



## 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           | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Update required to amend the end point table heading to '24 hour 11 $\beta$ -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 its intended effect (decrease target enzyme activity) in skin of patients with type 2 diabetes

Protection of trial subjects:

The Trial was monitored multiple times by the Sponsor over its 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:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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          |
| <b>Arm title</b>                       | 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

|  |                          |
|--|--------------------------|
| <b>Arm title</b>                       | 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).

| <b>Number of subjects in period 1</b> | AZD4017 | Placebo to match<br>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<br>(gestational age < 37 wks) |                   | 0     |  |
| Newborns (0-27 days)                                  |                   | 0     |  |
| Infants and toddlers (28 days-23<br>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 <sup>[1]</sup> |
|-----------------|--|

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)           |  |  |

|                                   |  |
|-----------------------------------|--|
| <b>Attachments (see zip file)</b> | End Point Figures/GC SHealD Figures.docx<br>File note explaining change in heading /2020.10.29 Incorrect |
|-----------------------------------|--|

### Statistical analyses

No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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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 |
|-----------------|------------|

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### Dictionary used

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|                    |       |
|--------------------|-------|
| Dictionary name    | CTCAE |
| Dictionary version | 5     |

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

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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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported