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Protocol for a randomised, double-blinded, placebo-controlled, double-dummy 6-week clinical trial comparing the treatment effects of the glucagon-like peptide 1 receptor agonist liraglutide versus the bile acid sequestrant colesevelam on bile acid malabsorption

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ABSTRACT

Introduction Bile acid malabsorption (BAM) is a socially debilitating disease characterised by high stool frequency and urgency caused by a spillover of bile acids into the colon. Bile acid sequestrants (BASs) have limited therapeutic effect but represent the only available treatment option. Cases reporting total remission of BAM-related symptoms after treatment with liraglutide, a glucagon-like peptide 1 analogue, prompted us to design a clinical trial investigating the therapeutic effect of this compound in patients with BAM.

Methods and analysis Fifty adult individuals with moderate or severe BAM as assessed by the ^{75}selenium-homotaurocholic acid test (SeHCAT) will, after a run-in period of 10 days with no BAM treatment, be randomised to either treatment with the BAS colesevelam or liraglutide (double blinded) for 6 weeks. Daily symptom diaries and questionnaires will be filled in. Blood and faecal samples will be collected and SeHCAT will be performed at baseline, after week 3 and at end of trial. The primary endpoint is change in daily stool frequency. Secondary endpoints include changes from baseline in questionnaires, biochemistry, SeHCAT and faecal bile acid content and microbial composition.

Ethics and dissemination The study complies with Danish and European Union legislation and is approved by the Danish Medicines Agency, the Regional Scientific Ethics Committee of the Capital Region of Denmark and the Danish Data Protection Agency. The study is monitored by the Capital Region of Denmark's good clinical practice unit. All results, positive, negative and inconclusive, will be disseminated at national and/or international scientific meetings and in peer-reviewed scientific journals.

Trial registration number EudraCA: 2018-003575-34; Pre-results.

Strengths and limitations of this study

- This is the first randomised clinical trial investigating the glucagon-like peptide 1 receptor agonist liraglutide for the treatment of ^{75}selenium-homotaurocholic acid test (SeHCAT)-verified bile acid malabsorption (BAM).
- The primary endpoint is change in daily stool frequency and the study is powered to establish non-inferiority between liraglutide treatment and the currently recommended treatment for BAM, the bile acid sequestrant colesevelam.
- The study may not be powered to conclude on the secondary endpoints, which include changes from baseline in self-reported symptoms of BAM, biochemistry, BAM as assessed by SeHCAT and faecal bile acid content and microbial composition.

INTRODUCTION

Irritable bowel syndrome (IBS) is the most common bowel disorder with an estimated prevalence in the general population of around 10%.[1–3] Patients experience symptoms such as abdominal pain, diarrhoea and changes in the pattern of bowel movements without any apparent evidence of underlying pathology.[1 2] In particular, diarrhoea-predominant IBS (IBS-D), which has a reported population prevalence of around 4%,[4 5] has debilitating effects and a negative impact on quality of life[6 7] and, thus, huge societal and economic implications by occupying healthcare resources and causing loss of productivity.[7] A substantial proportion

(~30%) of patients with IBS-D have turned out to suffer from bile acid malabsorption (BAM).[8–10]

Under normal conditions, bile acids are reabsorbed from the small intestine through a combination of passive absorption and active transport with the latter being predominant in the ileum. Active transport is believed to be the major route for conjugated bile acid uptake, whereas the passive or facilitative absorption along the small intestine may be most significant for unconjugated bile acids.[11 12] Only small amounts of bile acids are excreted via faeces. BAM symptoms are caused by spillover of unabsorbed bile acids from the small intestine to the colon. In the colon, bile acids increase the osmotic gradient and, thus, trigger increased fluid secretion, and they also cause irritation of the colonic mucosa, increased mucosal permeability and mucous secretion and colonic contractions decreasing colonic transit time.[13] This causes abdominal pain and diarrhoea, and additional symptoms may include constipation, bloating, faecal urgency and/or faecal incontinence.[13] The commonly used test for diagnosis of BAM is the ^{75}selenium-homotaurocholic acid test (SeHCAT) that measures the 7-day retention of orally administered ^{75}selenium-labelled bile acid using a gamma camera. Retention of ≥15% is consistent with a normal result, 10%–15% is considered mild BAM, 5%–10% moderate and <5% retention is considered severe BAM.[14] The test has high sensitivity and specificity and the radioactive dose is equivalent to a standard chest X-ray.[15 16]

