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The effects of empagliflozin on appetite and weight regulation in diabetics

Submission date
20/07/2016

Recruitment status
No longer recruiting

Registration date
20/07/2016

Overall study status
Completed

Last Edited
26/10/2022

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Type 2 diabetes mellitus (T2DM) is a lifelong condition which causes a person's blood sugar level to become too high. People are more likely to develop diabetes if they are overweight, do not exercise, eat an unhealthy diet or are of an older age. People with type 2 diabetes are at an increased risk of cardiovascular disease such as heart attacks and strokes compared to those without the disease. The purpose of this study is to look at the effects of a new diabetes medication known as Empagliflozin (Jardiance™) which is a type of drug known as an "SGLT-2 inhibitor". These drugs are taken by mouth and are already licensed and used in the UK as a diabetes treatment, they have been shown to improve diabetes control and reduce weight. They work by increasing the amount of glucose (sugar) in the urine, which helps to lower the amount of blood glucose in the body. Therefore, glucose is lost through urine in the form of calories, and this results in weight loss over a few months of treatment. However, although these drugs are associated with weight loss, the amount of weight loss seen in people that take this particular drug is less than would be expected considering the amount of calories that are being lost as glucose in their urine.This might be due to how Empagliflozin (Jardiance™) affects a person's appetite. This study will look at a number of different appetite hormones and weight (i.e., whether or not weight changes) in participants who are given Empagliflozin (Jardiance™). The study is also interested in finding out the effect of being on a low calorie diet in addition to taking these drugs.

Who can participate?
Adults aged between 30 and 70 who have T2DM managed by lifestyle control or metformin.

What does the study involve?
Participants are randomly allocated to one of four groups. Those in the first group take tablets containing 25mg Empagliflozin (Jardiance™) once a day for 24 weeks. Those in the second group also take 25mg Empagliflozin (Jardiance™) tablets as well as following a low energy diet. This involves calculating the energy requirements of each participants using body measurements, age and activity levels, and then using written dietary advice on how to make sure less energy is consumed than this amount. Those in the third group take a placebo (dummy pill) once a day for the 24 weeks of the study. Finally, those in the fourth group take a placebo and follow the same low energy diet as those in the second group. Throughout the study, participants attend study

visits at the start and then after 2, 6, 12 and 24 weeks. At these visits, samples of blood are taken in order to measure levels of hormones relating to appetite, as well as having a body scan to measure their weight and body composition.

What are the possible benefits and risks of participating?
There are no direct benefits of participating, however participants will receive £50 at the end of the study to acknowledge their involvement, as well as having travel costs up to £10 and parking reimbursed. Empagliflozin (Jardiance™) is considered to be a safe drug. However, there is a risk of Ketoacidosis and Diabetic Ketoacidosis. This is where because of low blood sugar, body fat is broken down for energy, causing a build-up of a potentially harmful by-product called ketones. There is also a risk of getting a water infection, particularly in female participants. There is a small risk of pain or bruising when blood samples are taken.

Where is the study run from?
Leicester Diabetes Centre (UK)

When is the study starting and how long is it expected to run for?
March 2015 to October 2018

Who is funding the study?
Boehringer Ingelheim Ltd (UK)

Who is the main contact?
Dr Cat Taylor
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Contact information

Type(s)
Scientific

Contact name
Ms Natasha Wileman

Contact details
Diabetes Research Centre
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Additional identifiers

Clinical Trials Information System (CTIS)
2015-001594-40

ClinicalTrials.gov (NCT)
NCT02798744

Protocol serial number

30653

Study information

Scientific Title
SGLT-2 Inhibitor Empagliflozin Effects on Appetite and Weight Regulation: A randomised double-blind placebo-controlled trial (SEESAW)

Acronym
SEESAW

Study objectives
The aim of this study is to investigate the cause for the discrepancy in predicted and observed weight loss with empagliflozin by measuring appetite regulation, energy expenditure and change in weight and body composition.

Ethics approval required
Old ethics approval format

Ethics approval(s)
East Midlands – Derby Research Ethics Committee, 19/04/2016, 16/EM/0040

Study design
Randomised; Interventional; Design type: Treatment, Prevention, Drug, Dietary

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Specialty: Diabetes, Primary sub-specialty: Both; UKCRC code/ Disease: Metabolic/ Diabetes mellitus, Metabolic/ Diabetes mellitus

Interventions
Participants will be randomised to one of four treatment groups on a 1:1:1:1 format with stratification by age [1.≤50years 2.>50years] and Body Mass Indices (BMI) [1. BMI 25.0-29.9kg/m2 2. BMI ≥30.0kg/m2] at the Baseline visit (Visit 1).

Group 1: Participants take Empagliflozin (Jardiance™) 25mg orally for 24 weeks
Group 2: Participants take Empagliflozin (Jardiance™) 25mg orally for 24 weeks + energy restriction diet
Group 3: Participants take a placebo 25mg orally for 24 weeks
Group 4: Participants take a placebo 25mg orally for 24 weeks + energy restriction diet

The daily energy restriction diet for each participant in groups 2 and 4 will be determined using the results of the Indirect Calorimeter and the Mifflin-St Jeor equation (MSJE) which uses height, weight and age to calculate resting energy expenditure and multiplying by the appropriate activity factor (Mifflin 1990). The factor will depend on level of activity categorised

as sedentary, lightly active, moderately active, very active and extra active. The participant will be advised using standard written dietary information on how to maintain this daily energy restriction throughout the study with regular encouragement from the study team by face-to-face and telephone contact. Target energy intake will be reassessed at visit 3 (6 weeks) and visit 4 (12 weeks).

Appetite regulation will be assessed at baseline and 24 weeks by measuring appetite hormones including total and acylated ghrelin, glucagon-like peptide 1 (GLP-1) and total Peptide Y-Y (PYY). Other biochemical analysis will include UGE, insulin, glucose, glucagon and leptin. Body composition will be assessed by measuring weight, waist circumference and body fat percentage (using DEXA). Energy expenditure, insulin sensitivity and secretion, and substrate utilisation will be assessed using indirect calorimetry as well as physical activity measures.

Intervention Type
Other

Phase
Phase IV

Primary outcome(s)
Total Peptide Y-Y (PYY) concentration in blood samples is measured 8 times per visit at 0 weeks, 2 weeks, 6 weeks, 12 weeks and 24 weeks.

Key secondary outcome(s))
1. Ghrelin and GLP-1 concentration in blood samples is measured 8 times per visit at 0 weeks, 2 weeks, 6 weeks, 12 weeks and 24 weeks
2. 2. Weight and body composition is measured by DEXA scanning at baseline and 24 weeks
3. Resting energy expenditure is measured using indirect calorimetry at 0 weeks, 2 weeks, 6 weeks, 12 weeks and 24 weeks
4. Physical activity is measured using physical activity monitors at the familiarisation visit and at 6 weeks, 12 weeks and 24 weeks
5. Full Blood Count, Urea & Electrolytes, Liver Function Test, lipids, HbA1c, C-Reactive Protein, Urine Glucose Excretion, Fasting Plasma Glucose, Free Fatty Acids will be measured once per visit at the familiarisation visit and at 0 weeks, 2 weeks, 6 weeks, 12 weeks and 24 weeks
6. Insulin, glucose, glucagon and leptin will be measured 8 times per visit 0 weeks, 2 weeks, 6 weeks, 12 weeks and 24 weeks

Completion date
31/07/2019

Eligibility

Key inclusion criteria
1. Male and postmenopausal female participants aged between 30-70 years of age inclusive
2. Type 2 diabetes on diet and lifestyle control or stable dose of metformin only for at least 3 months
3. Stable weight (less than 5% change in body weight in last 3 months) – determined by self-reporting or documentation in clinical records
4. HbA1c 48-86mmol/mol (6.5 - 10%)
5. eGFR≥60ml/min/1.73m2
6. BMI ≥ 25kg/m2

7. Able and willing to give informed consent
8. Able to understand English

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
68

Key exclusion criteria
1. Females who are not postmenopausal (as menstrual cycle can affect appetite hormone concentrations) which is defined as “2 years post last menstrual period <50 years of age or 1 year post last menstrual period >50 years of age.”
2. Type 2 diabetes on any other glucose lowering treatment except metformin
3. Patients with Type 1 diabetes
4. Patients on loop diuretics
5. Age <30 years and >70 years
6. BMI <25kg/m2
7. Not able to give informed consent
8. Not able to understand English
9. Moderate to severe renal impairment (eGFR<60ml/min/1.73m2)
10. Unstable diabetes i.e. HbA1c >86mmol/mol (10%), recent hospital admission with diabetic emergency in last 3 months
11. Patients with familial renal glycosuria
12. Patients with recurrent balanitis, vaginal or urinary tract infections
13. Shift workers
14. Patients who have participated in another study of an investigational medicinal product in the last 3 months
15. Active malignancy
16. Serious illness with a life-expectancy of less than 1 year
17. Hypersensitivity to Empagliflozin (Jardiance™) or to any of the excipients
18. Patients with latent autoimmune diabetes in adults (LADA)
19. Patients with a history of chronic pancreatitis
20. Evidence of conditions that lead to restricted food intake or severe dehydration
21. Patients with a history of excessive alcohol consumption
22. Patients on a severely calorie restricted diet (i.e., ≤800 calories per day)

Date of first enrolment
20/09/2016

Date of final enrolment
31/12/2017

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Leicester Diabetes Centre
Leicester General Hospital
Gwendolen Road
Leicester
United Kingdom
LE5 4PW

Sponsor information

Organisation
University of Leicester

ROR
https://ror.org/04h699437

Funder(s)

Funder type
Industry

Funder Name
Boehringer Ingelheim Ltd

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due as the participant information sheet and consent, original protocol and IRAS form did not include this detail. Approvals for the study were granted on the conditions set out in the IRAS application (e.g. that data would not be made available).

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		13/05/2022	26/10/2022	Yes	No
Basic results		04/09/2020	04/09/2020	No	No
HRA research summary			28/06/2023	No	No
Protocol file	version 7.0	20/03/2018	19/10/2022	No	No
Statistical Analysis Plan		12/12/2019	30/12/2019	No	No