



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 11 β -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 have 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	Subject, Investigator, Monitor, 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			
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			
Units: years			
arithmetic mean	38.7	35.6	
standard deviation	± 12.4	± 11.1	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	16	16	32
BMI			
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			
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			
Units: years			
arithmetic mean	39	36.5	
standard deviation	± 12.7	± 11	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	15	15	
BMI			
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 linear 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 and by making it more pictorial. We drafted 5 new posters which were reviewed by the ethics committee. Protocol: The original wording was not clear on who was eligible to participate and needed to be changed. 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