# Clinical trial results:
# Targeting Iatrogenic Cushing's Syndrome with 11-hydroxysteroid dehydrogenase type 1 Inhibition

## Summary

| | |
|---|---|
| EudraCT number | 2016-003060-40 |
| Trial protocol | GB |
| Global end of trial date | 27 February 2019 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 19 November 2021 |
| First version publication date | 19 November 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | TICSI |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03111810 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | 212634 : IRAS ID |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | University of Oxford |
| Sponsor organisation address | Churchill Hospital, Oxford, United Kingdom, |
| Public contact | CTRG (via Heather House), University of Oxford, Clinical Trials and Research Governance, ctrg@admin.ox.ac.uk |
| Scientific contact | CTRG (via Heather House), University of Oxford, Clinical Trials and Research Governance, ctrg@admin.ox.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 | 30 September 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 February 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 February 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Our main research objectives is…

1. To demonstrate the beneficial effect of the selective 11β-HSD1 inhibitor, AZD4017, upon the prednisolone-induced deterioration in glucose uptake into skeletal muscle and glucose production by the liver.

Protection of trial subjects:

Potential risks and side effects of the interventions, were explained to participants prior to commencing treatment. AEs were recorded by the investigators as part of the study. All studies were performed in a CRU fully equipped for dealing with emergencies. A physician will be present throughout the studies and the research nurses receive regular training in BLS. Venipuncture for the screening sample may cause momentary discomfort. Insertion of a venous cannula under local anesthetic on the study day normally only causes momentary discomfort because of the 'sting' of the anesthetic. Cannulation sites may bruise and there is a possible risk for clotting or infection. We minimized these risks by the use of good clinical practice and sterile techniques. The potential risk of low blood sugar at the end of the clamp procedure was minimized by ensuring all volunteers are provided with a meal and their blood sugar levels are measured repeatedly to ensure that they are stable at the end of the procedure. At the screening visit we assessed the volunteer’s hemoglobin status to ensure there was no anemia. As a precaution we advised participants to refrain from blood donation for 3 months after the study. During the course of the study day we ensured participants stayed well hydrated and before leaving the CRU at the end of the study we ensured that they had a light meal. We also provided advice regarding the 24-48 hour period after the study to ensure that they consumed sufficient non-alcoholic fluid, food and did not undertake any strenuous exercise or activities. Any stable isotope that we introduced directly into the blood will had been sterility and pyrogenicity tested. The DEXA scans performed on the 2 study days involved exposure to a small radiation dose. There was a small risk of infection and bruising after inserting microdialysis catheters or taking fat and muscle biopsies. This risk was minimized by the use of sterile techniques and applying pressure on wounds.

Background therapy:

Prednisolone is widely used in routine clinical practice (indeed at higher dose and for longer durations) and is generally well tolerated and safe. Possible side effects of the prednisolone treatment that may be anticipated in advance including the possibility of mild fluid retention and ankle swelling and difficulty in sleeping. Volunteers will be warned about these possible effects.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 05 June 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 32 |
| Worldwide total number of subjects | 32 |
| EEA total number of subjects | 0 |

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) | 32 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment period: 25/5/2017 to 13/2/2019
Territory: Oxford, UK

### Pre-assignment

Screening details:

Male volunteers without diabetes
- BMI 20-30
- Age 18-60
- BP<160/100mmHg or on stable antihypertensive therapy for >3months
- No known hypercholesterolaemia or on stable lipid lowering therapy for >3 months
- No contraindications to AZD4017 or prednisolone treatment

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Subject, Data analyst, Carer, Assessor |

Blinding implementation details:

randomization schedule will be drawn up by Almac group who will be providing packaged and labeled AZD4017/placebo on behalf of AstraZeneca. All investigators will remain blinded and a 'dummy' randomization schedule will be reviewed and signed off by the investigative team prior to shipment of the study medication (Quality Assurance Agreement in place). Randomization will be in blocks of 4 volunteers (2 AZD4017 and 2 to placebo). Blinding will be by means of scratch cards.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo and prednisolone |

