The effects of empagliflozin on appetite and weight regulation in diabetics

Submission date	Recruitment status No longer recruiting	[X] Prospectively registered		
20/07/2016		[X] Protocol		
Registration date 20/07/2016	Overall study status Completed	[X] Statistical analysis plan		
		[X] Results		
Last Edited 26/10/2022	Condition category Nutritional, Metabolic, Endocrine	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 cat.taylor@leicester.ac.uk

Contact information

Type(s) Scientific

Contact name Ms Natasha Wileman

Contact details Diabetes Research Centre Gwendolen Road Leicester United Kingdom LE5

Additional identifiers

EudraCT/CTIS number 2015-001594-40

IRAS number

ClinicalTrials.gov number NCT02798744

Secondary identifying numbers 30653

Study information

Scientific Title

SGLT-2 Inhibitor Empagliflozin Effects on Appetite and Weight Regulation: A randomised doubleblind 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

Secondary study design Randomised controlled trial

Study setting(s) Not specified

Study type(s) Treatment

Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

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 measure

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.

Secondary outcome measures

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

Overall study start date

01/03/2015

Completion date

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

Age group

Adult

Sex Both

Target number of participants

Planned Sample Size: 76; UK Sample Size: 76

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 England

United Kingdom

Study participating centre Leicester Diabetes Centre

Leicester General Hospital Gwendolen Road Leicester United Kingdom LE5 4PW

Sponsor information

Organisation

University of Leicester

Sponsor details

University Road Leicester England United Kingdom LE1 7RH

Sponsor type Hospital/treatment centre

ROR

Funder(s)

Funder type Industry

Funder Name Boehringer Ingelheim Ltd

Results and Publications

Publication and dissemination plan

Results of the study will be submitted for presentation and/or poster presentations at applicable and relevant conferences. Submissions will be made once final study data is available, from October 2018 onward.

Intention to publish date

31/12/2020

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?
<u>Statistical Analysis Plan</u>	version 7.0	12/12/2019	30/12/2019	No	No
Basic results		04/09/2020	04/09/2020	No	No
<u>Protocol file</u>		20/03/2018	19/10/2022	No	No
Results article		13/05/2022	26/10/2022	Yes	No
HRA research summary		28/06/2023	No	No	