ISRCTN74621291 https://doi.org/10.1186/ISRCTN74621291

A study looking at the effects of blocking stress hormone activation on skin function and wound healing in patients with type 2 diabetes

Submission date
16/10/2017

Recruitment status
No longer recruiting

Registration date
18/10/2017

Overall study status
Completed

Last Edited
18/10/2022

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
Diabetes is a condition that causes blood sugar to become too high. Diabetes is the fastest-growing health problem in the UK affecting over three million people in England. Most of these cases are “type 2” diabetes caused by an unhealthy lifestyle and obesity. By 2035, diabetes will affect 1 in 10 people in the UK. The number of diabetes complications of is also increasing. These include foot ulcers which can lead to amputation. Treatments for foot ulcers often fail and diabetes costs the NHS £1 million an hour. During stress, the body produces the hormone cortisol (a glucocorticoid) which causes skin thinning, poor wound healing and infections. Cortisol is activated in skin by the enzyme 11β-HSD1. Studies in patients with diabetes showed that blocking this enzyme improved disease by reducing body weight, blood sugar and cholesterol levels. Blocking this enzyme could also improve skin function and wound healing. The aim of this study is to test healing in patients with type 2 diabetes using 11β-HSD1.

Who can participate?
Adults with type 2 diabetes.

What does the study involve?
Participants are asked to attend a short screening visit to check heart function, blood pressure and blood tests. Participants are randomly allocated to one of two groups. Those in the first group receive tablets containing the test drug. Those in the second group receive tablets which do not contain the test drug (dummy). Participants are asked to take the tablet for 35 days twice daily. Participants are asked to provide two 24 hour urine samples, four blood samples and five skin biopsies (two at one visit and three at another visit). Skin biopsies are taken from the arm after numbing the area with an injection. Participants are also measured for skin thickness, water loss, water content and nerve function using pain-free probes. Weight, height, blood pressure, waist and hip circumference are also recorded.

What are the possible benefits and risks of participating?
Patients taking the drug tablets may notice a temporary improvement in their diabetes such as lower blood pressure, lower blood sugar, lower cholesterol and weight loss. Patients will

contribute to research which may lead to new treatments which they may benefit from in the future. They will be paid £180 in total for their time and travel. The study has been designed with patient safety and comfort as our top priority and has full ethical approval. Possible but unlikely risks include biopsy infection, discovery of previously unknown health issues or side-effects such as mild to moderate stomach upset or headache. If these occur we will take appropriate medical action.

Where is the study run from?
1. St James's University Hospital (UK)
2. Chapel Allerton Hospital (UK)

When is the study starting and how long is it expected to run for?
January 2016 to May 2019 (updated 31/03/2020, previously: April 2019)

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Ana Tiganescu, a.tiganescu@leeds.ac.uk

Contact information

Type(s)
Public

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT03313297

Clinical Trials Information System (CTIS)
2017-001351-31

Protocol serial number

34599

Study information

Scientific Title
GC-SHealD (Glucocorticoids and Skin Healing in Diabetes) :A double-blind, randomized, placebo-controlled phase II pilot trial investigating efficacy, safety and feasibility of 11β-hydroxysteroid dehydrogenase type 1 inhibition by AZD4017 to improve skin function and wound healing in patients with type 2 diabetes

Acronym
GC-SHealD

Study objectives
The aim of this study is to test healing in patients with T2DM using the selective 11β-HSD1 inhibitor AZD4017 which is approved for use in clinical trials.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West - Greater Manchester Central Research Ethics Committee, 10/08/2017, ref: 17/NW /0283

Primary study design
Interventional

Study design
Randomised; Interventional; Design type: Treatment, Process of Care, Drug

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Specialty: Diabetes, Primary sub-specialty: Type 2; UKCRC code/ Disease: Metabolic and Endocrine/ Diabetes mellitus, Skin/ Other disorders of the skin and subcutaneous tissue

Interventions
This study aims to conduct a double-blind, randomised, parallel group, placebo-controlled phase II pilot trial of 35 days' duration with 400mg oral AZD4017 twice daily (n=15) or placebo (n=15) in patients with type 2 diabetes mellitus. Participants are followed up for 7 days after treatment cessation.

Taking part does affect routine diabetes treatment or access to care. The study involves 8 hospital visits. Patients receive either tablets containing the test drug or tablets which do not contain the test drug (dummy). These are given in a random way and neither patients nor the research team will know which tablets were provided until the end of the study. The tablets containing the drug AZD4017 blocks the enzyme to lower cortisol levels. AZD4017 has already been studied in human volunteers and is safe and well tolerated at the dose and duration in this study. Participants are asked to attend a short screening visit to check heart function, blood

pressure and blood tests. Participants who pass screening will be enrolled into the trial. They are asked to provide two 24 hour urine samples, four blood samples and five skin biopsies (two at one visit and three at another visit). Skin biopsies are taken from the arm after numbing the area with an injection. They are smaller than a ballpoint pen lid hole, do not require stitches and will not leave a noticeable scar. Participants are also measured for skin thickness, water loss, water content and nerve function using pain-free probes. Weight, height, blood pressure, waist and hip circumference are also recorded.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
AZD4017

Primary outcome(s)
11β-HSD1 activity in skin measured by evaluating conversion of radiolabelled 11β-HSD1 substrate (cortisone) to 11β-HSD1 product (cortisol) at baseline and day 28.

Key secondary outcome(s)
1. Systemic 11β-HSD1 activity is measured by evaluating tetrahydrocortisol to tetrahydrocortisone urinary metabolites ratios at baseline and day 35
2. AZD4017 in plasma and skin is measured by pharmacokinetic analysis at day 28
3. Adverse Event-related participant withdrawals (safety) will be measured by reviewing patient notes at day 42
4. Clinical evaluation of biopsy site (safety) will be measured by reviewing the patient notes at days 2, 7, 28, 30, 35 and 42
5. Body mass index (safety) will be measured as body weight (in kilograms to the nearest 100 grams) divided by the square of the body height (in metres to the nearest centimetre) at baseline and day 35
6. Waist-hip ratio (safety) will be measured as waist measurement (to the nearest cm) divided by hip measurement (to the nearest cm) at baseline and day 35
7. Blood pressure (safety) will be measured systolic (maximum) pressure over diastolic (minimum) pressure at baseline, day 35 and day 42
8. Blood tests (safety) will be conducted for HbA1c, lipids (total and high density lipoprotein cholesterol and triglycerides), full blood count, liver function (alanine and aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, albumin and bilirubin), estimated glomerular filtration rate, kidney function (sodium, potassium, urea and creatinine), adrenal function (testosterone and dehydroepiandrosterone sulphate) and thyroid function (thyroid stimulating hormone and free thyroxine) at baseline and days, 7, 28, 35 and 42
9. Adverse event reporting (safety) will be measured by reviewing the patient notes at baseline and days 2, 7, 28, 30, 35 and 42
10. Sudomotor nerve function (skin function) will be conducted using a Sudoscan device at baseline and day 35
11. Skin hydration (skin function) will be measured using a Corneometer CM 825 device at baseline and day 35
12. Epidermal barrier function (skin function) will be measured by evaluating trans-epidermal water loss (TEWL) using a Tewameter TM 300 device at baseline and day 35
13. Epidermal barrier integrity (skin function) will be measured by evaluating the number of D-

Squame tape strips required to induce barrier disruption (TEWL of 40-50 g/h/m2) at baseline and day 28
14. Epidermal barrier recovery (skin function) will be measured by evaluating TEWL after barrier disruption at baseline and days 2, 7, 28, 30 and 35
15. Skin thickness (skin function) will be measured by Optical Coherence Tomography imaging at baseline and day 35
16. Wound healing (skin function) will be measured by Optical Coherence Tomography imaging of biopsy wounds at days 2, 7, 30 and 35
17. Skin RNA-seq gene expression profiling (skin function) will be measured by RNA extraction and Next Generation Sequencing of mRNA at baseline and day 28
18. Feasibility will be measured by evaluating eligibility, recruitment, consent, randomization, adherence, retention and data completeness captured using Logs, Informed Consent Forms, Pharmacy Records and Diary Cards at the end of the study

Completion date
21/05/2019

Eligibility

Key inclusion criteria
1. Able and willing to consent
2. T2DM with HbA1c ≤11% (≤97 mmol/mol) at screening while taking standard therapy at a stable dose for ≥10 weeks
3. Aged 18 and older

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
28

Key exclusion criteria
1. Women of child-bearing potential
2. Active leg/foot ulceration
3. Clinically relevant acute ECG anomalies
4. Uncontrolled hypertension
5. Endocrine disorder (other than T2DM), including type 1 or secondary diabetes (except treated hypothyroidism)

6.Gilbert's disease
7. Alanine aminotransferase and/or aspartate aminotransferase and/or alkaline phosphatase >1.5x ULN
8. Bilirubin >1.5x ULN
9. eGFR <45 ml/min/m2
10. CK >2x ULN
11. Drug abuse within the last year
12. Any GC treatment within 3 months of screening
13. Anti-coagulant medication
14. Probenecid therapy
15. Medical/surgical procedure or trauma during IMP administration or one week after IMP cessation (excluding skin biopsies)
16. Involvement in trial planning and/or conduct
17. Participation in other clinical study within 1 month
18. Deemed inappropriate to participate by the trial team

Date of first enrolment
06/04/2018

Date of final enrolment
25/01/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Chapel Allerton Hospital
Chapeltown Road
Leeds
United Kingdom
LS7 4SA

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository: Unblinded anonymised full Case Report Form data will be stored as an electronic spreadsheet file in the Research Data Leeds Repository Research Data Leeds repository http://archive.researchdata.leeds.ac.uk

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/02/2022	04/02/2022	Yes	No
HRA research summary			28/06/2023	No	No

Protocol (preprint)	non-peer-reviewed protocol in preprint	26/03/2021	15/06 /2021	No	No
Protocol file	version 2	24/10/2018	18/10 /2022	No	No
Statistical Analysis Plan			18/10 /2022	No	No