Glucose absorption inhibitors given during insulin withdrawal in type 1 and type3c diabetes

Submission date	Recruitment status No longer recruiting	Prospectively registered		
28/12/2019		[] Protocol		
Registration date	Overall study status	[] Statistical analysis plan		
02/01/2020	Completed	[X] Results		
Last Edited 07/08/2020	Condition category Nutritional, Metabolic, Endocrine	Individual participant data		

Plain English summary of protocol

Background and study aims

Diabetes is a lifelong condition that causes a person's blood glucose (sugar) level to become too high.

Dapagliflozin is a new class of drug called a SGLT-2 inhibitor that is taken once a day. It is currently prescribed as a glucose lowering medication in people with type 2 diabetes. The drug may also be beneficial in people with type 1 diabetes to reduce the frequency of low blood glucose levels (<4.0mmol/L) and reduce insulin requirements.

Diabetic ketoacidosis occurs when the body is unable to use blood sugar (glucose) because there isn't enough insulin. Instead, it breaks down fat as an alternative source of fuel. This causes a build-up of a potentially harmful by products called ketones. Ketones are bad because they make the blood acid and other chemical processes in the cells do not work normally when the blood and tissues are too acid.

Case reports and early pilot clinical trials indicate that when SGLT2 inhibitors are prescribed in patients with known insulin deficiency they may be at risk of developing the potentially life threatening state of ketoacidosis in the presence of a normal glucose level. This condition can be very frightening and may need treatment in an intensive care unit.

When people take the study medication they may not be aware they are at risk of developing ketoacidosis because blood glucose levels may not increase, and the only sign that they have developed ketoacidosis is that their ketone levels have increased or they become unwell and start to vomit. However, unlike blood glucose levels, people do not routinely measure their ketone levels, therefore, an increase in ketones is unlikely to be detected (or may be missed).

The aim of this research is to develop an understanding of how Dapagliflozin regulates blood glucose levels in periods of insulin deficiency. The metabolic assessment day involves inducing a state of insulin deficiency in a controlled way and monitoring glucose and ketone levels. Ketone levels will rise. The study will be stopped and insulin given before the ketones produce a state of acidosis (ketoacidosis). It is not the intention to induce ketoacidosis but to understand how the drug works in insulin deficient patients.

Who can participate?

Patients with type 1 (where the pancreas doesn't produce any insulin) or type 3c (insulin deficiency following pancreatic conditions such as chronic pancreatitis or pancreatic surgery) diabetes, aged 18 – 65 years with HbA1c is greater or equal to 6.5% and less than 9%.

What does the study involve?

Participation in the study will last approximately 64 days.

Participants will be required to attend three visits. One will be a screening visit and the other two visits will be metabolic assessment days. Participants will need to attend at 22.00 the night before the metabolic study day and will go home the next evening around 18.00.

Participants will be randomly allocated to receive Dapagliflozin or placebo for seven days, after which they will have a metabolic assessment. Later, the participants will receive the opposite treatment, again for seven days, followed by another assessment.

To prevent developing ketoacidosis during the metabolic assessment day, the study will be stopped in the event of blood glucose rising above 18mmol/L, bicarbonate dropping below 15mmol/L or if blood becomes acidic, evidenced by venous pH falling below 7.35 or point of care capillary 3-beta Hydroxybutyrate level of >5.0.

What are the possible benefits and risks of participating?

The results of the study will potentially provide a better understanding of how the class of drug works in people with type 1 and type 3c diabetes. Participants' diabetes control may change while taking the study drug and they will receive advice on blood sugar control from the study clinician. Participants are not likely to experience any immediate benefits but there may be benefits for future people with type 1 and type 3c diabetes.