Arm description:

Placebo

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | placebo and prednisolone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

placebo; one tablet twice daily and prednisolone; 20mg once daily for 7 days

| | |
|---|---|
| **Arm title** | AZD4017 and prednisolone |

Arm description:

AZD4017 and prednisolone given for 7 days

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

Dosage and administration details:

AZD4017; 400mg twice daily and prednisolone; 20mg once daily for 7 days.

| **Number of subjects in period 1** | Placebo and prednisolone | AZD4017 and prednisolone |
|---|---|---|
| Started | 16 | 16 |
| Completed | 16 | 16 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo and prednisolone |
| Reporting group description: | |
| Placebo | |
| Reporting group title | AZD4017 and prednisolone |
| Reporting group description: | |
| AZD4017 and prednisolone given for 7 days | |

| Reporting group values | Placebo and prednisolone | AZD4017 and prednisolone | Total |
|---|---|---|---|
| Number of subjects | 16 | 16 | 32 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 16 | 16 | 32 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 38.7 | 35.6 | |
| standard deviation | ± 12.4 | ± 11.1 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 16 | 16 | 32 |
| BMI<br>Units: kg/m2 | | | |
| arithmetic mean | 25.8 | 24.4 | |
| standard deviation | ± 1.9 | ± 2.5 | - |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | Subjects included in analysis - Placebo and prednisolone |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Subjects included in analysis completed the protocol correctly. | |
| Subject analysis set title | Subjects included in analysis - AZD4017 and prednisolone |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Subject were included in the analysis only if they completed the trial as set out by the protocol. | |

| **Reporting group values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | |
|---|---|---|---|
| Number of subjects | 15 | 15 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 15 | 15 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 39 | 36.5 | |
| standard deviation | ± 12.7 | ± 11 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 15 | 15 | |
| BMI<br>Units: kg/m2 | | | |
| arithmetic mean | 25.8 | 24.5 | |
| standard deviation | ± 2 | ± 2.5 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo and prednisolone |
| Reporting group description: Placebo | |
| Reporting group title | AZD4017 and prednisolone |
| Reporting group description: AZD4017 and prednisolone given for 7 days | |
| Subject analysis set title | Subjects included in analysis - Placebo and prednisolone |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Subjects included in analysis completed the protocol correctly. | |
| Subject analysis set title | Subjects included in analysis - AZD4017 and prednisolone |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Subject were included in the analysis only if they completed the trial as set out by the protocol. | |

### Primary: Change observed in glucose disposal (Low insulin) from pre-treatment measurement to post-treatment assessment

| | |
|---|---|
| End point title | Change observed in glucose disposal (Low insulin) from pre-treatment measurement to post-treatment assessment |
| End point description: | |
| End point type | Primary |
| End point timeframe: Change from pre-treatment measurement to post-treatment measurement. | |

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: mg/kg/min | | | | |
| arithmetic mean (standard deviation) | 4.61 (± 2.28) | 4.59 (± 1.98) | | |

| | |
|---|---|
| **Attachments (see zip file)** | Glucose Disposal (Low insulin)/Screenshot 2021-11-02 at |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Generalised linear models |
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |

| | |
|---|---|
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| P-value | < 0.05 [2] |
| Method | Generalised linear models |

Notes:

[1] - Per Protocol

[2] - 0.17

## Secondary: M/I value (Low insulin)

| | |
|---|---|
| End point title | M/I value (Low insulin) |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Change from pre-treatment to post-treatment.

