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Bile Acid Remediation of Diabetes and Obesity Study (BARDOS)

Use of bile acids to investigate the mechanisms of diabetes remission and weight loss conferred by metabolic surgery.

29th June 2021

Version 2.2

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Clinical Queries

Clinical queries should be directed to Miss Yasmin Tabbakh who will direct the query to the appropriate person

Sponsor

Imperial College Healthcare NHS Trust is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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This protocol describes the BARDOS study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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Glossary of abbreviations

RYGB	Roux-en-Y gastric bypass
T2DM	Type 2 diabetes mellitus
BA	Bile acids
GLP-1	Glucagon like peptide-1
PYY	Peptide YY
GIP	Glucose-dependent insulinotropic peptide
OXM	Oxyntomodulin
CDCA	Chenodeoxycholic acid
UDCA	Ursodeoxycholic acid
MMT	Mixed meal tolerance
REE	Resting energy expenditure
VAS	Visual analogue scale
GCP	Good clinical practice
AE	Adverse events
SAE	Serious adverse events

1. Study summary

Objectives:
To demonstrate that treatment for 6 weeks with oral bile acids (BA) can increase anorectic gut hormone secretion, insulin secretion and sensitivity, and reduce body weight in patients with type 2 diabetes (T2DM) +/- obesity.

Type of study:
A double-blind mechanistic randomised controlled study comparing placebo vs chenodeoxycholic acid (CDCA) vs ursodeoxycholic acid (UDCA) for 6 weeks in patients with T2DM +/- obesity.

Study design and methods:
We will interrogate the mechanisms underlying the effects of these BA on metabolism by measuring the following outcomes at baseline, and at 3, 6 and 8 weeks.

- *Primary:*
    1. Gut hormone secretion following a standardised mixed meal tolerance (MMT) test.
- *Secondary:*
    1. Bodyweight change.
    2. Insulin sensitivity (hepatic and peripheral) using the two-step euglycaemic hyperinsulinaemic clamp method.
    3. Energy expenditure utilising indirect calorimetry.
- *Exploratory:*
    1. Impact of bile acid treatment on gut bacteria diversity and the metabolome.

Study duration:
No more than 8 weeks per participant

Estimated total study duration:
24 months

Planned end date:
31/01/2024

Total number of participants:
36

2. Introduction

2.1 Background

Metabolic surgeries such as the Roux-en-Y gastric bypass (RYGB) are highly effective and durable treatments for type 2 diabetes and obesity, leading to durable weight loss, reduction in mortality and morbidity and remission of diabetes in patients.[1] Multiple mechanisms are thought to underly the efficacy of surgery. There is mounting evidence that the increased delivery of bile acids (BA) to the small intestine mediates some of the benefits of bariatric surgery.[2] In particular, the diversion created by RYGB leads to delayed mixing of food with bile/pancreatic juices compounded by an increased delivery of bile acids to the terminal ileum where the BA are reabsorbed in the enterohepatic recirculation of BA. This leads to elevated

levels of serum BA.[3,4] It is hypothesized that these elevated BA may in turn trigger multiple favourable effects for metabolism based mainly on animal model studies.[2]
Currently, there is limited mechanistic evidence for the metabolic effects of BA in patients with obesity and type 2 diabetes. Although animal models can be helpful, there are many key differences in the metabolism of BA between humans and mice which makes the findings of animal studies difficult to extend to humans[5] As a result, clinical studies are required to substantiate the hypothesis that increased delivery of BA to the gut is a key mechanism mediating the beneficial effects of bariatric surgery on obesity and diabetes.

2.2 Hypotheses

The increased flow of BA to the small intestine is responsible for orchestrating multiple metabolic benefits after bariatric surgery (Figure 1). We aim to look at three mechanisms.

1. Synergetic increases in gut hormone secretion
I hypothesise that the BA chenodeoxycholic acid (CDCA) and ursodeoxycholic acid (UDCA) are able to stimulate the secretion of enteroendocrine L-cell gut hormones such as Glucagon like peptide -1(GLP-1), oxyntomodulin (OXM) and peptide YY(PYY). This hypothesis is based on in vitro data that suggest Takeda g-protein receptor 5/G-protein bile acid receptor 1 (TGR5)/GPBAR1 activation is capable of triggering GLP-1 secretion[6] and increases in L-cell differentiation and number.

2. Improvements in insulin sensitivity.
I hypothesise that UDCA is capable of improving insulin sensitivity. This hypothesis is based on studies which show tauro-UDCA, the taurine conjugate which is produced by metabolism of UDCA, improves hepatic and muscle insulin sensitivity in obese volunteers.[7]

3. Increases in energy expenditure.
I hypothesise that CDCA is capable of increasing resting energy expenditure. This hypothesis is based on evidence that CDCA activates brown adipose tissue thermogenesis.[8] Additional energy expenditure/thermogenesis has the advantage that this will improve weight loss.

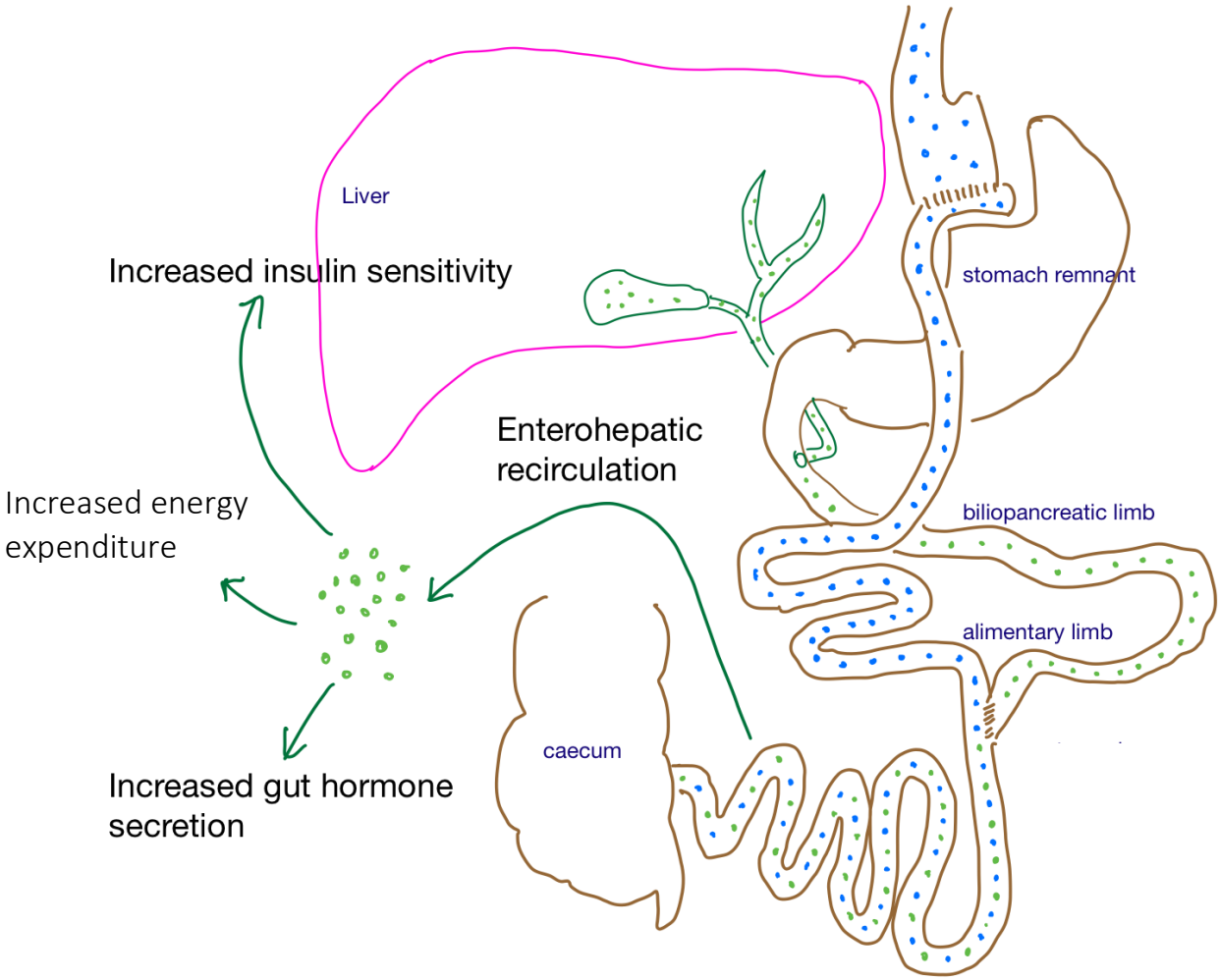


Figure 1: Impact of Roux-en-Y gastric bypass on flow of food (blue dots) and bile acids (green dots), and hypothesised impact on metabolism.

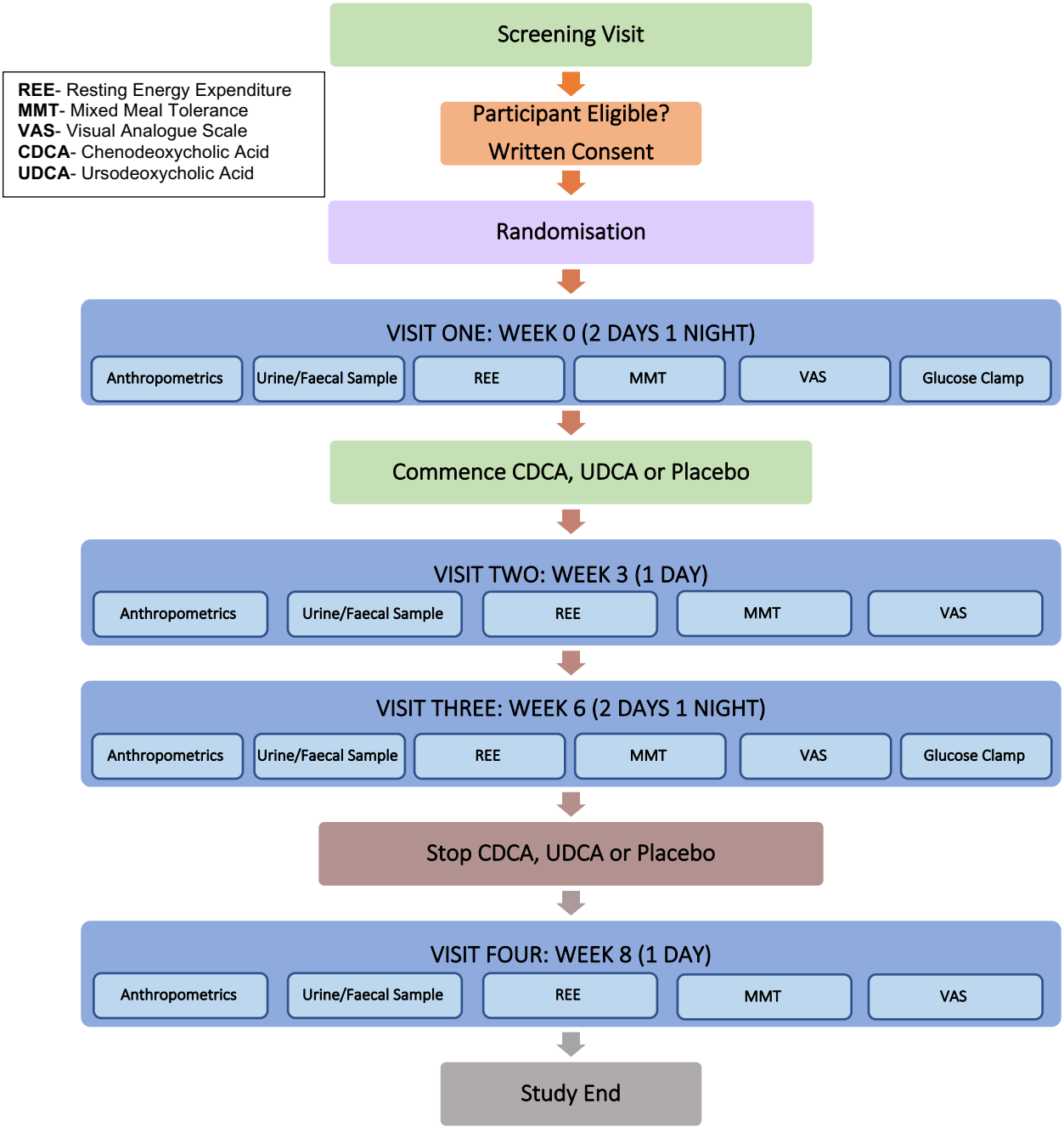
2.3 Preliminary data

In house preliminary data substantiate hypothesis 1, i.e. that single dose CDCA and UDCA have significant stimulatory gut hormone secretion (manuscript submitted). The gut hormones GLP-1, OXM and PYY are well known to improve insulin secretion and to suppress appetite, hence leading to reductions in weight and improvements in glycaemia. Our previous studies have shown that the combination of GLP-1, OXM and PYY synergizes to induce a rapid weight loss in volunteers with diabetes and obesity (4.4 kg on average over 28 days)[9]. Furthermore, the combination is capable of normalising blood glucose levels. Therefore, the BA-triggered simultaneous release of multiple gut hormones after eating can explain some of the improvements in metabolism seen with bariatric surgery.

2.4 Study objectives

To study the effects, over a 6-week period, of increased BA delivery to the small intestine in people with T2DM +/- obesity.
Primary objectives:
1. Gut hormone secretion
Secondary objectives:
2. Bodyweight change
3. Insulin sensitivity
4. Energy expenditure
Exploratory objectives:
1. Impact of bile acid treatment on gut bacteria and the metabolome

3. Trial design



BARDOS is a double-blind mechanistic randomised study with three arms comparing placebo vs CDCA (up to 13-16mg/kg/day, maximum 1000mg a day) vs UDCA (up to 12-16mg/kg, maximum 1750mg a day) daily for six weeks in 36 patients with T2DM +/- obesity. The study will be conducted at the NIHR Imperial Clinical Research Facility where the pilot study was conducted. The end of the study is defined by the last visit of the last participant.

3.1 Recruitment strategy

We have planned to recruit 12 volunteers with T2DM per group (36 in total). Please see power calculation in section 5.

The following recruitment volunteer pools will be used:

