Clinical trial results:
A double-blind, randomized, placebo-controlled phase II pilot trial investigating efficacy, safety and feasibility of 11-hydroxysteroid dehydrogenase type 1 inhibition by AZD4017 to improve skin function and wound healing in patients with type 2 diabetes

Summary

EudraCT number	2017-001351-31
Trial protocol	GB
Global end of trial date	12 May 2019

Results information

Result version number	v2 (current)
This version publication date	30 November 2020
First version publication date	29 August 2020
Version creation reason	• Correction of full data set Update required to amend the end point table heading to '24 hour 11β-HSD1 activity % conversion/24 hours'. Please see attached file note detailing the change
Summary attachment (see zip file)	GC-SHealD supplementary figures (GC SHealD Figures (1).docx)

Trial information

Trial identification

Sponsor protocol code	ED17/93260

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	Worsley Building, Leeds, United Kingdom, LS2 9JT
Public contact	Ana Tiganescu, University of Leeds, 0113 3438336, a.tiganescu@leeds.ac.uk
Scientific contact	Ana Tiganescu, University of Leeds, 0113 3438336, a.tiganescu@leeds.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2019
Global end of trial reached?	Yes
Global end of trial date	12 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

We will determine if the treatment is able to achieve it's intended effect (decrease target enzyme activity) in skin of patients with type 2 diabetes

Protection of trial subjects:

The Trial was was monitored multiple times by the Sponsor over it's life cycle, and was conducted in accordance with GCP. The Chief Investigator retained overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol,principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996.

Background therapy:

Chronic, non-healing wounds e.g. diabetic foot ulcers (DFU) are a common worldwide health problem that have substantial medical and socioeconomic importance and represent a major unmet clinical need [1]. In Europe, 1-1.5% of the population has a problem wound at any one time. The average cost per episode is 6,650€ for leg ulcers and 10,000€ for foot ulcers, accounting for 2-4% of the healthcare budget and likely to escalate with an increasingly elderly and diabetic population [2]. In the Leeds/Bradford region the overall prevalence of wounds is 2.8-3.6 people per 1000 population [3], up to 50% of which are chronically inflamed, non-healing wounds. Costs for wound care in the UK are estimated at £2.03-3.8 million per 100,000 population [4] and diabetes currently accounts for approximately 10% of the total health resource expenditure and is projected to account for around 17% in 2035/2036 [5].

Evidence for comparator:

The profound atrophogenic effects of glucocorticoids (GC) on human skin structure and function are well documented, causing decreased collagen content, increased transepidermal water loss (TEWL), dermal and epidermal thinning, telangiectasia, impaired wound healing (WH) and increased infection risk [6-13]. Keratinocytes, melanocytes, fibroblasts and sebocytes play significant roles as GC targets in these processes [11, 14]. These effects arise from GC excess including systemic [7, 8] and topical [10] GC therapy, Cushing’s disease [6] and psychological stress [13, 15-17].

Actual start date of recruitment	03 July 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible participants will be identified using medical records from the Diabetes Clinic at St. James's University Hospital by the Chief Investigator or an authorized member of the direct care team. Potentially eligible participants will be selected using a computerized search and review of medical records.

Pre-assignment

Screening details:

Assenting patients will then be invited to attend a screening visit where they will be formally assessed for eligibility and asked to provide written, informed consent.The original Informed Consent Form will be filed in the Trial Master File (TMF), with one copy given to the patient and one filed in the hospital notes.

Period 1

Period 1 title	Main Trial Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Treatment groups will be allocated on a fully randomised basis. A randomization schedule will be generated by the dedicated trials pharmacy representative who has signed/dated the staff delegation log and is not otherwise associated with this study. Patients will be randomised in a 1:1 treatment allocation ratio to either AZD4017 or placebo. The randomization schedule will be stored in a password protected file accessible only to the dedicated trials pharmacy

Arms

Are arms mutually exclusive?	Yes
Arm title	AZD4017

Arm description: -

Arm type	Experimental
Investigational medicinal product name	AZD4017
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The AZD4017 tablets and matching placebo will be supplied to the dedicated trial pharmacy by Almac in bottles of 32, 200mg tablets with a unique kit number (sufficient for 8 days per bottle); 4 bottles will be dispensed at Visit 1 and 1 bottle will be dispensed at Visit 4

Arm title	Placebo to match AZD4017

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo to match AZD4017
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The AZD4017 tablets and matching placebo will be supplied to the dedicated trial pharmacy by Almac in bottles of 32, 200mg tablets with a unique kit number (sufficient for 8 days per bottle); 4 bottles will be dispensed at Visit 1 and 1 bottle will be dispensed at Visit 4 (sufficient for 5 days overage per participant).

Number of subjects in period 1	AZD4017	Placebo to match AZD4017
Started	14	14
Completed	14	13
Not completed	0	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups

Reporting group title	Main Trial Period

Reporting group description: -

Reporting group values	Main Trial Period	Total	
Number of subjects	28	28	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	60.21		
standard deviation	± 13.67	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	22	22	

End points

End points reporting groups

Reporting group title	AZD4017
Reporting group description: -	
Reporting group title	Placebo to match AZD4017
Reporting group description: -	

Primary: 24hr 11bHSD1 activity radioassay (% conv per 24 hrs): Day 28

End point title	24hr 11bHSD1 activity radioassay (% conv per 24 hrs): Day 28[1]
End point description:	
End point type	Primary
End point timeframe:	
Measured at Day 28 of treatment.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please see Figure 1 of the attached document for full details of Primary Endpoint analysis performed

End point values	AZD4017	Placebo to match AZD4017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	13		
Units: % conv/hr				
arithmetic mean (standard deviation)	12.58 (± 5.64)	12.38 (± 4.51)		

Attachments (see zip file)	End Point Figures/GC SHealD Figures.docx File note explaining change in heading /2020.10.29 Incorrect

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Any reported AE will record the following information directly into the CRF at Visits 2, 3, 4, 5 and 6
- Type of AE defined by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 preferred term
- Date of onset
- Severity

Adverse event reporting additional description:

Any reported AE will record the following information directly into the CRF at Visits 2, 3, 4, 5 and 6
- Type of AE defined by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 preferred term
- Date of onset
- Severity (defined by CTCAE v5.0)
- Relation to study intervention
- Date of Resolution

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5

Frequency threshold for reporting non-serious adverse events: 5 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: One Adverse Event was reported on the trial. Please see Figure 2 of the attached document
for full details.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2018	Protocol was amended to v2.0, to include an extra TEWL measurement at visits 2, 3 and 5.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported