Comparison of radiographic and MRI changes in liraglutide and placebo treatment of obese patients with Knee OA: 52 weeks results from the LOSEIT study, a double-blind, randomized trial

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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 (PMIDs 24103073 and 25896063). The majority of successful weight losses are short-lived since the maintenance of a clinically significant weight loss over time remains a challenge for health-care providers (HCPs), patients, and societies (PMID 25896063). This challenge occurs due to several behavioural and physiological mechanisms stimulating weight regain. These include lowering of energy expenditure, reduced satiety, and increased hunger (PMID 25896063).

Osteoarthritis (OA) is the most common type of arthritis, characterised by pain and physical disability (PMID 11033593). In addition, over 10% of all people aged more than 55 years of age have symptomatic OA, primarily involving the knees (PMID 11156538). Due to the pivotal role of the knee in basic mobility and locomotion, knee OA is associated with significant impairments and limitations in 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 (PMID 11360143). Obesity and knee OA share pathogenic phenotypes, and the development of one disease increases the risk of the other and may trigger the onset of a vicious cycle (PMID 24751192).

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 obesity. Recently published data, investigating the use of liraglutide 3 mg in an obese population with dyslipidaemia and/or hypertension, revealed a long-term positive impact on both body weight and related health benefits (doi.org/10.1016/S0140-6736(17)30069-7).

OBJECTIVE:

To evaluate the radiographic changes (joint space narrowing) and changes on MRI (MOAKS score synovitis and bone edema) in obese patients with knee OA after 52 weeks of either liraglutide or placebo.

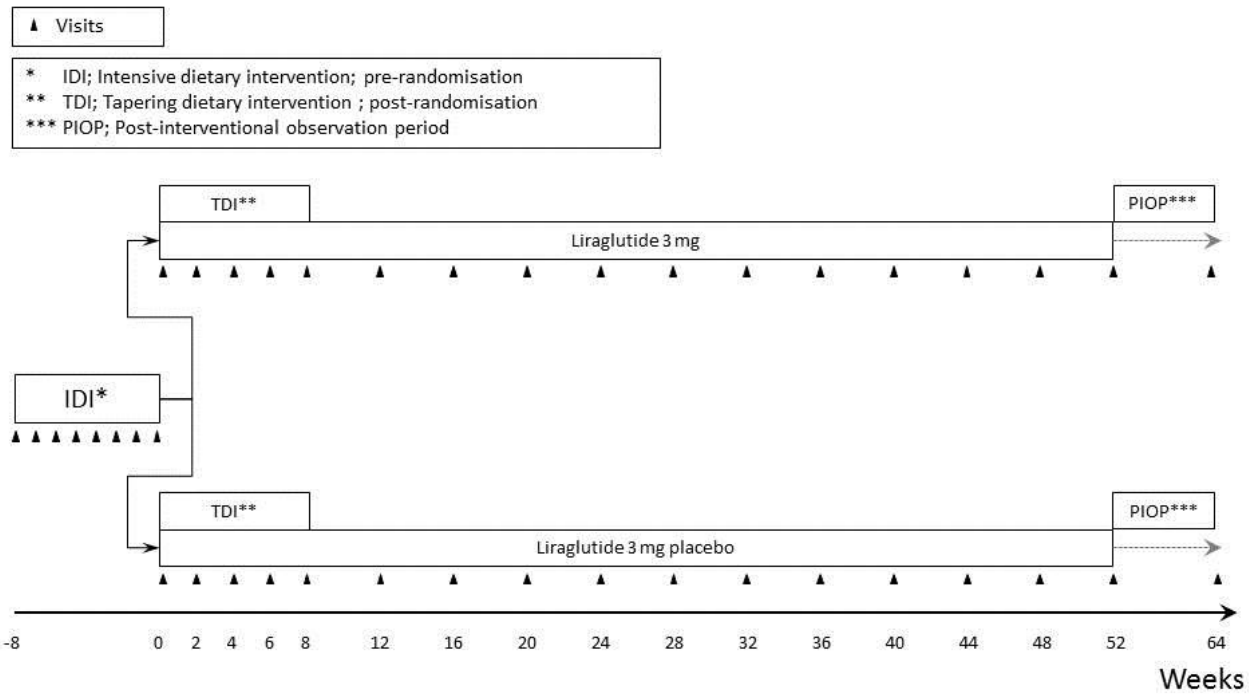
METHODS AND ANALYSIS

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 IDI period. If successfully achieving a weight loss of minimum 5 % during this period, participants will continue with an 8-week tapering dietary intervention (TDI), from week 0 to 8, and be randomised to receive either liraglutide 3 mg or identically appearing placebo throughout the

52-week main trial period. 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*).

Amenable patients will receive written and verbal information about the trial and the procedures involved. 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 1000 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 by a standard liquid energy intake protocol. To facilitate compliance with 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 8-week IDI will be randomised to receive either liraglutide 3 mg or placebo for a subsequent 52-week main trial period.
The initial 8 weeks of the main trial phase consist of an 8-week TDI period (week 0 to 8) focusing on a re-introduction of regular meals combined with two formula diet products per day. 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 daily meal replacement with a formula diet from week 8 to 52 to administer by themselves.

For the main trial phase (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
    - *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 3 mg placebo*
    - *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).

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 health care providers 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

In order 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

X-ray

Standard semi-flexed posterior-anterior X-rays of the target knee is performed in all of the above mentioned patients at baseline and Kellgren-Lawrence (KL) grades of the target knee will be performed using the IB LAB ANALYZER JSX^{PLUS} or IB LAB KOALA (Knee OsteoArthritis Labeling Assistant) by IB Lab GmbH, Austria. X-rays at randomization and 60 weeks following treatment are used for assessing the degree of radiographic KOA progression. For this, joint space width, joint space area will be measured and standardized automatically for comparability between patients and different timepoints. The measures are aggregated to a joint space narrowing score in the 2 groups (JSN assessment) using the same software[1],[2]

MRI

OSIRIX® will be used to score the static MR images inhouse according to the MOAKS (MRI in OA Knee Score) (REF) bonemarrow lesions (total score and sum of count y/n), and synovitis, where synovitis is scored semi-quantitatively as "effusion-synovitis" and "Hoffa synovitis" at randomization and 52 weeks (REF).

Statistics:

Analysis will be performed using the modified intent-to-treat (ITT) approach, which included patients who had received at least 1 dose of study drug.

Radiographic end points (delta JSW or JSN and delta MOAKS) will be analyzed with an ANCOVA model with ranks of scores that included factors for baseline radiographic score rank (KL) and BMI. In addition to the ANCOVA results, 95% confidence intervals (95% CIs) of the estimates were determined. To supplement the

[1] Law, A., Assi, L., Harrison, A., Howe, F. A., & Sofat, N. (2018). FRI0556 Automated scoring of knee osteoarthritis (OA) on routine radiographs identifies disease severity in OA. https://ard.bmj.com/content/77/Suppl_2/803.1

[2] Ljuhar R, Norman B, Ljuhar D, Haftner T, Hladuvka J, Bui Thi Mai P, Canhão H, Branco J, Rodrigues A, Gouveia N, Nehrer S, Fahrleitner-Pammer A, Dimai HP, A clinical study to examine thresholds of joint space width and joint space area for identification of knee osteoarthritis, https://ard.bmj.com/content/75/Suppl_2/871.1

analyses of progression rate, radiographic nonprogression (change ≤0.0, and ≤SD) will be analyzed using Chi-square.

The changes from baseline in JSN and MOAKS will be presented in cumulative probability plots to fully visualize all radiographic data. Frequency distributions of the observed cumulative proportion, i.e., scores ranked from the lowest to the highest values per treatment group, and presented as a cumulative proportion of all scores, were plotted against the variables' actual values (change scores). From the cumulative probability, the proportion of observations below each possible progression level can be read on the x-axis.

Linear extrapolation of actual change from baseline was the primary approach for analysis of the radiographic end points. Only patients with an acceptable baseline image and at least 1 post-baseline image will be included in the analysis. Sensitivity analyses will be performed to confirm that the imputation method, the population analyzed, and the method of analysis did not significantly affect the radiographic outcomes of the study.

Depending on degree of missing data (if more than 5%) we decide to evaluate the impact of imputation by extrapolation, a set of analyses will be performed using the LOCF approach, carrying forward the last available total joint damage score without linear extrapolation. According to this method, dropouts were treated as though they had no further disease progression.

Furthermore, a linear regression analysis on delta JSN and delta MOAKS will be performed to study predictive factors of OA progression on imaging. Acceptable collinearity will be 0.2. And the following co-variates will be included based on a priori selection of important clinical impacting factors. Baseline KL score, BMI, treatment arm, activity, VASpain, and QoL. Stratification on weightloss during study will also be studied as a dose-effect mechanism.

Results:

Table 1 demographics, clinical status and imaging status

Figure 1: Patient flow-chart

Figure 2: Cumulative probability distribution of joint space narrowing and delta moaks score at 52 weeks

Table 2: Linear-regression analysis

ETHICS

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

FUNDING STATEMENT

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