BAM is typically divided into three types based on the underlying cause: (1) type 1 BAM or secondary BAM encompasses patients with ileal pathology such as Crohn's disease or ileal resection; (2) in type 2 BAM or idiopathic BAM, no apparent underlying pathology is evident and (3) type 3 BAM includes other underlying causes, for example, coeliac disease.[17] It is being debated whether decreased absorption capacity (as indicated by the term BAM) or overproduction of bile due to defective negative feedback of bile acid synthesis is the major contributor to the spillover of bile to the colon.[18] Type 1 and 3 BAM are generally managed by treating the underlying conditions. Conventional antidiarrheal pharmacotherapy (codeine and loperamide) seem inefficient in the treatment of BAM.[19] Standard treatment of type 2 BAM is orally administered bile acid sequestrants (BASs)[13] that work by forming a complex with bile acids preventing the aforementioned effects of free bile acids in the colon. However, BASs are only effective in some patients[10 13] and, furthermore, they are associated with gastrointestinal side effects such as dyspepsia, constipation, nausea, borborygmi, flatulence, bloating and abdominal pain in up to 30% of patients.[20] The therapeutic limitations and the abovementioned community-based prevalence estimates of BAM (~1.1% of the general population[9]) combined with the debilitating effects and negative impact on quality of life[6 7] underline an unmet need for effective treatment strategies in patients with BAM. Along these lines, the UK National Institute for Health and Care Excellence research recommendations have stressed that in order to address the severe individual and societal implications of BAM, relevant research is crucial to improve the management of the disease.[21]

Two published cases who experienced total remission of their BAM symptoms after treatment with the glucagon-like peptide 1 receptor (GLP-1R) agonist (GLP-1RA), liraglutide (initiated due to overweight and type 2 diabetes),[22] made us speculate whether patients with BAM may benefit from liraglutide treatment. Both cases experienced a relapse of symptoms when treatment was paused and renewed remission after reinitiating liraglutide treatment uptitrated to 1.8 mg/day. In addition to the glucose-lowering and satiety-promoting effects of GLP-1, it is well known that this gut hormone (secreted from enteroendocrine L cells) reduces upper gastrointestinal motility.[23 24] Interestingly, treatment with liraglutide (for diabetes (1.8mg/day)[21] and obesity (3 mg/day),[25 26] respectively) was recently shown to be associated with the formation of gallstones,[26] and, thus, potentially to interact with the enterohepatic circulation of bile acids. In line with this notion, the GLP-1RA, exenatide has been reported to reduce gallbladder emptying in healthy subjects[27] and liraglutide was recently shown to delay gallbladder refilling.[28] Also, liraglutide has been shown to inhibit small intestinal motility, flow and transit time.[24 29]

The pathophysiology of BAM combined with evidence suggesting that the effects of GLP-1R activation may lead to reductions in postprandial gallbladder emptying, release of bile into the small intestine and small intestinal flow and transit time could result in increased reabsorption of bile acids, thereby alleviating spillover of bile to the colon in patients with BAM. Furthermore, a greater GLP-1-induced absorption of bile acids in the small intestine may increase the activation of the nuclear bile acid receptor farnesoid X receptor (FXR), and thereby result in FXR-dependent production of small intestinal fibroblast growth factor 19 (FGF19) known to reduce bile acid synthesis.[30 31] In line with this notion, low circulating FGF19 concentrations have been observed in patients with BAM.[18] Despite the seemingly fit between BAM pathophysiology and the pharmacodynamics of liraglutide, treatment with liraglutide (or other GLP-1RA) has so far not been investigated for the treatment of BAM. Therefore, we have initiated the treatment of bile acid malabsorption with liraglutide (BAM-LIRA) trial.

Hypothesis

We hypothesise that liraglutide-induced activation of the GLP-1R will reduce the exposure of colonic mucosa to bile acids (by the mechanisms alluded to above) and translate into amelioration or improvement in BAM symptoms in patients with BAM to the same extent as conventional BAS treatment (non-inferiority).

Objectives

The overall objective of the present study is to provide proof of concept that treatment with the subcutaneously administered GLP-1RA, liraglutide (Victoza), is

Box 1 Endpoints

Primary endpoint

- Proportion of patients experiencing ≥25% reduction in stool frequency at the end of the 6-week intervention period, with a 15% non-inferiority margin between patients with bile acid malabsorption (BAM) randomised to double-blinded treatment with liraglutide and colesevelam, respectively.

Secondary endpoints

- Proportion of patients experiencing remission of BAM-related diarrhoea (≤2 formed or semiformed stools per day).
- Symptomatic relief of BAM symptoms as assessed by questionnaires filled out once a week.
- Proportion of patients tolerating treatment (ie, maintaining treatment throughout the 6-week treatment period) and not tolerating treatment, respectively.
- Change in health-related quality of life score as assessed by questionnaires filled out every third week.
- Change in percent retention of bile acid (as assessed by ^{75}selenium-homotaurocholic acid test (SeHCAT)) from baseline (of note, SeHCAT results represent exploratory secondary endpoints as colesevelam treatment—in contrast to liraglutide treatment—is expected to reduce retention of bile acids).
- Fasting serum/plasma concentrations of total bile acids, fractionated bile acids, low-density lipoprotein, high-density lipoprotein, very low-density lipoprotein and total cholesterol, triglycerides, free fatty acids, 7α-hydroxy-4-cholesten-3-one (named C4, a marker of bile acid synthesis), fibroblast growth factor 19, glucose, glycated haemoglobin A1c, insulin, C peptide and glucagon.
- Faecal content of bile acids and microbiota composition will be evaluated as exploratory secondary endpoints.

Box 2 Eligibility criteria

Inclusion criteria

- Caucasian ethnicity.
- ^{75}Selenium-homotaurocholic acid test-verified moderate or severe bile acid malabsorption with 7-day retentions of 5%–10% and <5%, respectively.
- Normal haemoglobin (for men 133.63–169.05 g/L; for women 117.53–152.95 g/L).
- Age≥18 years and <75 years.
- Informed and written consent.
- Body mass index >18.5 kg/m^2 and <40 kg/m^2.
- Glycated haemoglobin A1c<48 mmol/mol (6.5%).

Exclusion criteria

- History of/ present hepatobiliary disorder (except for simple non-alcoholic steatosis) and/or alanine aminotransferase and/or serum aspartate aminotransferase >3 times upper limit of normal).
- Gastrointestinal disease (except for bile acid malabsorption), previous intestinal resection or previous major intra-abdominal surgery.
- Diabetes mellitus.
- Nephropathy with estimated glomerular filtration rate <60 mL/min/1.73 m^2.
- Treatment with medicine that cannot be paused for 12 hours.
- Hypothyroidism or hyperthyroidism, if not well regulated.
- Treatment with oral anticoagulants.
- Active or recent malignant disease.
- Any treatment or condition requiring acute or subacute medical or surgical intervention.
- Pregnancy (tested before entering the study), breast feeding or intention to become pregnant.
- Female of childbearing potential not using adequate contraceptive methods including intrauterine device, birth control pills, sexual abstinence or living in a relationship with a sterile partner.
- Known or suspected hypersensitivity to trial products or related products.
- Any condition considered incompatible with trial participation by the investigators.

as efficacious (as assessed by symptom relief, that is, response to treatment) and safe (as assessed by adverse effects and standard biochemistry) as treatment with the orally administered BAS colesevelam (Cholestagel) in the management of BAM and that it improves bile acid reabsorption (as assessed by SeHCAT) in these patients. The primary endpoint is proportion of patients experiencing response to treatment (ie, ≥25% reduction in stool frequency) at the end of the 6-week intervention period, with a 15% non-inferiority margin between patients with BAM randomised to double-blinded treatment with liraglutide and colesevelam, respectively. If non-inferiority is established, superiority will be evaluated. A range of secondary endpoints (see below) will also be evaluated (box 1).

Trial design

The BAM-LIRA trial is an investigator-initiated 6-week proof-of-concept study. It is designed as a randomised double-blinded double-dummy parallel-group non-inferiority study.

METHODS

Fifty non-diabetic patients with SeHCAT-verified moderate (5%–10% bile acid retention) or severe BAM (<5% retention) will be recruited. Participants will be randomised 1:1 to receive double-blinded (double dummy) subcutaneous liraglutide or oral colesevelam for 6 weeks after a 10-day washout period of any existing BAM treatment.

Randomisation

The randomisation of colesevelam and colesevelam placebo will be performed by the central pharmacy of the Capital Region of Denmark, using the website randomization.com and will be matched with liraglutide and liraglutide placebo by a study-independent person with no other involvement in the study.

Recruitment

Study participants will be recruited from gastroenterology outpatient clinics and nuclear medical departments performing SeHCAT procedures in the Capital Region of Denmark as well as from private gastroenterology clinics. Potential study participants will be asked if a medical doctor may contact them and inform them about the project. Participants will be included according to specific inclusion criteria (box 2) including severe or

Box 3 Faecal and blood samples

At screening

- Blood samples: Haemoglobin, albumin, potassium, sodium, creatinine, alanine transaminase, aspartate transaminase, bilirubin, glucose, glycated haemoglobin A1c (HbA1c), cholesterol, triglycerides and thyroid-stimulating hormone.

At baseline, 3-week and 6-week visits

- Blood samples: Albumin, creatinine, alanine transaminase, aspartate transaminase, bilirubin, glucose, HbA1c, low-density lipoprotein, high-density lipoprotein, very low-density lipoprotein and total cholesterol, triglycerides, C peptide and insulin.
- Faecal samples: Total bile acids and microbiota composition.

moderate BAM, normal haemoglobin A1c and informed consent (written and verbal), and exclusion criteria (box 2) including gastrointestinal diseases other than BAM and women of childbearing potential not using efficient contraception.

Procedures and visits

After screening for eligibility (boxes 2 and 3), participants will enter a run-in period of 10 days without any treatment for their BAM. Prior to initiation of study drugs, participants will be randomised 1:1 to 6 weeks of treatment with (1) once-daily subcutaneous dosing of the liraglutide (weekly uptitration by 0.6 mg, from 0.6 mg to 1.8 mg) and two times per day oral dosing of colesevelam placebo or (2) two times per day oral dosing of the BAS colesevelam (1875 mg) and one daily subcutaneous dose of liraglutide placebo (the same uptitration regimen as for liraglutide).

Faecal and blood samples will be collected and SeHCATs will be performed at randomisation, at week 3 and at the end of study (figure 1). Daily symptom diaries based on the Bristol Stool-form Scale will be used to record stool frequency and consistency throughout the run-in period and the intervention period. Patients will be asked at visits and informed to record any adverse events in their symptom diaries. Questionnaires regarding symptoms of BAM and quality of life will be answered every week and every third week, respectively. Data will be stored in a digital case report form using the system Research Electronic Data Capture (REDCap) (Vanderbilt University, Nashville, Tennessee, USA). In case of emergencies, unblinding will be made on an individual basis and will not affect other participants.

The study was initiated in March 2019 and last patient last visit is expected in first quarter of 2021.

Patient and public involvement

No patients or the public were involved in the development of this protocol.