Where is the study run from? Royal Surrey County Hospital, Guildford, UK

When is the study starting and how long is it expected to run for? January 2018 to August 2019

Who is funding the study? 1. Diabetes UK 2. AstraZeneca, UK

Who is the main contact? Dr Roselle Herring roselle.herring@nhs.net

Contact information

Type(s) Scientific

Contact name Dr Roselle Herring

ORCID ID https://orcid.org/0000-0002-8267-6236

Contact details

Cedar Centre Royal Surrey County Hospital Egerton Road Guildford United Kingdom GU2 7XX +44 (0)1483 571122 Ext 2414 roselle.herring@nhs.net

Additional identifiers

EudraCT/CTIS number 2015-002094-38

IRAS number 215268

ClinicalTrials.gov number Nil known

Secondary identifying numbers 3, IRAS 215268

Study information

Scientific Title

Metabolic effects of an SGLT2 inhibitor (dapagliflozin) during a period of acute insulin withdrawal and development of ketoacidosis in people with type 1 diabetes

Acronym

SIDS

Study objectives

 Treatment with Dapagliflozin will result in a statistically significant difference in fasting plasma glucose concentration at 600 minutes following insulin cessation (or at last measured concentration prior to rescue) when compared to treatment with placebo in each of two independent studies performed on Type 1 and Type 3c people with diabetes.
Treatment with Dapagliflozin will result in a statistically significant difference lipid flux of Dapagliflozin when compared to placebo following insulin withdrawal

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approved 07/02/2017, South Central - Berkshire B Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT; +44 (0)207 104 8199; nrescommittee.southcentral-berkshireb@nhs.net), ref: 17/SC/0005

Study design

Phase IV single centre randomized double-blind controlled trial

Primary study design Interventional

Secondary study design Randomised cross over trial

Study setting(s) Hospital

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

Type 1 diabetes and Type 3c diabetes

Interventions

Participants received in random order 7 days of placebo or dapagliflozin.

The expected duration of participant participation is approx. 64 days.

Randomisation procedure:

The participant will be assigned a study identification number and randomised to receive in random order Dapagliflozin or placebo.

To prevent developing ketoacidosis during the metabolic assessment day, the study will be stopped in the event of blood glucose rising above 18mmol/L, bicarbonate dropping below 15mmol/L or if blood becomes acidic, evidenced by venous pH falling below 7.35 or point of care capillary 3-beta Hydroxybutyrate level of >5.0.

Intervention Type Drug

Phase Phase IV

Drug/device/biological/vaccine name(s)

Dapagliflozin

Primary outcome measure

Plasma glucose concentration at 600 minutes following insulin cessation or at the time of glycaemic rescue, whichever occurs first, measured by blood test

Secondary outcome measures

1. Endogenous glucose production

- 2. Peripheral glucose uptake
- 3. Glycerol rate of appearance

Stable isotopes of glucose and glycerol will be infused from -120 to 600 minutes. From -120 to 0 minutes, blood samples will be taken to measure glucose and glycerol enrichment

4. Urinary glucose excretion

Urine samples will be collected at 2 hour intervals for measurement of spot glucose and urinary ketones (acetoacetic acid and acetone) until 600 minutes

5. Non-esterified fatty acid production 6. Ketone body production NEFA, and 3-beta hydroxybutyrate will be taken at 20minute intervals until 180 minutes and then at 30minute intervals until 600 minutes

Overall study start date

21/08/2015

Completion date 01/08/2019

Eligibility

Key inclusion criteria

1. Able in the opinion of the investigator, and willing to give informed consent obtained before any study-related activities

2. Type 1 diabetes or type 3c (chronic pancreatitis or undergone pancreatic surgery) according to clinical judgment

3. Duration of type 1 or type 3c diabetes (chronic pancreatitis or undergone pancreatic surgery) greater than 12 months

4. Current treatment basal bolus insulin regime or insulin pump therapy

5. Aged 18 – 65 years

6. BMI of less than 35

7. HbA1c of greater or equal to 6.5% and less than 9%

8. Able and willing to complete the study

9. Patients who are or who have previously been involved in research are eligible provided they have not received an investigational drug within one month of entry into the study

Participant type(s)

Patient

Age group

Adult

Lower age limit 18 Years

Sex Both

Target number of participants 12

Total final enrolment

Key exclusion criteria

1. Cannot adequately understand verbal and / or written explanations given in English

2. LADA –latent autoimmune diabetes in adults due to differing nature of the illness/Type 1

3. Confirmed excessive and compulsive drinking of alcohol i.e. alcohol abuse as determined from

GP medical notes by the Fast Alcohol Screening Test (FAST) or history of previous alcohol abuse 4. Restricted food intake (e.g. on VLC diets) - as this depletes the person of calories and may affect your data. Consider excluding Individuals on a severe calorie restricted diet <800cals/day. Determined by history

5. Diagnosis of osteoporosis confirmed by DEXA scan

6. Proliferative retinopathy that has required acute treatment within last three months

7. Moderate to severe renal impairment (creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m²

8. History of unstable or rapidly progressing renal disease

9. Severe hepatic insufficiency / and or significant abnormal liver function defines as aspartate aminotransferase (AST) >3x upper limit of normal (ULN) and / or alanine aminotransferase (ALT) > 3ULN

10. Positive serologic evidence of current infectious liver disease including Hepatitis B viral antibody IGM, Hepatitis B surface antigen and Hepatitis C virus antibody

11. Congestive heart failure defined as New York Heart Association (NYHA) class III and IV, unstable or acute congestive heart failure. Note: eligible patients with congestive heart failure, especially:

11.1. Uncontrolled cardiac arrhythmias

11.2. Uncontrolled hypertension (BP greater than 160/90)

12. Mental incapacity

13. Pregnancy or breastfeeding women

14. Those of child-bearing potential not taking adequate contraception precautions. Adequate protection is defined as barrier protection, oral contraceptive pill or intrauterine device

15. Volume depleted patients, patients at risk of volume depleting due to co-existing conditions or concomitant medications, such as loop diuretics should have careful monitoring of their volume status

16. History of unstable angina.

17. Recent Cardiovascular Events in a patient:

17.1. Acute Coronary Syndrome (ACS) within 2 months prior to enrolment

17.2. Hospitalisation for unstable angina or acute myocardial infarction within 2 months prior to enrolment

17.3. Acute Stroke or TIA within 2 months prior to enrolment

17.4. Less than 2 months post coronary artery revascularization

17.5. History of diabetic ketoacidosis (DKA) requiring medical intervention (e.g. Accident and Emergency and/or hospitalisation) within 1 month prior to the Screening visit

18. Known or suspected allergy to study products

19. Known lactose-intolerant

20. Any other medical or psychological conditions that would interfere with the study participation

Date of first enrolment

29/01/2018

Date of final enrolment

01/08/2019

Locations

Countries of recruitment England

United Kingdom

Study participating centre

Centre for Endocrinology Diabetes and Research Royal Surrey County Hospital Egerton Road Guildford United Kingdom GU2 7XX

Sponsor information

Organisation University of Leicester

Sponsor details

Diabetes Research Centre/Department of Health Sciences University of Leicester Leicester England United Kingdom LE5 4PW +44 (0)116 258 6481 uolsponsor@le.ac.uk

Sponsor type University/education

Website http://www.le.ac.uk/

ROR https://ror.org/04h699437

Funder(s)

Funder type Charity **Funder Name** Diabetes UK

Alternative Name(s) DIABETES UK LIMITED, British Diabetic Association

Funding Body Type Private sector organisation

Funding Body Subtype Trusts, charities, foundations (both public and private)

Location United Kingdom

Funder Name AstraZeneca

Alternative Name(s) AstraZeneca PLC, Pearl Therapeutics

Funding Body Type Government organisation

Funding Body Subtype For-profit companies (industry)

Location United Kingdom

Results and Publications

Publication and dissemination plan

Presentation at national and international conferences and publication in a peer-reviewed journal.

Intention to publish date

01/01/2020

Individual participant data (IPD) sharing plan

All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary Other

Study outputs							
Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?		
<u>Results article</u>	results	08/07/2020	07/08/2020	Yes	No		
HRA research summary			28/06/2023	No	No		