- The Imperial CRF has a large database of characterised volunteers with T2DM that have been recruited for previous studies.
- Patients attending diabetes clinics at Imperial Healthcare NHS Trust (Hammersmith Hospital, Charing Cross Hospital, St Mary's Hospital).
- The study will be adopted by the local Diabetes Research Network (through Clinical Research Network) to access patients seen in primary care. This will be done by sending out text messages to potential volunteers via their GP practices.
- Advertisements will also be placed to access volunteers across London and in primary care.

3.2 Inclusion criteria

- Male or female
- Age 18-80
- BMI ≥ 22kg/m^2
- Diagnosed with T2DM according to WHO 2006 [10] and WHO 2011[11] criteria ≥6 months but less than 10 years.
- HbA1c ≥42 mmol/mol and ≤75 mmol/mol
- If there are concerns about stability of glycaemic control then two measurements of HbA1c varying by no more than ±11 mmol/mol on two measurements separated by at least 30 days will be done. If no concerns regarding stability then this does not need to be done.
- T2DM treated either with lifestyle measures, monotherapy with metformin, sulphonylurea, sodium-glucose co-transporter-2 (SGLT-2) inhibitor, or dipeptidyl peptidase-4 (DPP-IV) inhibitor.
- Liver function tests up to 1.5x the upper limit of normal

3.3 Exclusion criteria

- Unable to give informed consent.
- Hepatobiliary, gastrointestinal or other disease which in the opinion of study investigators will compromise participant safety or scientific value of data obtained.
- Functional diarrhoea with stool frequency ≥5 times a day
- Current treatment with GLP-1 analogues or insulin.
- Sensitivity to CDCA or UDCA in the past
- Current pregnancy (women with childbearing potential will be asked to use high-reliability methods of contraception during the study)
- Alcohol in excess of NHS recommended weekly allowance or substance misuse

- Previous gut resection which in the opinion of the PI will affect results of the study

3.4 Screening visit

All participants will be interviewed by a GCP trained clinician, and informed consent obtained. They will be screened to assess whether they meet the inclusion criteria and this process will comprise a medical history, routine physical examination, basic investigations (full blood count, urea and electrolytes, liver function tests, thyroid function tests, fasting plasma glucose, HbA1c, lipid profile, urine dipstick and electrocardiogram). In those without a previous diagnosis of diabetes, an oral glucose tolerance test will be performed if necessary to establish the diagnosis.

The participants will need to come off their diabetes medication for the duration of the trial and they will be required to monitor their capillary blood glucose twice a day. We will phone the patients during the week they are not seen to check blood glucose measurements and compliance. If patients have a persistently raised blood glucose level >12mmol/L then they will be asked to restart their anti-diabetic medication and withdraw from the trial. If patients require training in order to measure their blood glucose levels from home, we will provide this. Participants will be free to withdraw from the study at any time.

3.5 Study visits

There will be four study visits in total:
Visit 1: baseline, prior to the first dose of BA
Visit 2: after 3 weeks
Visit 3: after 6 weeks
Visit 4: 2 weeks after bile acids are discontinued

For all study visits, the participants will be admitted to the Imperial CRF after an overnight fast and undergo the following procedures (anthropometrics, blood, urine, faecal samples, resting energy expenditure). Prior to each visit, all participants will be asked to refrain from strenuous exercise and consumption of alcohol or caffeine 24 hours before the study visit.

The mixed meal tolerance (MMT) test will happen on all four visits. The two-stage euglycemic hyperinsulinaemic_clamp studies will only be undertaken at visit 1 and visit 3 and will include an overnight stay. All women of child-bearing age will be asked to undergo a pregnancy test.

Commencement of CDCA or UDCA in divided doses or placebo will start after the baseline visit after all study procedures are complete

Table 1: Summary of activities on each visit

Visit	1	2	3	4
Week	0	3	6	8
Anthropometrics	X	X	X	X
Urine/faecal samples	X	X	X	X
Resting Energy Expenditure	X	X	X	X
MMT	X	X	X	X
Visual Analogue Scale	X	X	X	X
Two stage euglycaemic hyperinsulinaemic clamp	X		X	
Commencement of CDCA or UCDA or placebo	X			
Stop CDCA or UCDA or placebo			X	

Anthropometrics:
Measurement of height, weight, bioimpedance study of body fat percentage using a Tanita bioimpedance instrument.

Blood, urine, faecal samples:
These will be taken to monitor T2DM and liver function tests and for the metagenomic and metabolomic studies.

Resting energy expenditure (REE):
This will be measured over a period of 45 minutes using an indirect calorimeter (Gas Exchange Monitor, GEM Nutrition) to measure VO2 (rate of consumption of Oxygen), VCO2 (rate of production of Carbon Dioxide), respiratory quotient (VO_2/VCO_2). The Weir equations will be used to calculate REE, carbohydrate and fat oxidation rate. Protein oxidation rate will be estimated from a urine sample for urinary nitrogen excretion [12]

Mixed Meal Test:
The MMT stimulus used will be two 125 ml bottles of Ensure Compact®, containing 25.5 g protein, 23.4 g of fat, 72 g of carbohydrates, 600 kcal, (Abbott) consumed over 10 minutes (250mls in total). Blood samples for glucose, insulin, gut hormones, bile acids and other metabolites will be sampled prior to mixed meal consumption, at -60 minutes, and then at 0, 15, 30, 60, 90, 120, 180, and 240 minutes after meal consumption. At the end of the visit, the participant will be offered a snack.

Two-stage euglycaemic hyperinsulinaemic clamp (at visit 1 and visit 3):
Participants will undergo their MMT on the first day (as above). They will then consume a standardised lunch, dinner and snack and fast from 10pm onwards. If there are concerns

regarding glucose control, they will be commenced on a variable-rate insulin infusion overnight to keep their blood glucose stable between 4.0-6.0 mmol/l.
On day two, participants undergo the clamp studies. Two venous cannulas will be inserted, one for infusions and the other for blood sampling. At 120 min prior to the start of the clamp, participants will be given a priming bolus and infusion of stably labelled [6,6^2 H$_2$]-glucose for equilibration. After equilibration, a 20% dextrose infusion, spiked with a fixed amount of [6,6^{2}H$_2$]-glucose will be started.

Stage 1 of the clamp commences at t=0 min and consists of an insulin infusion at 0.5mU kg^{-1} min^{-1} (low dose) for 120 min to measure hepatic insulin sensitivity as assessed by Ra, the rate of endogenous glucose production. At 10 min intervals, glucose measurements (using a YSI blood glucose analyser) will be made to keep glucose levels at ±0.5 mmol/L of the baseline t=0 blood glucose value, with adjustment of the 20% dextrose infusion rate. Stage 2 of the clamp commences at t=120 min. The insulin infusion rate is increased to 1.5 mU kg^{-1} min^{-1}(high dose) for 180 min to measure peripheral insulin sensitivity as assessed by Rd, the rate of peripheral glucose uptake. At 10 min intervals, glucose measurements (using a YSI blood glucose analyser) will be made to keep glucose levels at ± 0.5 mmol/L of the baseline t=0 blood glucose value, with adjustment of the 20% dextrose infusion rate. Regular glucose monitoring is necessary to ensure safety and avoid the small risk of hypoglycaemia.

Blood samples will be obtained before the start of the tracer infusions, every 10 min during the final 30 min of the basal period and stages 1 and 2 of the clamp procedure and every 30 minutes between these periods to determine glucose enrichment and concentration, free fatty acid, insulin, c-peptide, glucagon, gut hormones, bile acids and metabolite concentrations. At the same time points participants will be asked to complete appetite visual analogue scales.

At the end of the study, participants will be fed a standardised meal and the glucose infusion continued for up to a further 20 minutes to prevent hypoglycaemia.

3.6 Interventions

CDCA will be supplied by Leadiant Biosciences. UDCA will be obtained as a licensed medication by the Imperial College Healthcare NHS Trust Pharmacy. CDCA is already licensed for cerebrotendinous xanthomatosis and UDCA licensed for dissolution of gallstones. The doses chosen are within the recommended allowance according to the British National Formulary. Tablets may be counted at the end to confirm adherence. Participants will be instructed to come off their diabetes medication 2 weeks prior to commencement of the study and then for its whole duration (10 weeks in total). They will restart after the study has completed.

4. Outcomes

We will interrogate the mechanisms underlying the effects of these BA on metabolism by measuring the following outcomes.

4.1 Primary:

- Post-prandial GLP-1 secretion following a standardised mixed meal tolerance test (MMT) as assessed by area-under-curve (AUC) of GLP-1 levels sampled over 240 minutes.

4.2 Secondary:

- Post prandial secretion of other gut hormones in response to MMT
- Fasting and post prandial secretion of bile acids and other metabolites such as FGF-

19 and FGF-21 in response to the MMT
- Bodyweight change measured as absolute and relative percentage change
- Insulin sensitivity (hepatic and peripheral) using a two-stage euglycaemic hyperinsulinaemic clamp, utilising stably labelled [$^2H_2$]- glucose at baseline and at 6 weeks
- Resting energy expenditure utilising indirect calorimetry[12]

4.3 Exploratory:
- Impact of bile acid treatment on gut bacteria diversity and the metabolome as assessed by 16s rRNA gene sequencing and metabolic phenotyping.[13,14]

5. Statistics

5.1 Randomisation

This will be a double-blind randomised controlled trial to reduce bias. Once volunteers have given their informed consent, they will be randomised using a computerised randomisation programme or website (www.sealedenevlope.com) with stratification for baseline HbA1c (42 to 58 vs 59 to 75).

5.2 Statistical justification

Statistical aspects of the trial have been discussed with the trial statistician Dr Aviva Petrie (UCL Eastman Dental Institute). The study is powered according to the primary outcome of total GLP-1 secretion during an MMT. AUC will be measured for each patient on CDCA, UDCA or placebo. One way ANOVA will be used to detect statistical significance. Using pilot data from the pilot study we have calculated that an n of 10 per group (30 in total) is capable of detecting a minimal clinically significant difference of mean AUC of 500 pmol·min/L with a power of 0.8 and alpha of 0.05 (one way ANOVA). To take account of volunteer dropout we have planned to recruit 12 per group (36 in total). Other data will be summarized using appropriate descriptive statistics, and exploratory linear models may also be used to compare mean values of continuous variables, or to compare categorical outcomes, between the three treatment groups

Data and all appropriate documentation will be stored for up to 5 years after the completion of the study, including the follow-up period.

6. Adverse events and reactions

6.1 Definitions of adverse events and reactions

Adverse event (AE): any untoward medical occurrence in a patient or clinical study subject.
Serious adverse event (SAE): any untoward and unexpected medical occurrence or effect that:
- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

Anticipated adverse events, based on the Summary of Product Characteristics (SPCs) for UDCA and CDCA are alteration of bowel habit (constipation or diarrhoea), pale colour stools, urticaria (rarely).

Non serious AEs
All such events, whether expected or not, should be recorded.

Serious AEs
An SAE form should be completed and faxed to the chief investigator within 24 hours. Hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs. All SAEs should be reported to the REC where in the opinion of the chief investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the chief investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

6.2 Contact details for reporting SAEs

SAEs must be reported to the chief investigator and the sponsor within 24hrs of becoming aware of the event:
CI details: Professor Tricia Tan
Sponsor details: Fax: 0203 311 0203 or email: RGIT@imperial.ac.uk
Please send SAE forms to: Section of Investigative Medicine, Division of Diabetes, Endocrinology & Metabolism, Imperial College London
Tel: 0208 383 3242 (Mon to Fri 09.00 – 17.00) or 07751236735 (24 hours, 7 days a week).

6.3 Follow-up AEs and SAEs

After the initial AE report, the chief investigator or appropriately qualified designee will proactively follow the subject at subsequent visits and contacts. Follow up information about a previously reported SAE must be reported to the sponsor within 24 hours of receiving it. AEs and SAEs will be followed until they resolve, stabilise to a level acceptable to the Investigator or delegates even after the reporting period or the subject is lost to follow-up. Additional measures may be carried out by the Investigator to elucidate as fully as possible the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations or consultation with other health care professionals. In the event that a subject becomes pregnant, the follow-up period will be deemed to have ended when the health status of the child has been determined on its birth.

6.4 Incidental findings

Significant incidental findings from results of any investigations within the study will be recorded accordingly and the patients informed. With their consent, their GP's will be written to in order to inform them of any results that my require ongoing follow up or investigations.

7. Regulatory issues

Ethics approval:
The Study Coordination Centre has obtained approval from the xxx Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Consent:
Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Confidentiality: The chief investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Indemnity: Imperial College Healthcare NHS trust holds negligent harm and non-negligent harm insurance policies which apply to this study.

Sponsor: Imperial College London will act as the main sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

Funding: Novo Nordisk UK Research Foundation and Leadiant Biosciences are funding this study.

Audits: The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

8. Study management

The day-to-day management of the study will be co-ordinated through:
Yasmin Tabbakh
Clinical Research Fellow.
Address: 6th Floor Commonwealth Building
Imperial College London at Hammersmith Campus
Du Cane Road,
London W12 ONN,

UK
Tel: 07964940097 E-mail:y.tabbakh@imperial.ac.uk

9. Reimbursement

Participants will receive £300 upon completion of the trial. These monetary payments will be reimbursement for their travel expenses and time off paid employment.

Researchers will not receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research.

10. Publication policy

Results from this study will be disseminated locally and to the wider scientific community at conferences and in open-access peer-reviewed journals and internal report as appropriate. Any data used for publication will be fully anonymised.

11. References

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