Intervention

Liraglutide (Victoza) and liraglutide placebo are supplied by Novo Nordisk A/S (Bagsværd, Denmark), the producer of Victoza. The pens for injection contain 18 mg of the GLP-1RA liraglutide in 3 mL sterile water with disodium phosphate and propylene glycol and phenol for conservation (pH 8.15). The placebo pens are indistinguishable from the Victoza pens and contain the same except from the liraglutide constituent. Liraglutide placebo is administered in the same way and volume as liraglutide. The placebo pens will be specially prepared for this study and will be used in this study only. The BAS colesevelam (Cholestagel) is supplied in pill form containing 625 mg of colesevelam. The colesevelam and the colesevelam placebo will be bought and formulated into identical capsules manufactured by the central pharmacy of the Capital Region of Denmark to ensure blinding.

Drug ordering and storage

The liraglutide and liraglutide placebo pens will be delivered in separate boxes and will be stored securely in a refrigerator at 2–8°C (distant from any freezer compartment). The cap will be kept on the pen in order to protect from light. Pens that are in use can be kept at temperatures 2–30°C for 1 month. Participants will be instructed to keep the pens away from direct sunlight to refrain using the pens if the injection fluid is unclear or coloured. The capsules containing colesevelam and colesevelam placebo will be delivered from the Central Pharmacy of the Capital Region of Denmark and will be kept dry and stored according to label.

Drug accountability

One investigator will be responsible for drug accountability. For each patient treated, the batch number of pens and containers will be documented. Patients will be asked to return pens and containers after use. After verification of drug accountability, proper destruction of pens, containers and capsules will be ensured. During the study, the participants will be informed to register drug use daily in order to document administration of drugs and to ensure compliance.

Sample size

Sample size has been calculated based on the primary binary outcome (response/no response): proportion of patients experiencing response to treatment (ie, ≥25% reduction in stool frequency). An online calculator designed for binary outcomes in parallel group non-inferiority trials has been used.[32] P values<0.05 will be accepted as statistically significant, that is, level of significance $(2\alpha)=5\%$. The power of the study $(1-\beta)$ is set to 80%, with $\beta=20\%$. Following BAS treatment, approximately 80% of patients with BAM have positive effects on bowel symptoms.[10 13 33 34] We assume that the response following liraglutide treatment is 90%, and we have chosen 15% as the non-inferiority limit, resulting in a sample size required per group of 25. Thus, if there is a true difference in favour of liraglutide treatment, then 50 patients are required to be 80% sure that the upper limit of a one-sided 95% CI (or equivalently a 90% two-sided CI) will exclude a difference in favour of the standard

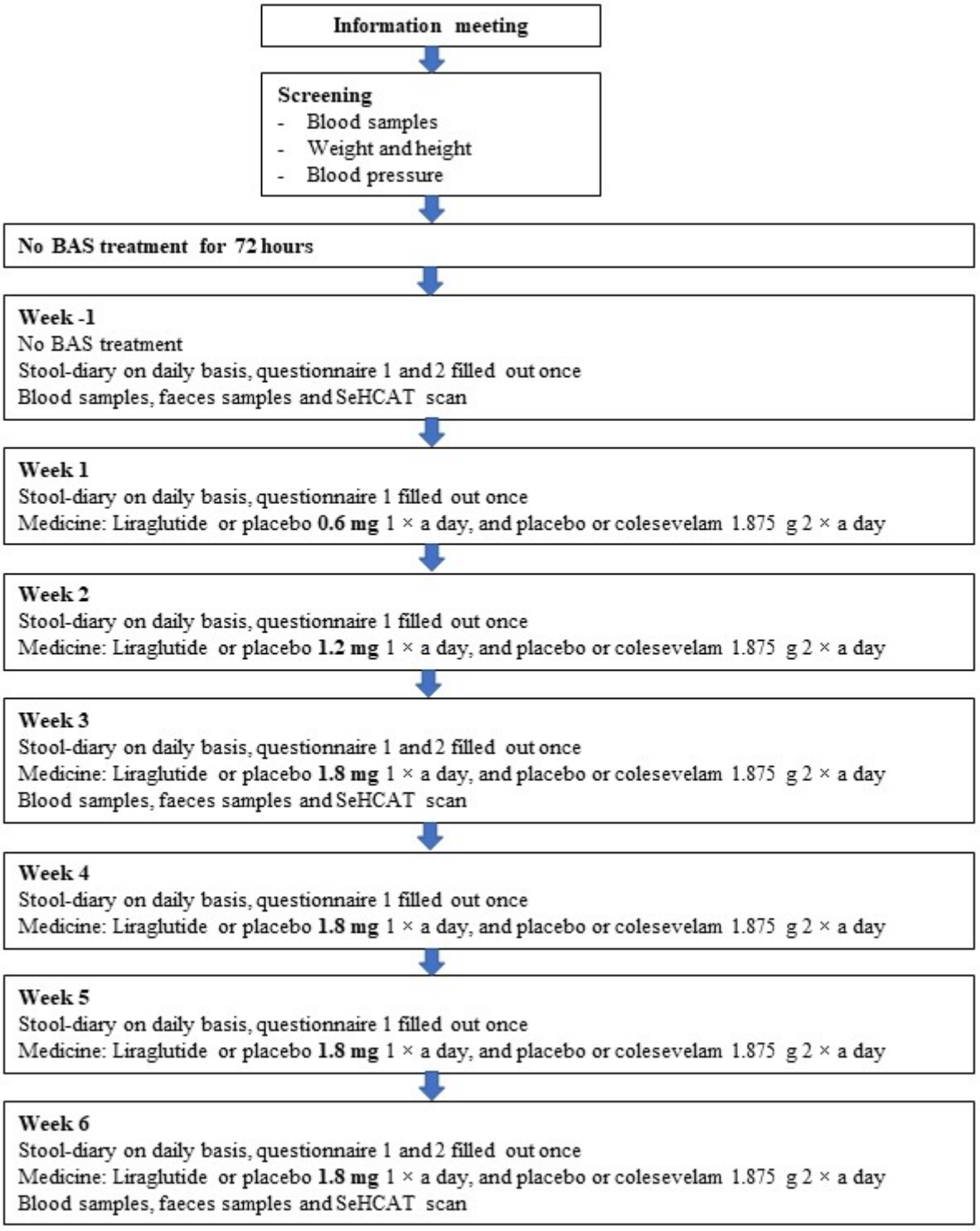

Figure 1 Study flowchart. Questionnaire 1 addresses symptom score and questionnaire 2 addresses quality of life. BAS, bile acid sequestrant; SeHCAT, ^{75}selenium-homotaurocholic acid test.

group of more than 15%. Dropouts will be replaced. The reason for dropouts will be documented and reported.

Data analysis

Continuous data will be presented by descriptive statistics with the number of observations, mean, SD, minimum, median and maximum. Substantially skewed data (ie, with mean<SD or otherwise implausible normal range) will be log transformed. Categorical data will be summarised with counts and percentages. Data from patients screened, but not randomised, will not be presented in any tables or listings.

Primary endpoint

A risk difference with 95% CIs will be calculated to compare the proportions of patients with positive response

(ie, ≥25% reduction in stool frequency) between the two treatment groups. If the CI excludes a more than 15% difference in favour of standard treatment, non-inferiority will be concluded. If non-inferiority is concluded, testing for superiority will be made.

Secondary endpoints

Total symptoms score, quality of life scores and biomarker values will be analysed using a constrained linear mixed model with inherent baseline adjustment and with an unstructured covariance pattern. Changes from baseline within and between groups will be reported with 95% CIs. Proportions of patients tolerating the treatment and proportion of patients experiencing remission of BAM-related diarrhoea within each group will be reported with exact binomial CIs and compared between groups using risk differences and Fisher's exact test. Changes in SeHCAT estimates will be analysed using a linear mixed model with an unstructured covariance pattern. Changes from baseline will be reported with 95% CIs.

Handling of missing data

In the primary analysis, all missing outcomes will be considered as a negative outcome (non-responders), that is, <25% reduction in stool frequency. Best-case and worst-case scenarios considering all missing data in a group as either positive or negative outcomes will be used for sensitivity analyses. Missing data for binary secondary outcomes will be handled similarly to the primary endpoint data. Missing data for continuous outcomes will be handled implicitly by maximum likelihood estimation in the constrained linear mixed models.

Adjustment for multiple testing

P values from the secondary analyses will be adjusted for multiple testing using the method of Benjamini and Hochberg controlling for false discovery rate.

Side effects, risks and disadvantages for participants

The summary of product characteristics (SPC) for Cholestagel[35] lists potential side effects and risks related to treatment with this drug. Side effects comprise nausea, vomiting, dyspepsia, abdominal pain, obstipation, flatulence and/or diarrhoea. Cholestagel constitutes a standard treatment of BAM and we do not expect any serious adverse events or persistent consequences for the participants. The pause of BAM treatment during the run-in period may cause BAM symptoms identical to the ones experienced before initiation of BAM treatment. The SPC for Victoza[36] lists diarrhoea, nausea, vomiting and constipation as very common side effects. The SPCs of Cholestagel and Victoza will be used as a reference to evaluate if any side effect was expected or not. According to the half-life for liraglutide and the poor absorption of colesevelam, is it considered safe that women of childbearing potential will be told to continue their contraception for a month after the study is finished. We will be monitoring the patients closely during the intervention and we expect only few and mild-to-moderate side effects, if any. Adverse events including serious adverse events will be documented and reported according to Danish and European Union legislation. The maximum amount of blood collected during the entire trial will not exceed 100 mL for each trial participant.

Study approval

The BAM-LIRA study is approved by the Danish Medicines Agency, the Regional Health Research Ethics Committee of the Capital Region of Denmark and the Danish Data Protection Agency and registered at the European Union Drug Regulating Authorities Clinical Trials (EudraCT) (2018-003575-34). The study will be conducted in accordance with good clinical practice as outlined in the Declaration of Helsinki and the International Conference on Harmonisation-Good Clinical Practise (ICH-GCP) guidelines and monitored by the Capital Region of Denmark's Good Clinical Practice Unit.

Ethics and dissemination

BAM is a common disease with symptoms that can be socially debilitating and often are considered taboo, making it difficult for many patients to maintain a normal work and social life. Furthermore, costs covering diagnostics and treatment are high and the disease bears the blame for many lost working days and lack of productivity. Both colesevelam and liraglutide are well known and commonly used medications. They are safe and we only expect mild-to-moderate and, in most cases, temporary side effects, if any. Therefore, we find the planned intervention (including 6 weeks of intervention) proportional to the potential positive results that the study may provide. Data from the study will be processed and results will be presented in one or more manuscripts for publication in scientific peer-reviewed journals. Also, the results of the study will be submitted for presentation at relevant national and/or international scientific meetings/conferences. Inconclusive, negative and positive results will be published and presented in accordance with Danish law concerning processing of personal data. All authors must fulfil criteria for authorship according to International Committee of Medical Journal Editors. All data from the study will be owned by the investigators.

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Correction notice This article has been corrected since it was first published. Middle name for the author 'Filip Krag Knop' has been corrected.

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Competing interests TV has served on scientific advisory panels, been part of speakers' bureaus for, served as a consultant to and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Gilead, Mundipharma, MSD/Merck, Novo Nordisk, Sanofi and Sun Pharmaceuticals. FKKK has served on scientific advisory panels, has been part of speaker's bureaus for, served as a consultant to and/or received research support from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly, Gubra, Lupin, MedImmune, MSD/Merck, Mundipharma, Norgine, Novo Nordisk, Sanofi and Zealand Pharma, and is a minority shareholder in Antag Therapeutics ApS.

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Patient consent for publication Not required.

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