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: mg/kg/min per mU/mL | | | | |
| median (inter-quartile range (Q1-Q3)) | 30.98 (18.72 to 35.45) | 28.11 (16.58 to 37.00) | | |

### Statistical analyses

| **Statistical analysis title** | Generalised liniear model |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other[3] |
| P-value | < 0.05 [4] |
| Method | Mixed models analysis |

Notes:

[3] - Change pre-treatment vs post-treatment

[4] - 0.15

## Secondary: Glucose Disposal (High insulin)

| | |
|---|---|
| End point title | Glucose Disposal (High insulin) |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Change in measurement of pre Vs post-treatment

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: mg/kg/min | | | | |
| arithmetic mean (standard deviation) | -2.88 (± 2.91) | -2.16 (± 2.89) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [5] |
| Method | generalised linear models |

Notes:

[5] - 0.26

**Secondary: M/I value (High insulin)**

| End point title | M/I value (High insulin) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: mg/kg/min per mU/ml | | | | |
| median (inter-quartile range (Q1-Q3)) | -3.72 (-7.25 to -0.98) | -0.51 (-3.76 to 2.53) | | |

### Statistical analyses

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [6] |
| Method | generalised linear models |

Notes:

[6] - 0.17

### Secondary: Ra glucose

| End point title | Ra glucose |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: mg/kg/min | | | | |
| median (inter-quartile range (Q1-Q3)) | 0.06 (-0.02 to 0.13) | 0.08 (-0.02 to 0.12) | | |

### Statistical analyses

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |

| | |
|---|---|
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [7] |
| Method | generalised linear models |

Notes:
[7] - 0.55

## Secondary: EGP

| | |
|---|---|
| End point title | EGP |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:
Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 14 | | |
| Units: mg/kg/min | | | | |
| median (inter-quartile range (Q1-Q3)) | 0.35 (0.12 to 0.49) | 0.16 (-0.03 to 0.29) | | |

## Statistical analyses

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [8] |
| Method | generalised linear models |

Notes:
[8] - 0.11

## Secondary: Fasting glucose

| | |
|---|---|
| End point title | Fasting glucose |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:
Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: mmol/l | | | | |
| arithmetic mean (standard deviation) | 0.1 (± 0.5) | 0.3 (± 0.3) | | |

**Statistical analyses**

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 |
| Method | generalised linear models |

**Secondary: Fasting insulin**

| End point title | Fasting insulin |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: mu/l | | | | |
| arithmetic mean (standard deviation) | 0.48 (± 1.99) | -0.2 (± 2.94) | | |

**Statistical analyses**

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [9] |
| Method | generalised linear models |

Notes:

[9] - 0.63

## Secondary: TAG (Basal)

| End point title | TAG (Basal) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: umol/l | | | | |
| arithmetic mean (standard deviation) | 258.2 (± 240.7) | -50 (± 198.4) | | |

### Statistical analyses

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [10] |
| Method | generalised linear models |

Notes:

[10] - 0.001

## Secondary: TAG (Low Insulin)

| End point title | TAG (Low Insulin) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: umol/l | | | | |
| median (inter-quartile range (Q1-Q3)) | 125.8 (18 to 155.9) | -46.9 (-134.9 to 3.5) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [11] |
| Method | generalised linear models |

Notes:

[11] - 0.0014

**Secondary: TAG (High insulin)**

| End point title | TAG (High insulin) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: umol/l | | | | |
| median (inter-quartile range (Q1-Q3)) | 58.1 (-6.9 to 90.2) | -40.7 (-190.5 to 2.4) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [12] |
| Method | generalised linear models |

Notes:

[12] - 0.0069

**Secondary: Glycerol (Basal)**

| End point title | Glycerol (Basal) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: umol/l | | | | |
| arithmetic mean (standard deviation) | 8.3 (± 9.9) | 3.3 (± 10.3) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |

| | |
|---|---|
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [13] |
| Method | generalised linear models |

Notes:
[13] - 0.39

### Secondary: Glycerol (Low insulin)

| | |
|---|---|
| End point title | Glycerol (Low insulin) |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:
Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: umol/l | | | | |
| median (inter-quartile range (Q1-Q3)) | 4.1 (3.3 to 6) | 1.5 (0.4 to 2.7) | | |

