history of other severe psychiatric disorders or diagnosis of an eating disorder
- Subjects with a lifetime history of a suicide attempt or history of any suicidal behaviour within the past month before entry into the trial
- Inability to speak Danish fluently
- A mental state impeding compliance with the programme

- Use of opioids or similar strong analgesics
- Allergic reactions to the active ingredients of Saxenda, such as hypotension, palpitations, dyspnoea and oedema

Data collection

Patients will take part in a series of examinations and tests throughout the study, including:

Knee injury and Osteoarthritis Outcome Score (KOOS)

The KOOS is designed to assess health related quality of life (QoL) in patients with knee injuries and knee OA [12]. The KOOS consists of 42 items covering five domains, namely, Pain, Symptoms, Activities of Daily Living, Sports and Recreation, and knee-related QoL. A normalized score is calculated for each domain with 100 indicating no symptoms and functional impairment and zero indicating extreme symptoms and functional impairment.

Western Ontario and McMaster Universities Arthritis Index (WOMAC)

WOMAC is a disease-specific questionnaire designed to assess pain, stiffness, and physical function in patients with hip and/or knee OA [13]. It consists of 24 items divided into three subscales concerning Pain, Stiffness, and Physical Function. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

Intermittent and Constant Osteoarthritis Pain questionnaire (ICOAP)

The ICOAP is a diagnosis-specific 11-item questionnaire designed to assess the pain experience within the last week among people suffering from knee and hip OA [14]. The questionnaire is divided into two domains, a 5-item scale for constant pain and a 6-item scale for intermittent pain. Normalized scores, for the two subscales and for the total pain score, ranges from zero (no pain) to 100 (extreme pain).

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation. Four constructs are assessed [15]. The first is the *severity of ideation*, rated on a 5-point ordinal scale. The second is the *intensity of ideation* subscale comprising 5 items each rated on a 5-point ordinal scale. The third is *the behaviour subscale*, which is rated on a nominal scale. And the fourth is the *lethality subscale*, which is rated on a 6-point ordinal scale, and if actual lethality is zero, potential lethality of attempts is rated on a 3-point ordinal scale. The Baseline-Screening version will be employed to assess

inclusion/exclusion criteria and to provide a pre-treatment assessment at Baseline. On all subsequent visits, the Since Last Visit version will be used.

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a diagnostic tool for mental health disorders [16]. The PHQ-9 is the depression subscale of the PHQ and contains nine questions related to depression disorder symptoms during the past 14 days. The answer categories are based on a 4-point response scale and the summed PHQ-9 score can range from zero to 27. A score of ≥15 is considered an indication of moderately severe or severe depression.

Binge Eating Scale (BES)

The BES is a self-report instrument that assesses the behavioural and emotional/cognitive symptoms associated with binge eating [17]. The BES is comprised of 16 items assessing key behavioural (e.g., rapid eating, eating large amounts of food), and affective/cognitive symptoms (e.g., guilt, feeling out of control or unable to stop eating) that precede or follow a binge. Each item contains three to four statements that are weighted response options, which reflect a range of severity for each characteristic. Participants are asked to select the statement that best describes their experience. The scale's possible total scores range from zero to 46, with higher scores indicating more severe binge eating symptoms.

Outcome Measures in Rheumatoid Arthritis Clinical Trials/Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria

The OMERACT-OARSI responder criteria include a composite index based on pain, function, and patient global [18]. For the purpose of assessing this, we will employ three questions regarding knee pain, physical function, and the patients' global assessment of disease impact on their daily life. The answers to each of these questions are given on 100 mm visual analogue scales (VAS).

To assess pain the patients are asked to indicate "the degree of knee pain in your daily life" (VAS-pain). The anchors on the 100 mm VAS are 0 = "No pain", and 100 = "Worst imaginable pain". To assess physical function the patients are asked to indicate "the degree of physical impairment of your knee in your daily life" (VAS-function). The anchors on the 100 mm VAS are 0 = "No impairment", and 100 = "Worst imaginable impairment". To assess the patients' global assessment of disease impact on their daily life the patients are asked to indicate "the overall impact of your knee osteoarthritis on your daily life" (VAS-global). The anchors on the 100 mm VAS are 0 = "No impact", and 100 = "Worst imaginable impact".

Categorization as a responder requires an improvement in the above-mentioned pain or function VAS scores of at least 50% and an absolute change of 20 mm. Alternatively, a response can be achieved by meeting at least 2 of the following 3 criteria: (1) an improvement of 20% and an absolute change of 10 mm in VAS-pain, (2) an improvement of 20% and an absolute change of 10 mm in VAS-function, or (3) an improvement of 20% and an absolute change of 10 mm in VAS-global.

Impact of Weight on Quality of Life-Lite (IWQoL-Lite)

The IWQoL-Lite is a 31-item, self-report, obesity-specific measure of health-related quality of life that consists of a total score and scores on each of five scales: physical function, self-esteem, sexual life, public distress, and work [19]. Scores range from zero to 100, where 100 represent the best HRQOL and zero represents the worst.

Treatment Related Impact Measure-Weight (TRIM-Weight)

The TRIM-Weight is an obesity treatment-specific patient reported outcomes measure designed to assess the key impacts of prescription anti-obesity medication and be applicable to the wide range of prescription medications currently available [20]. The TRIM-Weight is based on 22 items within seven thematic domains related to a patients experience with a weight loss medication; i) satisfaction in terms of weight loss, ii) the burden of taking the medication, iii) satisfaction in terms of appetite-control, iv) the impact of weight stabilization, mood swings, or tiredness, v) convenience, vi) discomfort, ad vii) impact on social aspects, productiveness and relationships. All items are scored on anchored rating scales with five levels of response (1–5) in which higher scores indicate better quality of life.

Short form 36 (SF-36)

The SF-36 is a generic, short-form health status questionnaire composed of 36 questions within eight multi-item domains assessing physical function, social function, role-emotional, role-physical, bodily pain, general health, mental health and vitality [21]. These can be combined into two summary scores (physical and mental health summary scores). For each summary score, the ordinal scores are transformed to a linear zero to 100 scale; zero indicating the least favourable health state and 100 indicating the best state of health.

Anthropometrics

Waist circumference will be measured mid-way between the lower rib margin and the iliac crest, while hip circumference will be measured at the point over the buttocks yielding the maximum circumference. Waist and hip circumferences will be measured to the nearest 1 cm. All anthropometric

measurements will be taken in accordance with the WHO report on measuring obesity.
Height without shoes will be measured using a stadiometer and rounded to the nearest 1 cm.
Body weight will be measured to the nearest 0.1 kg with a decimal weighing scale (TANITA BW-800, Tanita Europe BV Hoogoorddreef 56e, 1101BE Amsterdam, The Netherlands) with participants fasting and wearing underwear or light clothing, only.
The BMI (kg/m^2) will be calculated from body weight and height.

Blood samples

Standard biochemistry: C-reactive protein (CRP), alanine transaminase (ALT), calcium, creatinine, potassium, sodium, low-density lipoprotein (LDL), high-density lipoproteins (HDL), triglycerides (TG), and total cholesterol (TC). Haematology: Haemoglobin, leucocytes, differential cell count, and thrombocytes. Glucose metabolism: HbA1c and fasting plasma glucose (FPG).

Radiography

Radiographic examinations include standard clinical semi-flexed weight bearing posterior-anterior radiographs of both knees. During the examination patients will be facing the plate of the radiography equipment with the knees touching the cassette holder or a reclining table top. The radiography plate or cassette holder is placed so that the centre of the film will be at the level of the patient's tibiofemoral joint line. The radiography beam is centred between the knees with a 10 degrees cranio-caudal angle and the body weight will be distributed equally between the two legs. The radiographs will be assessed by use of the Kellgren & Lawrence (KL) grading system; a categorical grading scale of knee OA going from 0 to 4 by means of an evaluation of osteophytes, joint space narrowing, sclerosis, and altered bone shapes.

Vitals signs

Blood pressure (BP), systolic and diastolic, will be measured with the patient in sitting position with the legs uncrossed and the back and arm supported. Patients resting pulse will be measured following a resting-period of five minutes in a sitting position with the legs uncrossed and the back and arms supported. Patients will be instructed to avoid caffeine, smoking and physical activity within 30 minutes prior to both of these measurements.

Visit schedule

Table 1 Visit schedule

	Information	Screening	Enrolment	Pre-allocation	-	-	-	-	-	-	-	Allocation	Post-allocation	-	-	-	-	-	-	-	-	-	-	-	-	-	End of trial	-	Off-treatment follow-up
VISIT NAME	-Ty	-Tz	-Tx	-T8	-T7	-T6	-T5	-T4	-T3	-T2	-T1	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	Tx	Tz
WEEK NO.	x	x	x	-8	-7	-6	-5	-4	-3	-2	-1	0	2	4	6	8	12	16	20	24	28	32	36	40	44	48	52	x	64
INFORMATION & SCREENING																													
Motivation appraisal	X																												
Exchange of information	X																												
Eligibility screening & consent		X																											
X-ray & physical examination		X																											
Blood testing & urine stix		X																											
Medical & medication history		X																											
KOOS pain, WOMAC pain, C-SSRS & PHQ-9		X																											
Vital signs, height, body weight & ECG		X																											
INTERVENTION																													
IDI				X	X	X	X	X	X	X	X																		
TDI												X	X	X	X	X													
Lira 3 mg OR Lira 3 mg pbo												X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ASSESSMENTS																													
Physical examination			X									X															X	X	
Dietician (group session)				X	X	X	X	X	X	X	X	X	X	X	X	X													
Titration visit (MD)												X	X	X	X	X	(X)	(X)											
Medical history			X																										
Update of medical history												X															X	X	
Medication history			X									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
KOOS, WOMAC, SF-36, IWQoL-lite & O-O resp. crit.			X									X															X	X	
ICOAP			X									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
KOOS pain & WOMAC pain													X	X	X	X	X	X	X	X	X	X	X	X	X	X			
C-SSRS			X									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHQ-9 & BES			X									X															X	X	X
TRIM-weight													X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events report form				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs & waist and hip circumferences			X									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body weight			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood testing, height & DXA			X									X															X	X	
X-ray			X																								X	X	
ECG												X					X										X	X	X
Medicine hand-out												X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adherence assessment													X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

**Lira: Liraglutide; pbo: placebo, O-O resp.crit: OMERACT-OARSI responder criteria*

Outcomes

Patient characteristics

Height, age, gender, and KL grading will be collected and reported as patient characteristics.

Co-primary outcomes

The co-primary outcomes are changes in body weight and the KOOS pain subscale from baseline (week 0) to the last visit in the main trial period (week 52).

Confirmatory secondary outcomes

The confirmatory secondary outcomes are changes in the KOOS symptom, ADL, sport and recreation, and health related QoL subscales, the WOMAC pain, stiffness, and function subscales, the total score and subscales in the ICOAP questionnaire, BMI, waist circumference, or the waist/hip ratio from baseline (week 0) to the last visit in the main trial period (week 52). Moreover, the proportion of patients with ≥5 or ≥10 % weight loss at the last visit in the main trial period (week 52) also constitutes confirmatory secondary outcomes.

Supportive secondary outcomes

The supportive secondary outcomes are changes in biomarkers (*CRP, HbA1c, FPG, ALT, LDL, HDL, TG and TC*), BP, resting heart rate, the impact of weight on quality of life (*IWQoL-Lite*), treatment related impact on quality of life (*TRIM-weight*), and the general health status (*SF-36*) from baseline (week 0) to the last visit in the main trial period (week 52). Changes in proportion of patients meeting the criteria for metabolic syndrome or pre-diabetes from week 0 to 52 as well as the proportion of patients classified as responders (*the O-O responder criteria*) at the last *visit in the main trial period (week 52) also constitutes confirmatory secondary outcomes.*

Safety outcomes

The safety outcomes include the incidence of adverse events (AEs), suicidal behaviour and/or ideation (C-SSRS), depression (PHQ-9), binge eating (BES), and measures outside reference limits for haemoglobin, thrombocytes, leucocytes, differential cell count, creatinine, and electrolytes (+/- 2 SD), and for ALT and CRP (+ 150 %).

Data management

The collection, preservation and dissemination of the clinical data is specified in this clinical trial protocol and abide to the standard requirements for GCP-compliant data management in clinical trials.

The source data and documents, eCRF, protocol and amendments, drug accountability forms, correspondence, patient identification list, informed consent forms, and other essential GCP documents will be retained for at least 10 years after the study is completed at the study site. Data entries are quality ensured by double data entry, classification of data type (i.e. text and numbers) and/or range checks for data values.

All data collected during this project will be managed and quality certified by the Parker Institutes data management team, composed by the primary investigator, a data manager and a chief administrator. This team is responsible for ensuring data completeness and accuracy as well as source data verification. The latter will be performed by the monitor and the relevant investigators. The team is also responsible for ensuring operations of a secure database established for the collection of clinical data collected via the electronic case report form (eCRF) platform through a secure connection. All data obtained during the study will be documented in the individual eCRFs. reasons for any missing data will be noted in the database, and logging and tracking of data changes will be documented.

Randomisation

Participants will be randomised to treatment daily with liraglutide 3 mg/day or liraglutide placebo 3 mg at week 0, i.e. after the initial 8-week IDI period. Patients will be randomised in a 1:1 manner to receive either 3 mg/day liraglutide or identically appearing placebo; stratified randomisation will be based on gender (male vs. female), age (<60 years vs. ≥60 years), and obesity class (BMI; < 40 vs. ≥ 40 [kg/m^2]) status at trial enrolment (week -8). A computer-generated randomisation sequence will be produced using SAS PROC PLAN to generate the eight randomisation schedules before any participant is enrolled, allocating participants in permuted blocks of 2 to 6 to the daily liraglutide 3 mg/day or placebo group (1:1). The randomisation sequence is entered into the eCRF by a data manager.

Allocation concealment and blinding

The trial utilizes a computer-generated allocation process in which the patient identifier is coupled to one of the experimental arms when the physician clicks on the 'randomisation button', appearing at visit T0 in the eCRF system. Upon allocation to one of the two experimental arms the patient identifier is automatically coupled to specific pens, each of them labelled by a single and unique Dispensing Unit Number (DUN). The entire process is blinded for all investigators, clinical, academic, and administrative trial personnel.

Unblinding will only take place in exceptional circumstances when knowledge of the actual treatment is essential for further management of the patient. If unblinding is deemed necessary, the investigator will activate a data solution, within the eCRF, build for this specific purpose and controlled by an independent data manager and the chief administrator. The actual allocation will not be disclosed to

the patient and/or other study personnel including other site personnel, monitors, corporate sponsors or project office staff.

Sample size and power considerations

The co-primary outcomes are changes in body weight and KOOS-Pain from randomisation to the end of the trial, 52 weeks after randomisation. The sample size of 150 is designed to provide a reasonable power (>80%) to detect a 5-kg difference in body weight change between the groups, AND an 8-units difference in the KOOS-Pain. All power and sample size analyses were conducted using 'SAS Power and Sample Size', version 3.1 (SAS Institute Inc., Cary, North Carolina):

- Body weight: For a two-sample pooled t-test of a normal mean difference with a two-sided significance level of 0.05 (P<0.05), assuming a common standard deviation of 10 kg (conservatively estimated based on our previous weight loss trial in this patient population [22]), a sample size of 75 per group, has a power of 92% to detect a mean difference of 5.5 kg in the group mean change in body weight.
- KOOS-Pain: For a two-sample pooled t test of a normal mean difference with a two-sided significance level of 0.05 (P<0.05), assuming a common standard deviation of 15 KOOS-points, a sample size of 75 patients per group has a power of 90% to detect a mean difference in the group mean changes of 8 KOOS-Points (corresponding to a moderate Cohen's effect size of 0.5).

The combined power for the two endpoints is 83%.

Statistical methods

The prespecified efficacy analyses will be based on the data from the full-analysis set; i.e. the intention-to-treat (ITT) population - including all participants who are randomised and assessed at baseline. In case of missing data at week 52, the observation from enrolment will be carried forward in case of missing data in the ITT population. The safety analysis set includes all patients who are randomly assigned to a trial group and have had exposure to a trial drug (i.e., liraglutide 3 mg/day or placebo). This trial does not plan for any interim analyses.

The primary analysis will be the comparison between liraglutide and placebo using an Analysis of Covariance (ANCOVA) model with treatment, gender, age-, and obesity-stratification as fixed effects and with adjustment for the level at baseline as a covariate. From this model, the observed differences in weight change and KOOS pain change between liraglutide treatment and placebo will be estimated together with the associated 95% confidence interval and the *p*-value corresponding to the test of the hypothesis of no difference between treatments (i.e., the null hypothesis).

To establish the efficacy of liraglutide 3 mg/day compared to placebo in patients with overweight or obesity and knee OA, inducing and maintaining weight loss and pain relief over 52 weeks, endpoints are tested in a hierarchical manner in the order in which the endpoints are presented. Liraglutide 3 mg/day will be considered statistically significantly better than liraglutide placebo 3 mg/day placebo with respect to change in body weight if the null hypothesis is rejected (p<0.05). But, overall, liraglutide 3 mg/day will only be *confirmed* as statistically significantly better than placebo with respect to change in KOOS pain subscale, if it is ALSO statistically significantly better with respect to change in body weight.

Categorical changes for dichotomous end-points will be analysed with the use of logistic regression with the same fixed effects and covariates as the respective ANCOVA. Sensitivity analyses will be performed to assess the robustness of the primary analyses, including 'per protocol' scenarios, repeated-measures linear mixed models, and multiple-imputation techniques.

Management

The project management team consists of the Primary Investigator, Dr. Henrik Rindel Gudbergsen who is responsible for the execution of the project, the Sponsor-Investigator Professor Henning Bliddal who is responsible for the overall scientific planning of the project, and Chief Administrator Claus Bomhoff who is responsible for administrative and financial tasks. The steering committee (SC), led by the Primary Investigator, is the principal management body with respect to the operational and scientific facets of this trial. Members of the SC are the investigators involved in the development of this protocol and include HRG (chairman), HB (sponsor), MH, EW, HB, RC, MK, FK, AA, MUR, and LEK. The SC will ensure trial resources, schedule all trial related activities, and ensure execution of the trial.

The independent ethics committee (ICE) monitors any safety and/or ethical concerns arising during the project and to advise the SC. The members of the ICE are Lennart Jacobsson, Professor in Rheumatology, Department of Rheumatology, Sahlgrenska University Hospital, Gothenburg, Sweden and Karl Agner Kristensen MD, PhD, Specialist in Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, Lund University Hospital, Lund, Sweden.

Patient and Public Involvement

Via a formal review process, the authors retrieved input from an appointed knee OA patient advisor in a discussion focusing on the development of hypotheses, interventions and outcomes related to this study. The design of the study was not discussed with patients, whereas the burden of the study was assessed by all patients via an initial appraisal of their motivation to participate in the study and via a thorough description of the study in relation to the signing of the informed consent.

The institute's patient board and the appointed knee OA advisor were also involved in proposing potential routes for communication regarding recruitment of patients, including websites and patient associations. Patients will be informed, via dialogue and a briefing document, that they may access results on an individual basis throughout the trial and that the study personnel will engage in presenting the overall results for each individual patient once the trial is complete. Upon trial completion, patients will also be invited to a meeting where the project results are presented in a manner that is understandable by laymen.

ETHICS AND DISSEMINATION

The investigator will monitor each participant for clinical and laboratory evidence of adverse events (AEs) on a routine basis throughout the trial. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the participant, will be recorded. The investigator will assess and record any AE in detail, including the date of onset, description, severity, duration and outcome, relationship of the AE to trial drug, and any action(s) taken.

The treatment and investigations in this trial are associated with minimal discomfort for the participants. The injection is practically pain-free but may leave a small haemorrhage, resolving spontaneously within a few days in the vast majority of patients. Less commonly, the patients may experience abdominal pain, insomnia, reflux, gastritis, and dizziness. Uncommon AEs comprise dehydration, tachycardia, pancreatitis, cholecystitis, urticarial, and malaise.

When collecting blood samples some participants may experience minor discomfort when the needle penetrates the skin, and rarely a small bleeding occurs. The planned radiographs will be identical and obtained at the same frequency as recommended in the current care model at the involved outpatient clinics.

The participants included in the planned clinical trial will not receive any financial compensation. Neither the sponsor-investigator nor any of the other members of the project group has financial interest in neither the conduct nor the results of the trial.

All participants will be covered by a patient-insurance, according to national requirements and common conduct, during the conduction of the clinical trials.

The trial is approved by the regional ethics committee in the Capital Region of Denmark; approval ID H-16019969.

The successful planning and conduction of the LOSEIT trial may provide the basis for a significant improvement in the disease management of the many overweight citizens impacted by knee OA.

The number and timing of visits has been outlined to ensure observation of any safety issues as well as thorough management of medication hand-out and usage throughout the study.

Based on involvement of patients as well as the existing experience within the field of weight loss and knee OA management the study design is considered to be acceptable for patients as well as feasible to implement. Nevertheless, this study will deliver comprehensive insights into the practicality and acceptability of the interventions studied in this specific context, and provide valuable information regarding the generalizability of the interventions in question.

At the end of the trial, one or more manuscripts will be prepared for publication in peer-reviewed journals. The manuscripts will be written in accordance with the CONSORT Statement. The manuscripts will include positive, negative, as well as inconclusive results. In addition, the results from the trial will be presented as posters or oral presentations at national and/or international conferences.

Novo Nordisk A/S and The Cambridge Weight Plan had no influence on the study design, nor will they have any influence on the analyses and interpretation of data or the writing of manuscripts/abstracts based on trial data. Novo Nordisk A/S and The Cambridge Weight Plan will be given 4 weeks to review any manuscript/abstract or other means intended for publication or presentation of the data. All authors will qualify for authorship according to International Committee of Medical Journal Editors, 1997, and must have participated sufficiently in the work to take public responsibility for the content.

COMPETING INTERESTS STATEMENT

HG; has received speaker fees from Pfizer and MSD

MH, EEW, AO, HB, RC, MUR, CB, CD, EMB, BH and KE; none to declare

MB; has received speaker fees from Esaote, Abbvie, and UCB

FKK; has received lecture fees from, participated in advisory boards of and/or consulted for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD/Merck, Novo Nordisk, Sanofi and Zealand Pharma

AA; reports grants and personal fees from Global Dairy Platform, USA; McCain Foods, USA; McDonald's, USA; Arena Pharmaceuticals Inc, USA; Basic Research, USA; Dutch Beer Knowledge Institute, NL; Gelesis, USA; Novo Nordisk, DK; Orexigen Therapeutics Inc., USA; S-Biotek, DK, Twinlab, USA; Vivus Inc., USA; and grants from Arla Foods, DK; Danish Dairy Research Council, Nordea Foundation, DK outside the submitted work; and Royalties received for the book first published in Danish as "Verdens Bedste Kur" (Politiken, Copenhagen), and subsequently published in Dutch as "Het beste dieet ter wereld" (Kosmos Uitgevers, Utrecht/ Antwerpen), in Spanish as "Plan DIOGenes para el control del peso. La dieta personalizada inteligente" (Editorial Evergráficas, Léon), and in English as "World's Best Diet" (Penguin, Australia).

LEK; has received fees for speaking and consultancy from Pfizer, AbbVie, Amgen, Sanofi, UCB, Celgene, BMS, Biogen, Novo Nordisk, MSD, Novartis, Eli Lilly, and Janssen pharmaceuticals

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DATA SHARING STATEMENT

Once the trial has been completed data and information about the study may be accessed by contacting the corresponding author after obtaining and documenting legitimate approval from the Danish data authorities and to the extent possible according to Danish national law.

CONTRIBUTORSHIP STATEMENT

HG, EEW, MH, HB, RC, MB, FKK, MH, AA, EMB, and LEK have contributed by conceptualising, designing, writing, reviewing, and approving the protocol for this trial.

AO, MUR, CB, CD, BLH, and KE have contributed by writing, reviewing, and approving the protocol, and are all part of the acquisition of data from the trial.

Moreover, all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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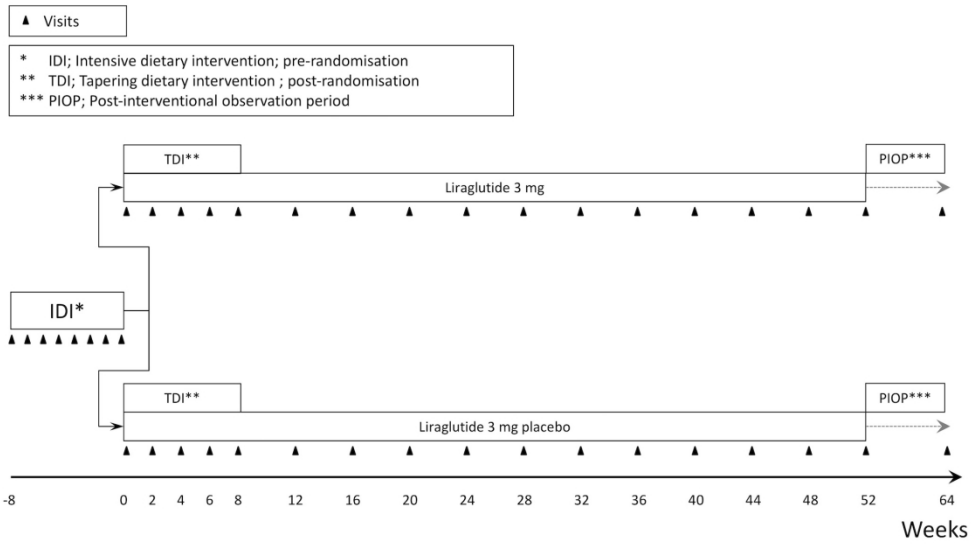

Figure 1

180x99mm (300 x 300 DPI)

BMJ Open

Effect of liraglutide on body weight and pain in patients with overweight and knee osteoarthritis: Protocol for a randomised, double blind, placebo-controlled, parallel group, single-centre trial

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Complete List of Authors:	Gudbergsen, Henrik; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Henriksen, Marius; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute; Copenhagen University Hospital Bispebjerg-Frederiksberg, Department of Physio- and Occupational Therapy Wæhrens, Eva ; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Overgaard, Anders; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Bliddal, Henning; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Christensen, Robin; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute; Odense Universitetshospital, Department of Rheumatology Boesen, Mikael; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute; Copenhagen University Hospital Bispebjerg-Frederiksberg, Department of Radiology Knop, Filip K; Steno Diabetes Center Copenhagen, Gentofte Hospital, Clinical Metabolic Physiology; University of Copenhagen, Faculty of Health and Medical Sciences, Department of Clinical Medicine Astrup, Arne; Univesity of Copenhagen, Department of Nutrition, Exercise and Sports, Rasmussen, Marianne; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Bartholdy, Cecilie; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Daugaard, Cecilie; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Bartels, Else; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Ellegaard, Karen; Copenhagen University Hospital Bispebjerg-Frederiksberg, The Parker Institute Heitmann, Berit; Copenhagen University Hospital Bispebjerg-Frederiksberg, Research Unit for Dietary Studies at The Parker Institute; Kobenhavns Universitet Det Samfundsvidenskabelige Fakultet, Department of Public Health, Section for General Medicine Kristensen, Lars Erik; Copenhagen University Hospital Bispebjerg-

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Primary Subject Heading:	Rheumatology
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Keywords:	overweight, osteoarthritis, Knee < ORTHOPAEDIC & TRAUMA SURGERY, weight loss, liraglutide, dietary intervention

TITLE

Effect of liraglutide on body weight and pain in patients with overweight and knee osteoarthritis: Protocol for a randomised, double blind, placebo-controlled, parallel group, single-centre trial

SHORT TITLE

Liraglutide 3 mg/day for knee osteoarthritis

ACRONYM

LOSEIT

BASED ON PROTOCOL VERSION

Version 6; the 30th of January 2017, 15:30

KEYWORDS

Obesity, overweight, osteoarthritis, knee, weight loss, liraglutide, diet, dietary intervention.

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AUTHORS

Henrik Gudbergsen, MD, PhD, [1 **],
Marius Henriksen, PT, MSc, PhD [1, 2],
Eva Ejlersen Wæhrens, OT, MSc, PhD [1],
Anders Overgaard, MD [1],
Henning Bliddal, MD, DMSc [1 **],
Robin Christensen, BSc, MSc, PhD [1, 3],
Mikael Boesen, MD, PhD [1, 4],
Filip K. Knop, MD, PhD [5, 6],
Arne Astrup, MD, DMSc [7],
Marianne Uggen Rasmussen, MPH, PhD [1],
Cecilie Bartholdy, PT, MSc, [1, 2],
Cecilie Daugaard, MD, [1, 3],
Else Marie Bartels, PhD, DSc, [1],
Karen Ellegaard, PT, MSc, PhD [1],
Berit Lilienthal Heitmann, DMD, PhD [8, 9], and
Lars Erik Kristensen, MD, PhD, DMSc [1]

[1] The Parker Institute, Copenhagen University Hospital Bispebjerg-Frederiksberg, Denmark
[2] Department of Physio- and Occupational Therapy, Copenhagen University Hospital Bispebjerg-Frederiksberg, Denmark
[3] Department of Rheumatology, Odense University Hospital, Denmark
[4] Department of Radiology, Copenhagen University Hospital Bispebjerg-Frederiksberg, Denmark
[5] Steno Diabetes Center Copenhagen, Clinical Metabolic Physiology, Copenhagen University Hospital Gentofte, Denmark
[6] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
[7] Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Copenhagen, Denmark
[8] Research Unit for Dietary Studies at The Parker Institute, Copenhagen University Hospital Bispebjerg-Frederiksberg, Denmark
[9] Department of Public Health, Section for General Medicine, University of Copenhagen, Copenhagen, Denmark

* Corresponding author, telephone +45 29 84 28 88, mail: rindelgudbergsen@gmail.com
** Sponsor-investigator, telephone +45 38 16 41 51, mail: henning.bliddal@regionh.dk

ABSTRACT

Introduction: With an increasing prevalence of citizens of older age and with overweight, the health issues related to knee osteoarthritis (OA) will intensify. Weight loss is considered a primary management strategy in patients with concomitant overweight and knee OA. However, there are no widely available and feasible methods to sustain weight loss in patients with overweight and knee OA. The present protocol describes a randomised controlled trial evaluating the efficacy and safety of the glucagon-like peptide-1 receptor agonist liraglutide in a 3 mg/day dosing in patients with overweight and knee OA.

Methods and analysis: 150 volunteer adult patients with overweight or obesity and knee OA will participate in a randomised, double blind, placebo-controlled, parallel group, and single-centre trial. The participants will partake in a run-in diet intervention phase (week -8 to 0) including a low-calorie diet and dietetic counselling. At week 0 patients will be randomised to either liraglutide 3 mg/day or liraglutide placebo 3 mg/day for 52 weeks as an add-on to dietetic guidance on re-introducing regular foods and a focus on continued motivation to engage in a healthy lifestyle. The co-primary outcomes are changes in body weight and the KOOS pain subscale from week 0 to week 52.

Ethics and dissemination: The trial has been approved by the regional ethics committee in the Capital Region of Denmark, the Danish Medicines Agency, and the Danish Data Protection Agency. An external monitoring committee (The Good Clinical Practice Unit at Copenhagen University Hospitals) will oversee the trial. The results will be presented at international scientific meetings and through publications in peer-reviewed journals.

Trial registrations: EudraCT: 2015-005163-16, ClinicalTrials.gov Identifier: NCT02905864, UTN: U1111-1171-4970

ARTICLE SUMMARY

Strengths and limitations of this study

- This will be the first randomised controlled trial examining the efficacy and safety of daily liraglutide 3 mg/day in patients with overweight and knee OA
- Participants will be randomised to receive either liraglutide 3 mg/day or liraglutide placebo 3 mg/day for 52 weeks as an add-on to dietetic guidance
- The selected primary and secondary outcomes are aligned with Outcome Measures in Rheumatology recommendations
- This trial has a strict focus on an adult population with clinical knee OA who can successfully go through an intensive dietary programme (the target being to lose at least 5% of their initial body weight)
- The trial has implication for the large number of patients impacted by overweight and knee OA

INTRODUCTION

Obesity is a serious medical condition with increasing incidence and prevalence worldwide. The achievement and maintenance of a healthy body weight is the main strategy for prevention and management of obesity-related diseases [1 2]. The majority of subjects with a successful weight loss regain weight over the subsequent years and the maintenance of a clinically significant weight loss over time remains a challenge for healthcare professionals, patients, and societies [1].

Osteoarthritis (OA) is the most common type of arthritis, characterised by pain and physical disability [3]. In addition, more than 10% of those aged more than 55 years have symptomatic OA, primarily involving the knees [4]. Due to the pivotal role of the knee in basic mobility and locomotion, knee OA is associated with significant impairments and limitations to basic activities of daily living, such as walking and moving around, self-care, and housekeeping activities, as well as participation in community life and recreational activities – all contributing to reduced quality of life and needs for assistance. Epidemiological data link obesity to the development of knee OA [5], obesity and knee OA share pathogenic phenotypes, and the development of one disease increases the risk of the other, potentially triggering the onset of a vicious cycle [6].

Glucagon-like peptide 1 (GLP-1) is an incretin hormone that stimulates endogenous insulin secretion in a glucose-dependent manner. GLP-1 also lowers blood glucagon levels, reduces gastric emptying by decreasing gastric motility, and increases satiety. These mechanisms have been exploited therapeutically in the treatment of type 2 diabetes for more than a decade, and recently the satiety promoting and body-weight lowering effects of the GLP-1 analogue liraglutide prompted the U.S. Food and Drug Administration and the European Medicines Agency to approve liraglutide in a once daily dose of 3 mg for the treatment of patients with overweight or obesity. Published data, investigating the use of liraglutide 3 mg/day in a population of patients with obesity as well as dyslipidaemia and/or hypertension, revealed a long-term positive impact on both body weight and related health benefits [7].

Scientific gap

The present trial has been designed to further investigate the potential of liraglutide 3 mg/day to safely induce and maintain long-term weight loss in patients with overweight or obesity and knee OA. Weight loss is strongly recommended as a management strategy of patients with concomitant overweight or obesity and knee OA, and improves both pain and function [8-11]. However, no widely available and feasible means to sustain weight loss in patients with overweight or obesity and knee OA has been presented.

Hypotheses

A diet intervention combined with liraglutide 3 mg/day, for 52 weeks, is sufficient to induce and maintain weight loss and to improve knee OA related pain symptoms. As such, the primary hypotheses to be tested are:

- In patients with overweight or obesity and knee OA a diet intervention combined with liraglutide 3 mg/day will induce and maintain a significantly greater weight loss compared to a diet intervention combined with an identically appearing liraglutide placebo treatment

- In patients with overweight or obesity and knee OA a diet intervention combined with liraglutide 3 mg/day will induce and maintain a significantly greater reduction in knee OA pain compared to a diet intervention combined with an identically appearing liraglutide placebo treatment

Objectives

The primary objectives are to establish the efficacy and safety of a diet intervention combined with liraglutide 3 mg/day, or placebo, in inducing and maintaining weight loss over 52 weeks and in improving symptomatic knee pain.

METHODS AND ANALYSIS

Trial design

The trial is designed as a single-centre, randomised, placebo-controlled, participant, investigator, and outcome assessor blinded, parallel-group trial. It contains three periods. Participants will initially be enrolled in an 8-week intensive dietary intervention (IDI) period. If successfully achieving a weight loss of minimum 5 % during this period participants will continue with a tapering dietary intervention (TDI) for 8 weeks (week 0 to 8) and be randomised to receive either liraglutide 3 mg/day or identically appearing placebo throughout the 52-week main trial period (week 0 to 52). The trial will be completed by a 12-week post-interventional observation period (PIOP) (figure 1).

Figure 1 Trial design

Trial conduct

Participants will be recruited within 12 months from the osteoarthritis outpatients' clinic at the Parker Institute at Copenhagen University Hospital, Bispebjerg and Frederiksberg. General practitioners and collaborating clinical hospital departments in the Capital Region will be informed about the possibility to refer patients to the project. In addition, the trial will be advertised in newspapers and on the Parker Institutes website (*www.parkerinst.dk*).

Potential study participants will initially partake in a motivational assessment including an interview in which the nature of the initial IDI is explained together with a description of the overall study, a thorough outline of the interventions and visits, and a session in which the investigator addresses any questions the potential participant may have. The study will not use any standardised scoring system to assess motivation, but during the interview the investigator will assess the individual's motivation for weight loss through both the IDI period and the subsequent participation in the randomised part of the study.

Before enrolment takes place, potential participants will be provided with written and verbal information about the trial and the procedures involved, in accordance with local requirements. Potential participants will have the opportunity to ask questions and have ample time to consider their participation. Following the signature of the informed consent form participants will be enrolled in the 8-week IDI period.

The IDI period is comprised of a supervised dietary weight loss programme in which participants receive a hypo-caloric formula diet containing 800 to 1.000 kcal/day. The formula diet consists of ready-to-use meal bars and powders to mix with water to make shakes, soups, or porridge. The weight loss programme consists of an 8-week period with full meal replacement according to a standard liquid energy intake protocol. To facilitate adherence to the programme, patients will be scheduled for weekly facility-based group sessions with 6-8 patients led by a dietician. The recommendations for daily nutrient intake will be met during this period.

Participants achieving a weight loss ≥5% during the IDI will be randomised to daily receive either liraglutide 3 mg/day or an identical placebo throughout the subsequent 52-week main trial period.
The initial 8 weeks of the main trial period consist of an 8-week TDI period (week 0 to 8) focusing on a partial re-introduction of regular meals in combination with formula diet products. In this period, all participants (irrespective of randomisation) will be scheduled to meet for group sessions led by a dietician every 2 weeks. No dietary consultancies will be offered from the trial after week 8, but to prevent attrition patients will be offered one to two daily meal replacements with a formula diet from week 8 to 52 to be administered by themselves. Participants will be instructed to aim for an intake of 1.200 kcal/day from week 0 to 8 and for an intake of 1.500 kcal/day from week 8 and onwards.

For the main trial period (drug intervention period running from week 0 to 52), participants will be randomised at week 0 to one of the two experimental arms described below:

- Liraglutide, 3 mg/day
    - *Arm description:* Subjects will be up titrated to liraglutide 3 mg once daily and stay on that dose for the remainder of the 52-week drug intervention period
    - *Drug:* Liraglutide 3 mg once daily administered in a 6 mg/mL, 3 mL pen for subcutaneous injection
    - *Dose escalation/titration scheme:* Initial dosage of 0.6 mg per day, escalated bi-weekly by 0.6 mg to 3 mg per day over a total of 8 weeks. Visits will be conducted at weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52

- *Liraglutide placebo, 3 mg/day*
    - *Arm description:* Subjects will be up-titrated to liraglutide 3 mg placebo once daily and stay on that dose for the remainder of the 52-week drug intervention period.
    - *Drug:* Liraglutide 3 mg placebo once daily administered in a 6 mg/mL drug equivalent volumes, 3 mL pen for subcutaneous injection
    - *Dose escalation scheme:* Initial dosage of a 0.6 mg drug equivalent volume per day, escalated bi-weekly by a 0.6 mg drug equivalent volume per day to a 3 mg drug equivalent volume per day over a total of 8 weeks. Visits will be conducted at weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52

Research nurses with experience in trials involving self-administered injections will instruct participants in the use of pens, and the materials used to support the verbal instructions will be the publicly available materials produced by Novo Nordisk for Liraglutide. Dose escalation will be based on safety as well as tolerability and if dose escalation is not feasible, then delayed increments are allowed. Subjects will be maintained at the highest tolerated dose level and the reduction of the achieved maintenance dose will lead to patient discontinuation.

The trial will end when the last patient has i) completed the last visit as well as the 12-week post-interventional observation period, ii) prematurely discontinued the intervention, or iii) withdrawn from the trial, whichever comes last.

For all potential trial participants, the following will be recorded: number of individuals initially assessed for eligibility, number excluded before enrolment (including reasons for non-eligibility), number enrolled, number randomised, and number withdrawn/dropped out during the trial (including

reasons for withdrawal or exclusion). From allocation and onwards study personnel will assess the use of study medication to evaluate adherence.

Prior to the start of the study, the sponsor-investigator will ensure that the other investigators are familiar with the protocol, eCRFs and other study documents and procedures. The sponsor-investigator will be visited by the monitor prior to trial commencement and thereafter on a regular basis. The monitor will check trial procedures, including safety assessments, drug handling, data recording and complete source data verification (SDV) procedures.

Visits, assessments and procedures will take place as visualized in table 1.

Trial site

The trial will be conducted at the Parker Institute at Copenhagen University Hospital, Bispebjerg and Frederiksberg. The Parker Institute is a well-established research institute and clinical department with secretariat, data managers, and GCP (Good Clinical Practice) educated healthcare professionals such as physicians, trained specialists in rheumatology and radiology, nurses, and laboratory technicians. Moreover, access to other departments and specialities within the hospital is available upon request if deemed necessary.

Trial population

To be enrolled in this trial, the following eligibility criteria, assessed at screening, must be met:

Inclusion criteria

- Informed consent obtained
- Clinical diagnosis of knee OA (American College of Rheumatology (ACR) criteria) with early to moderate radiographic changes (Kellgren-Lawrence (KL) grades 1, 2, or 3)
- Age ≥ 18 years and < 75 years
- Body mass index (BMI) ≥ 27 kg/m^2
- Stable body weight during the previous 3 months (< 5 kg self-reported weight change)
- Motivated for weight loss
- Achieved at least 5% weight loss during the initial 8-week IDI (assessed at allocation visit; T0)

Exclusion criteria

- On-going participation, or participation within the last 3 months, in an organised weight loss programme (or within the last 3 months)

- Current or history of treatment with medications that may cause significant weight gain for at least 3 months before this trial
- Current use or use within 3 months before this trial of GLP-1 receptor agonist, pramlintide, sibutramine, orlistat, zonisamide, topiramate, or phentermine
- Type 1 diabetes
- Type 2 diabetes treated with glucose-lowering drugs other than metformin
- Alloplasty in target knee joint (most symptomatic knee at screening)
- End stage disease in target knee joint (Kellgren-Lawrence grade 4)
- Immuno-inflammatory disease
- Chronic wide-spread pain
- Pregnancy or insufficient anti-conception therapy for female fertile patients
- Breast-feeding
- Estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x above upper normal range (UNR)
- Elective surgery scheduled during the trial duration period, except for minor surgical procedures
- Surgical procedures such as arthroscopy or injections into a knee within 3 months prior to enrolment
- Previous surgical treatment for obesity (excluding liposuction >1 year before trial entry)
- Thyroid stimulating hormone (TSH) outside of the range of 0.4-6.0 mIU/L
- Obesity secondary to endocrinologic or eating disorders, or to treatment with medicinal products that may cause weight gain
- Family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2
- Inflammatory bowel disease
- Congestive heart failure, New York Heart Association (NYHA) class III-IV
- Diabetic gastroparesis
- History of or current diagnosis of pancreatitis (acute and/or chronic) or pancreatic cancer
- History of cancer with the exception of in-situ malignancies of the skin or cervix uteri
- History of major depressive disorder, a PHQ-9 (Patient Health Questionnaire-9) score of more than 15, or a history of other severe psychiatric disorders or diagnosis of an eating disorder
- Subjects with a lifetime history of a suicide attempt or history of any suicidal behaviour within the past month before entry into the trial
- Inability to speak Danish fluently
- A mental state impeding compliance with the programme

- Use of opioids or similar strong analgesics
- Allergic reactions to the active ingredients of Saxenda, such as hypotension, palpitations, dyspnoea and oedema

Data collection

Patients will take part in a series of examinations and tests throughout the study, including:

Knee injury and Osteoarthritis Outcome Score (KOOS)

The KOOS is designed to assess health related quality of life (QoL) in patients with knee injuries and knee OA [12]. The KOOS consists of 42 items covering five domains, namely, Pain, Symptoms, Activities of Daily Living, Sports and Recreation, and knee-related QoL. A normalized score is calculated for each domain with 100 indicating no symptoms and functional impairment and zero indicating extreme symptoms and functional impairment.

Western Ontario and McMaster Universities Arthritis Index (WOMAC)

WOMAC is a disease-specific questionnaire designed to assess pain, stiffness, and physical function in patients with hip and/or knee OA [13]. It consists of 24 items divided into three subscales concerning Pain, Stiffness, and Physical Function. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

Intermittent and Constant Osteoarthritis Pain questionnaire (ICOAP)

The ICOAP is a diagnosis-specific 11-item questionnaire designed to assess the pain experience within the last week among people suffering from knee and hip OA [14]. The questionnaire is divided into two domains, a 5-item scale for constant pain and a 6-item scale for intermittent pain. Normalized scores, for the two subscales and for the total pain score, ranges from zero (no pain) to 100 (extreme pain).

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation. Four constructs are assessed [15]. The first is the *severity of ideation*, rated on a 5-point ordinal scale. The second is the *intensity of ideation* subscale comprising 5 items each rated on a 5-point ordinal scale. The third is *the behaviour subscale*, which is rated on a nominal scale. And the fourth is the *lethality subscale*, which is rated on a 6-point ordinal scale, and if actual lethality is zero, potential lethality of attempts is rated on a 3-point ordinal scale. The Baseline-Screening version will be employed to assess

inclusion/exclusion criteria and to provide a pre-treatment assessment at Baseline. On all subsequent visits, the Since Last Visit version will be used.

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a diagnostic tool for mental health disorders [16]. The PHQ-9 is the depression subscale of the PHQ and contains nine questions related to depression disorder symptoms during the past 14 days. The answer categories are based on a 4-point response scale and the summed PHQ-9 score can range from zero to 27. A score of ≥15 is considered an indication of moderately severe or severe depression.

Binge Eating Scale (BES)

The BES is a self-report instrument that assesses the behavioural and emotional/cognitive symptoms associated with binge eating [17]. The BES is comprised of 16 items assessing key behavioural (e.g., rapid eating, eating large amounts of food), and affective/cognitive symptoms (e.g., guilt, feeling out of control or unable to stop eating) that precede or follow a binge. Each item contains three to four statements that are weighted response options, which reflect a range of severity for each characteristic. Participants are asked to select the statement that best describes their experience. The scale's possible total scores range from zero to 46, with higher scores indicating more severe binge eating symptoms.

Outcome Measures in Rheumatoid Arthritis Clinical Trials/Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria

The OMERACT-OARSI responder criteria include a composite index based on pain, function, and patient global [18]. For the purpose of assessing this, we will employ three questions regarding knee pain, physical function, and the patients' global assessment of disease impact on their daily life. The answers to each of these questions are given on 100 mm visual analogue scales (VAS).

To assess pain the patients are asked to indicate "the degree of knee pain in your daily life" (VAS-pain). The anchors on the 100 mm VAS are 0 = "No pain", and 100 = "Worst imaginable pain". To assess physical function the patients are asked to indicate "the degree of physical impairment of your knee in your daily life" (VAS-function). The anchors on the 100 mm VAS are 0 = "No impairment", and 100 = "Worst imaginable impairment". To assess the patients' global assessment of disease impact on their daily life the patients are asked to indicate "the overall impact of your knee osteoarthritis on your daily life" (VAS-global). The anchors on the 100 mm VAS are 0 = "No impact", and 100 = "Worst imaginable impact".

Categorization as a responder requires an improvement in the above-mentioned pain or function VAS scores of at least 50% and an absolute change of 20 mm. Alternatively, a response can be achieved by meeting at least 2 of the following 3 criteria: (1) an improvement of 20% and an absolute change of 10

mm in VAS-pain, (2) an improvement of 20% and an absolute change of 10 mm in VAS-function, or (3) an improvement of 20% and an absolute change of 10 mm in VAS-global.

Impact of Weight on Quality of Life-Lite (IWQoL-Lite)

The IWQoL-Lite is a 31-item, self-report, obesity-specific measure of health-related quality of life that consists of a total score and scores on each of five scales: physical function, self-esteem, sexual life, public distress, and work [19]. Scores range from zero to 100, where 100 represent the best HRQOL and zero represents the worst.

Treatment Related Impact Measure-Weight (TRIM-Weight)

The TRIM-Weight is an obesity treatment-specific patient reported outcomes measure designed to assess the key impacts of prescription anti-obesity medication and be applicable to the wide range of prescription medications currently available [20]. The TRIM-Weight is based on 22 items within seven thematic domains related to a patients experience with a weight loss medication; i) satisfaction in terms of weight loss, ii) the burden of taking the medication, iii) satisfaction in terms of appetite-control, iv) the impact of weight stabilization, mood swings, or tiredness, v) convenience, vi) discomfort, ad vii) impact on social aspects, productiveness and relationships. All items are scored on anchored rating scales with five levels of response (1–5) in which higher scores indicate better quality of life.

Short form 36 (SF-36)

The SF-36 is a generic, short-form health status questionnaire composed of 36 questions within eight multi-item domains assessing physical function, social function, role-emotional, role-physical, bodily pain, general health, mental health and vitality [21]. These can be combined into two summary scores (physical and mental health summary scores). For each summary score, the ordinal scores are transformed to a linear zero to 100 scale; zero indicating the least favourable health state and 100 indicating the best state of health.

Anthropometrics

Waist circumference will be measured mid-way between the lower rib margin and the iliac crest, while hip circumference will be measured at the point over the buttocks yielding the maximum circumference. Waist and hip circumferences will be measured to the nearest 1 cm. All anthropometric measurements will be taken in accordance with the WHO report on measuring obesity.

Height without shoes will be measured using a stadiometer and rounded to the nearest 1 cm.

Body weight will be measured to the nearest 0.1 kg with a decimal weighing scale (TANITA BW-800, Tanita Europe BV Hoogoorddreef 56e, 1101BE Amsterdam, The Netherlands) with participants fasting

and wearing underwear or light clothing, only.

The BMI (kg/m^2) will be calculated from body weight and height.

Blood samples

Standard biochemistry: C-reactive protein (CRP), alanine transaminase (ALT), calcium, creatinine, potassium, sodium, low-density lipoprotein (LDL), high-density lipoproteins (HDL), triglycerides (TG), and total cholesterol (TC). Haematology: Haemoglobin, leucocytes, differential cell count, and thrombocytes. Glucose metabolism: HbA1c and fasting plasma glucose (FPG).

Radiography

Radiographic examinations include standard clinical semi-flexed weight bearing posterior-anterior radiographs of both knees. During the examination patients will be facing the plate of the radiography equipment with the knees touching the cassette holder or a reclining table top. The radiography plate or cassette holder is placed so that the centre of the film will be at the level of the patient's tibiofemoral joint line. The radiography beam is centred between the knees with a 10 degrees cranio-caudal angle and the body weight will be distributed equally between the two legs. The radiographs will be assessed by use of the Kellgren & Lawrence (KL) grading system; a categorical grading scale of knee OA going from 0 to 4 by means of an evaluation of osteophytes, joint space narrowing, sclerosis, and altered bone shapes.

Vitals signs

Blood pressure (BP), systolic and diastolic, will be measured with the patient in sitting position with the legs uncrossed and the back and arm supported. Patients resting pulse will be measured following a resting-period of five minutes in a sitting position with the legs uncrossed and the back and arms supported. Patients will be instructed to avoid caffeine, smoking and physical activity within 30 minutes prior to both of these measurements.

Visit schedule

Table 1 Visit schedule

	Information	Screening	Enrolment	Pre-allocation	-	-	-	-	-	-	-	Allocation	Post-allocation	-	-	-	-	-	-	-	-	-	-	-	-	-	End of trial	-	Off-treatment follow-up
VISIT NAME	-Ty	-Tz	-Tx	-T8	-T7	-T6	-T5	-T4	-T3	-T2	-T1	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	Tx	Tz
WEEK NO.	x	x	x	-8	-7	-6	-5	-4	-3	-2	-1	0	2	4	6	8	12	16	20	24	28	32	36	40	44	48	52	x	64
INFORMATION & SCREENING																													
Motivation appraisal	X																												
Exchange of information	X																												
Eligibility screening & consent		X																											
X-ray & physical examination		X																											
Blood testing & urine stix		X																											
Medical & medication history		X																											
KOOS pain, WOMAC pain, C-SSRS & PHQ-9		X																											
Vital signs, height, body weight & ECG		X																											
INTERVENTION																													
IDI				X	X	X	X	X	X	X	X																		
TDI												X	X	X	X	X													
Lira 3 mg OR Lira 3 mg pbo												X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		
ASSESSMENTS																													
Physical examination			X									X															X	X	
Dietician (group session)				X	X	X	X	X	X	X	X	X	X	X	X	X													
Titration visit (MD)												X	X	X	X	X	(X)	(X)											
Medical history			X																										
Update of medical history												X															X	X	
Medication history			X									X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
KOOS, WOMAC, SF-36, IWQoL-lite & O-O resp. crit.			X									X															X	X	
ICOAP			X									X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
KOOS pain & WOMAC pain													X	X	X	X	X	X	X		X	X	X	X	X	X			
C-SSRS			X									X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
PHQ-9 & BES			X									X															X	X	X
TRIM-weight													X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Adverse events report form				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Vital signs & waist and hip circumferences			X									X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Body weight			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Blood testing, height & DXA			X									X															X	X	
X-ray			X																								X	X	
ECG												X					X										X	X	X
Medicine hand-out												X	X	X	X	X	X	X	X		X	X	X	X	X	X			
Adherence assessment													X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	

**Lira: Liraglutide; pbo: placebo, O-O resp.crit: OMERACT-OARSI responder criteria*

Outcomes

Patient characteristics

Height, age, gender, and KL grading will be collected and reported as patient characteristics.

Co-primary outcomes

The co-primary outcomes are changes in body weight and the KOOS pain subscale from baseline (week 0) to the last visit in the main trial period (week 52).

Confirmatory secondary outcomes

The confirmatory secondary outcomes are changes in the KOOS symptom, ADL, sport and recreation, and health related QoL subscales, the WOMAC pain, stiffness, and function subscales, the total score and subscales in the ICOAP questionnaire, BMI, waist circumference, or the waist/hip ratio from baseline (week 0) to the last visit in the main trial period (week 52). Moreover, the proportion of patients with ≥5 or ≥10 % weight loss at the last visit in the main trial period (week 52) also constitutes confirmatory secondary outcomes.

Supportive secondary outcomes

The supportive secondary outcomes are changes in biomarkers (*CRP, HbA1c, FPG, ALT, LDL, HDL, TG and TC*), BP, resting heart rate, the impact of weight on quality of life (*IWQoL-Lite*), treatment related impact on quality of life (*TRIM-weight*), and the general health status (*SF-36*) from baseline (week 0) to the last visit in the main trial period (week 52). Changes in proportion of patients meeting the criteria for metabolic syndrome or pre-diabetes from week 0 to 52 as well as the proportion of patients classified as responders (*the O-O responder criteria*) at the last *visit in the main trial period (week 52) also constitutes confirmatory secondary outcomes.*

Safety outcomes

The safety outcomes include the incidence of adverse events (AEs), suicidal behaviour and/or ideation (C-SSRS), depression (PHQ-9), binge eating (BES), and measures outside reference limits for haemoglobin, thrombocytes, leucocytes, differential cell count, creatinine, and electrolytes (+/- 2 SD), and for ALT and CRP (+ 150 %).

Data management

The collection, preservation and dissemination of the clinical data is specified in this clinical trial protocol and abide to the standard requirements for GCP-compliant data management in clinical trials.

The source data and documents, eCRF, protocol and amendments, drug accountability forms, correspondence, patient identification list, informed consent forms, and other essential GCP documents will be retained for at least 10 years after the study is completed at the study site. Data entries are quality ensured by double data entry, classification of data type (i.e. text and numbers) and/or range checks for data values.

All data collected during this project will be managed and quality certified by the Parker Institutes data management team, composed by the primary investigator, a data manager and a chief administrator. This team is responsible for ensuring data completeness and accuracy as well as source data verification. The latter will be performed by the monitor and the relevant investigators. The team is also responsible for ensuring operations of a secure database established for the collection of clinical data collected via the electronic case report form (eCRF) platform through a secure connection. All data obtained during the study will be documented in the individual eCRFs. reasons for any missing data will be noted in the database, and logging and tracking of data changes will be documented.

Randomisation

Participants will be randomised to treatment daily with liraglutide 3 mg/day or liraglutide placebo 3 mg at week 0, i.e. after the initial 8-week IDI period. Participants will be randomised in a 1:1 manner to receive either 3 mg/day liraglutide or identically appearing placebo; stratified randomisation will be based on gender (male vs. female), age (<60 years vs. ≥60 years), and obesity class (BMI; < 40 vs. ≥ 40 [kg/m^2]) status at trial enrolment (week -8). A computer-generated randomisation sequence will be produced using SAS PROC PLAN to generate the eight randomisation schedules before any participant is enrolled, allocating participants in permuted blocks of 2 to 6 to the daily liraglutide 3 mg/day or placebo group (1:1). The randomisation sequence is entered into the eCRF by a data manager.

Allocation concealment and blinding

The trial utilizes a computer-generated allocation process in which the patient identifier is coupled to one of the experimental arms when the physician clicks on the 'randomisation button', appearing at visit T0 in the eCRF system. Upon allocation to one of the two experimental arms the patient identifier is automatically coupled to specific pens, each of them labelled by a single and unique Dispensing Unit Number (DUN). The entire process is blinded for all investigators, clinical, academic, and administrative trial personnel.

Unblinding will only take place in exceptional circumstances when knowledge of the actual treatment is essential for further management of the patient. If unblinding is deemed necessary, the investigator will activate a data solution, within the eCRF, build for this specific purpose and controlled by an independent data manager and the chief administrator. The actual allocation will not be disclosed to the

patient and/or other study personnel including other site personnel, monitors, corporate sponsors or project office staff.

Sample size and power considerations

The co-primary outcomes are changes in body weight and KOOS-Pain from randomisation to the end of the trial, 52 weeks after randomisation. The sample size of 150 is designed to provide a reasonable power (>80%) to detect a 5-kg difference in body weight change between the groups, AND an 8-units difference in the KOOS-Pain. All power and sample size analyses were conducted using 'SAS Power and Sample Size', version 3.1 (SAS Institute Inc., Cary, North Carolina):

- Body weight: For a two-sample pooled t-test of a normal mean difference with a two-sided significance level of 0.05 (P<0.05), assuming a common standard deviation of 10 kg (conservatively estimated based on our previous weight loss trial in this patient population [22]), a sample size of 75 per group, has a power of 92% to detect a mean difference of 5.5 kg in the group mean change in body weight.
- KOOS-Pain: For a two-sample pooled t test of a normal mean difference with a two-sided significance level of 0.05 (P<0.05), assuming a common standard deviation of 15 KOOS-points, a sample size of 75 patients per group has a power of 90% to detect a mean difference in the group mean changes of 8 KOOS-Points (corresponding to a moderate Cohen's effect size of 0.5).

The combined power for the two endpoints is 83%.

Statistical methods

The prespecified efficacy analyses will be based on the data from the full-analysis set; i.e. the intention-to-treat (ITT) population - including all participants who are randomised and assessed at baseline. In case of missing data at week 52, the observation from enrolment will be carried forward in case of missing data in the ITT population. The safety analysis set includes all patients who are randomly assigned to a trial group and have had exposure to a trial drug (i.e., liraglutide 3 mg/day or placebo). This trial does not plan for any interim analyses.

The primary analysis will be the comparison between liraglutide and placebo using an Analysis of Covariance (ANCOVA) model with treatment, gender, age-, and obesity-stratification as fixed effects and with adjustment for the level at baseline as a covariate. From this model, the observed differences in weight change and KOOS pain change between liraglutide treatment and placebo will be estimated together with the associated 95% confidence interval and the *p*-value corresponding to the test of the hypothesis of no difference between treatments (i.e., the null hypothesis).

To establish the efficacy of liraglutide 3 mg/day compared to placebo in patients with overweight or obesity and knee OA, inducing and maintaining weight loss and pain relief over 52 weeks, endpoints are tested in a hierarchical manner in the order in which the endpoints are presented. Liraglutide 3 mg/day will be considered statistically significantly better than liraglutide placebo 3 mg/day placebo with respect to change in body weight if the null hypothesis is rejected ($p<0.05$). But, overall, liraglutide 3 mg/day will only be *confirmed* as statistically significantly better than placebo with respect to change in KOOS pain subscale, if it is ALSO statistically significantly better with respect to change in body weight. Categorical changes for dichotomous end-points will be analysed with the use of logistic regression with the same fixed effects and covariates as the respective ANCOVA. Sensitivity analyses will be performed to assess the robustness of the primary analyses, including 'per protocol' scenarios, repeated-measures linear mixed models, and multiple-imputation techniques.

Management

The project management team consists of the Primary Investigator, Dr. Henrik Rindel Gudbergsen who is responsible for the execution of the project, the Sponsor-Investigator Professor Henning Bliddal who is responsible for the overall scientific planning of the project, and Chief Administrator Claus Bomhoff who is responsible for administrative and financial tasks. The steering committee (SC), led by the Primary Investigator, is the principal management body with respect to the operational and scientific facets of this trial. Members of the SC are the investigators involved in the development of this protocol and include HRG (chairman), HB (sponsor), MH, EW, HB, RC, MK, FK, AA, MUR, and LEK. The SC will ensure trial resources, schedule all trial related activities, and ensure execution of the trial.

The independent ethics committee (ICE) monitors any safety and/or ethical concerns arising during the project and to advise the SC. The members of the ICE are Lennart Jacobsson, Professor in Rheumatology, Department of Rheumatology, Sahlgrenska University Hospital, Gothenburg, Sweden and Karl Agner Kristensen MD, PhD, Specialist in Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, Lund University Hospital, Lund, Sweden.

Patient and Public Involvement

Via a formal review process, the authors retrieved input from an appointed knee OA patient advisor in a discussion focusing on the development of hypotheses, interventions and outcomes related to this study. The design of the study was not discussed with patients, whereas the burden of the study was assessed by all patients via an initial appraisal of their motivation to participate in the study and via a thorough description of the study in relation to the signing of the informed consent.

The institute's patient board and the appointed knee OA advisor were also involved in proposing potential routes for communication regarding recruitment of patients, including websites and patient

associations. Patients will be informed, via dialogue and a briefing document, that they may access results on an individual basis throughout the trial and that the study personnel will engage in presenting the overall results for each individual patient once the trial is complete. Upon trial completion, patients will also be invited to a meeting where the project results are presented in a manner that is understandable by laymen.

ETHICS AND DISSEMINATION

The investigator will monitor each participant for clinical and laboratory evidence of adverse events (AEs) on a routine basis throughout the trial. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the participant, will be recorded. The investigator will assess and record any AE in detail, including the date of onset, description, severity, duration and outcome, relationship of the AE to trial drug, and any action(s) taken.

The treatment and investigations in this trial are associated with minimal discomfort for the participants. The injection is practically pain-free but may leave a small haemorrhage, resolving spontaneously within a few days in the vast majority of patients. Less commonly, the patients may experience abdominal pain, insomnia, reflux, gastritis, and dizziness. Uncommon AEs comprise dehydration, tachycardia, pancreatitis, cholecystitis, urticarial, and malaise.

When collecting blood samples some participants may experience minor discomfort when the needle penetrates the skin, and rarely a small bleeding occurs. The planned radiographs will be identical and obtained at the same frequency as recommended in the current care model at the involved outpatient clinics.

The participants included in the planned clinical trial will not receive any financial compensation. Neither the sponsor-investigator nor any of the other members of the project group has financial interest in neither the conduct nor the results of the trial.

All participants will be covered by a patient-insurance, according to national requirements and common conduct, during the conduction of the clinical trials.

The trial is approved by the regional ethics committee in the Capital Region of Denmark; approval ID H-16019969.

The successful planning and conduction of the LOSEIT trial may provide the basis for a significant improvement in the disease management of the many overweight citizens impacted by knee OA.

The number and timing of visits has been outlined to ensure observation of any safety issues as well as thorough management of medication hand-out and usage throughout the study.

Based on involvement of patients as well as the existing experience within the field of weight loss and knee OA management the study design is considered to be acceptable for patients as well as feasible to

implement. Nevertheless, this study will deliver comprehensive insights into the practicality and acceptability of the interventions studied in this specific context, and provide valuable information regarding the generalizability of the interventions in question.

At the end of the trial, one or more manuscripts will be prepared for publication in peer-reviewed journals. The manuscripts will be written in accordance with the CONSORT Statement. The manuscripts will include positive, negative, as well as inconclusive results. In addition, the results from the trial will be presented as posters or oral presentations at national and/or international conferences.

Novo Nordisk A/S and The Cambridge Weight Plan had no influence on the study design, nor will they have any influence on the analyses and interpretation of data or the writing of manuscripts/abstracts based on trial data. Novo Nordisk A/S and The Cambridge Weight Plan will be given 4 weeks to review any manuscript/abstract or other means intended for publication or presentation of the data. All authors will qualify for authorship according to International Committee of Medical Journal Editors, 1997, and must have participated sufficiently in the work to take public responsibility for the content.

COMPETING INTERESTS STATEMENT

HG; has received speaker fees from Pfizer and MSD

MH, EEW, AO, HB, RC, MUR, CB, CD, EMB, BH and KE; none to declare

MB; has received speaker fees from Esaote, Abbvie, and UCB

FKK; has received lecture fees from, participated in advisory boards of and/or consulted for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD/Merck, Novo Nordisk, Sanofi and Zealand Pharma

AA; reports grants and personal fees from Global Dairy Platform, USA; McCain Foods, USA; McDonald's, USA; Arena Pharmaceuticals Inc, USA; Basic Research, USA; Dutch Beer Knowledge Institute, NL; Gelesis, USA; Novo Nordisk, DK; Orexigen Therapeutics Inc., USA; S-Biotek, DK, Twinlab, USA; Vivus Inc., USA; and grants from Arla Foods, DK; Danish Dairy Research Council, Nordea Foundation, DK outside the submitted work; and Royalties received for the book first published in Danish as "Verdens Bedste Kur" (Politiken, Copenhagen), and subsequently published in Dutch as "Het beste dieet ter wereld" (Kosmos Uitgevers, Utrecht/ Antwerpen), in Spanish as "Plan DIOGenes para el control del peso. La dieta personalizada inteligente" (Editorial Evergráficas, Léon), and in English as "World's Best Diet" (Penguin, Australia).

LEK; has received fees for speaking and consultancy from Pfizer, AbbVie, Amgen, Sanofi, UCB, Celgene, BMS, Biogen, Novo Nordisk, MSD, Novartis, Eli Lilly, and Janssen pharmaceuticals

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DATA SHARING STATEMENT

Once the trial has been completed data and information about the study may be accessed by contacting the corresponding author after obtaining and documenting legitimate approval from the Danish data authorities and to the extent possible according to Danish national law.

CONTRIBUTORSHIP STATEMENT

HG, EEW, MH, HB, RC, MB, FKK, MH, AA, EMB, and LEK have contributed by conceptualising, designing, writing, reviewing, and approving the protocol for this trial.

AO, MUR, CB, CD, BLH, and KE have contributed by writing, reviewing, and approving the protocol, and are all part of the acquisition of data from the trial.

Moreover, all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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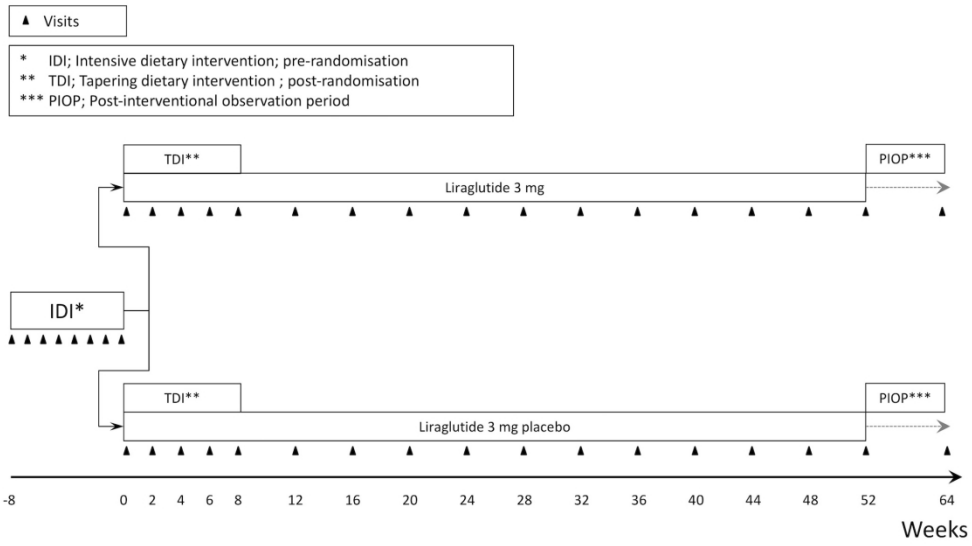

Figure 1

180x99mm (300 x 300 DPI)