### Statistical analyses

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [14] |
| Method | generalised linear models |

Notes:
[14] - 0.11

### Secondary: Glycerol (High insulin)

| | |
|---|---|
| End point title | Glycerol (High insulin) |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:
Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 15 | | |
| Units: umol/l | | | | |
| median (inter-quartile range (Q1-Q3)) | 2.8 (1.9 to 4.9) | 0.2 (-1.2 to 1.1) | | |

**Statistical analyses**

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [15] |
| Method | generalised linear models |

Notes:

[15] - 0.089

**Secondary: Adipose interstitial fluid - Glycerol (Basal)**

| End point title | Adipose interstitial fluid - Glycerol (Basal) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13 | 12 | | |
| Units: umol/l/hr | | | | |
| median (inter-quartile range (Q1-Q3)) | 30.3 (-60 to 101.5) | 47.8 (-9.8 to 77.9) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [16] |
| Method | generalised linear models |

Notes:

[16] - 0.3

## Secondary: adipose interstitial fluid - Glycerol (Low insulin)

| End point title | adipose interstitial fluid - Glycerol (Low insulin) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13 | 11 | | |
| Units: umol/l/hr | | | | |
| arithmetic mean (standard deviation) | 87.3 (± 109.3) | 36.6 (± 71) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [17] |
| Method | generalised linear models |

Notes:

[17] - 0.38

## Secondary: adipose interstitial fluid - Glycerol (High insulin)

| End point title | adipose interstitial fluid - Glycerol (High insulin) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 12 | | |
| Units: umol/l/hr | | | | |
| median (inter-quartile range (Q1-Q3)) | 71.8 (28.1 to 109.3) | -3.9 (-15.4 to 46.8) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [18] |
| Method | generalised linear models |

Notes:

[18] - 0.16

**Secondary: NEFA (Basal)**

| End point title | NEFA (Basal) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: umol/l | | | | |

| | | | | |
|---|---|---|---|---|
| median (inter-quartile range (Q1-Q3)) | 129.2 (-5.1 to 196.9) | -4.6 (-93.4 to 241.2) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [19] |
| Method | generalised linear models |

Notes:

[19] - 0.72

**Secondary: NEFA (Low insulin)**

| End point title | NEFA (Low insulin) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: umol/l | | | | |
| median (inter-quartile range (Q1-Q3)) | 33.2 (21.3 to 71.4) | 2.4 (-4.1 to 69.5) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |

| | |
|---|---|
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [20] |
| Method | generalised linear models |

Notes:
[20] - 0.25

## Secondary: NEFA (High insulin)

| | |
|---|---|
| End point title | NEFA (High insulin) |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:
Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: umol/l | | | | |
| median (inter-quartile range (Q1-Q3)) | 16.3 (2.1 to 55.8) | 1.2 (-9.5 to 43.4) | | |

### Statistical analyses

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [21] |
| Method | generalised linear models |

Notes:
[21] - 0.66

## Secondary: Ra palmitate (Basal)

| | |
|---|---|
| End point title | Ra palmitate (Basal) |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:
Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 11 | | |
| Units: mg/kg/min | | | | |
| arithmetic mean (standard deviation) | -0.12 (± 0.69) | 0.1 (± 0.86) | | |

**Statistical analyses**

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [22] |
| Method | generalised linear models |

Notes:

[22] - 0.51

**Secondary: Ra palmitate (Low insulin)**

| End point title | Ra palmitate (Low insulin) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 11 | | |
| Units: mg/kg/min | | | | |
| median (inter-quartile range (Q1-Q3)) | 0.16 (-0.15 to 0.32) | 0.1 (-0.05 to 0.41) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [23] |
| Method | generalised linear models |

Notes:

[23] - 0.62

## Secondary: Ra palmitate (High insulin)

| End point title | Ra palmitate (High insulin) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 11 | | |
| Units: mg/kg/min | | | | |
| median (inter-quartile range (Q1-Q3)) | -0.03 (-0.22 to 0.15) | -0.17 (-0.44 to -0.03) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [24] |
| Method | generalised linear models |

Notes:

[24] - 0.31

## Secondary: Daytime blood pressure - systolic

| End point title | Daytime blood pressure - systolic |
|---|---|

| End point description: |
|---|

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: mmhg | | | | |
| arithmetic mean (standard deviation) | 2.5 (± 6.1) | 2.4 (± 7) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 28 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [25] |
| Method | generalised linear models |

Notes:

[25] - 0.66

**Secondary: Daytime blood pressure - diastolic**

| End point title | Daytime blood pressure - diastolic |
|---|---|
| End point description: | |

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 0.3 (± 5.8) | 1.4 (± 6.2) | | |

### Statistical analyses

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 28 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [26] |
| Method | generalised linear models |

Notes:

[26] - 0.92

### Secondary: Nighttime blood pressure - systolic

| End point title | Nighttime blood pressure - systolic |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 13 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 4.6 (± 10.6) | 1 (± 11.5) | | |

### Statistical analyses

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |

| | |
|---|---|
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [27] |
| Method | generalised linear models |

Notes:
[27] - 0.19

## Secondary: Nighttime blood pressure - diastolic

| | |
|---|---|
| End point title | Nighttime blood pressure - diastolic |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:
Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 13 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 4.6 (± 8.6) | 0.7 (± 8.1) | | |

### Statistical analyses

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [28] |
| Method | generalised linear models |

Notes:
[28] - 0.03

## Secondary: Osteocalcin

| | |
|---|---|
| End point title | Osteocalcin |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:
Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: ng/ml | | | | |
| median (inter-quartile range (Q1-Q3)) | -3.86 (-5.78 to -2.74) | 0 (-3.46 to 2.18) | | |

**Statistical analyses**

| Statistical analysis title | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [29] |
| Method | generalised linear models |

Notes:

[29] - <0.0001

**Secondary: VZV OX40**

| End point title | VZV OX40 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| End point values | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: % | | | | |
| median (inter-quartile range (Q1-Q3)) | -0.3 (-1.85 to 0) | -0.4 (-0.55 to -0.1) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [30] |
| Method | generalised linear models |

Notes:

[30] - 0.81

**Secondary: PHA OX40**

| End point title | PHA OX40 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change in measurement of pre Vs post-treatment

| **End point values** | Subjects included in analysis - Placebo and prednisolone | Subjects included in analysis - AZD4017 and prednisolone | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 15 | | |
| Units: % | | | | |
| arithmetic mean (standard deviation) | -21.7 (± 14) | -10.2 (± 14.4) | | |

**Statistical analyses**

| **Statistical analysis title** | Generalised linear models |
|---|---|
| Comparison groups | Subjects included in analysis - Placebo and prednisolone v Subjects included in analysis - AZD4017 and prednisolone |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [31] |
| Method | generalised linear models |

Notes:

[31] - 0.046

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: Overall trial up to 30 days post treatment. | |
| Assessment type | Non-systematic |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 10.0 |
| **Reporting groups** | |
| Reporting group title | Non-serious adverse events |

Reporting group description: -

| Serious adverse events | Non-serious adverse events | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

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

| Non-serious adverse events | Non-serious adverse events | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 32 (15.63%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | | |
| occurrences (all) | 3 | | |
| Irritability | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | | |
| occurrences (all) | 1 | | |
| Endocrine disorders | | | |
| Thyroid disorder | Additional description: Elevated TSH which normalised after 14 days. | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | | |
| occurrences (all) | 1 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 08 February 2018 | We changed the poster advertisement to make it more noteworthy by changing some of the wording<br>and by making it more pictorial. We drafted 5 new posters which were reviewed by the ethics<br>committee.<br>Protocol: The original wording was not clear on who was eligible to participate and needed to be changed.<br>Patient Information Leaflet: There was a typographical error. It should read 8 weeks instead of 4-5 weeks. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported