Clinical trial results:
Assessing the therapeutic efficacy and safety of an 11-hydroxysteroid dehydrogenase type 1 inhibitor (AZD4017) in idiopathic intracranial hypertension (IIH).

Summary

EudraCT number	2013-003643-31
Trial protocol	GB
Global end of trial date	10 February 2017

Results information

Result version number	v1 (current)
This version publication date	29 August 2019
First version publication date	29 August 2019
Summary attachment (see zip file)	11β-Hydroxysteroid Dehydrogenase Type 1 inhibition in Idiopathic Intracranial (IIHDT results preprint.pdf)

Trial information

Trial identification

Sponsor protocol code	RG_13-022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02017444
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TT
Public contact	Dr Birgit Whitman, University of Birmingham, +44 1214158011, B.Whitman@bham.ac.uk
Scientific contact	Dr Birgit Whitman, University of Birmingham, +44 1214158011, B.Whitman@bham.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	25 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2016
Global end of trial reached?	Yes
Global end of trial date	10 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate whether 12 weeks of a 11β-hydroxysteroid dehydrogenase inhibitor (AZD4017) is effective and safe for reducing the raised intracranial pressure (pressure of fluid around the brain) observed in patients with idiopathic intracranial hypertension, compared to a placebo ('dummy' drug with no active properties).

In the original grant application and early versions of the protocol, the primary outcome measure was stated as the change in ICP between baseline and 12 weeks. Following adoption of the study by the University of Birmingham Clinical Trials Unit, the primary outcome was changed to ICP at 12 weeks, with adjustment for baseline ICP in the analysis. This change was made blind to any data analysis.

Protection of trial subjects:

The trial was discussed with potential participants and written information presented detailing the exact nature of the trial and the potential risks involved. It was clearly stated that participants were free to withdraw from the trial at any time and for any reason, with no obligation to give the reason for withdrawal and without affecting their future care.

Since the effects of AZD4017 on unborn children are unknown, participants had pregnancy tests before randomisation and at intervals throughout the trial. Participants were also required to use one form of highly effective contraception.

Informed by earlier trials investigating AZD4017, a panel of safety bloods were monitored throughout the trial, including renal function, liver function, thyroid function and creatine kinase.

An independent Data Monitoring and Ethics Committee reviewed data including Adverse Events and safety blood results.

Background therapy:

Although weight loss is generally advised for patients with IIH, the management of IIH varies considerably owing to a lack of supporting evidence.

During trial design and registration, there was no evidence supporting the use of any particular medical treatment for IIH.

For progressive or acute deterioration of vision in IIH, surgical techniques such as cerebrospinal fluid (CSF) shunting, optic nerve sheath fenestration, or venous sinus stenting have been used to prevent blindness. However, there is limited evidence to support these surgical interventions.

Evidence for comparator:

AZD4017 was compared to placebo rather than a current medical treatment of IIH due to the lack of evidence for any other active treatment noted above.

Actual start date of recruitment	25 April 2014
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: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	31
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 31 participants were recruited from 3 UK NHS Trusts between April 2014 and August 2016.

Pre-assignment

Screening details:

Patients were eligible for pre-screening (slit lamp examination for papilloedema Frisen grading ≥1 and a blood test) if they were female, ≥18 years old, with a confirmed diagnosis of active IIH (Modified Dandy criteria). Screening before randomisation then involved a lumbar puncture to confirm raised ICP and a urine pregnancy test.

Period 1

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

Blinding implementation details:

The trial drug and placebo was blinded, randomised, and packaged by Almac, contract manufacturing organisation on behalf of AstraZeneca. If unblinding was required, unblinding codes were held in the Pharmacy Departments of each Trust, as well as by the Trial Statistician with reasons for unblinding to be recorded.

Arms

Are arms mutually exclusive?	Yes
Arm title	AZD4017

Arm description:

An oral selective 11β-HSD1 inhibitor, AZD4017, at 400mg twice daily for 12 weeks.

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

Dosage and administration details:

400mg twice daily (am and pm) for 12 weeks

Arm title	Placebo arm

Arm description:

A matched placebo 400mg twice daily for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	n/a
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400mg twice daily (am and pm) for 12 weeks

Number of subjects in period 1	AZD4017	Placebo arm
Started	17	14
Completed	17	12
Not completed	0	2
Physician decision	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	AZD4017
Reporting group description:	
An oral selective 11β-HSD1 inhibitor, AZD4017, at 400mg twice daily for 12 weeks.	
Reporting group title	Placebo arm
Reporting group description:	
A matched placebo 400mg twice daily for 12 weeks.	

Reporting group values	AZD4017	Placebo arm	Total
Number of subjects	17	14	31
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)	17	14	31
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age in years			
Units: years			
arithmetic mean	30.1	32.4	
standard deviation	± 5.9	± 8	-
Gender categorical Units: Subjects			
Female	17	14	31
Male	0	0	0
Ethnicity Units: Subjects			
White British	16	13	29
Asian/Asian British - Pakistani	1	0	1
Asian/Asian British - Other Asian	0	1	1
Number on acetazolamide Units: Subjects			
Number on acetazolamide	6	4	10
Not on acetazolamide	11	10	21
IIH Symptoms			
Headache			
Units: Subjects			
Headache	16	14	30
No headache	1	0	1
Frisén Grading, number			

Worst eye only			
Units: Subjects			
Frisén Grade 1	4	2	6
Frisén Grade 2	9	5	14
Frisén Grade 3	0	3	3
Frisén Grade 4	2	1	3
Frisén Grade 5	1	0	1
Not recorded	1	3	4
IIH Symptoms			
Visual loss			
Units: Subjects			
Visual loss	4	8	12
No visual loss	13	6	19
IIH Symptoms			
Pulsatile tinnitus			
Units: Subjects			
Pulsatile tinnitus	12	13	25
No Pulsatile tinnitus	5	1	6
IIH Symptoms			
Diplopia			
Units: Subjects			
Diplopia	7	5	12
No Diplopia	10	9	19
IIH Symptoms			
Transient visual obscurations			
Units: Subjects			
Transient visual obscurations	6	6	12
No Transient visual obscurations	11	8	19
Opening LP pressure, cmCSF			
Units: cmCSF			
arithmetic mean	33.7	32.7	
standard deviation	± 6.3	± 4.8	-
Weight, kg			
Units: kilograms			
arithmetic mean	97.9	108.4	
standard deviation	± 21.3	± 42.3	-
BMI (weight (kg)/ height (m2)			
Units: kg/m2			
arithmetic mean	37.3	41.2	
standard deviation	± 7.2	± 16.6	-
HIT-6 score			
Units: HIT-6			
arithmetic mean	63.8	63.4	
standard deviation	± 8.2	± 8.1	-
Perimetric mean deviation			
Worst eye only			
Units: dB			
arithmetic mean	-6.1	-3.4	
standard deviation	± 5.4	± 6.8	-
Log visual acuity			
Worst eye only			

Units: LVA			
arithmetic mean	0.08	0.13	
standard deviation	± 0.23	± 0.22	-
Log contrast sensitivity			
Worst eye only			
Units: LCS			
arithmetic mean	1.63	1.63	
standard deviation	± 0.22	± 0.16	-
OCT, thickness in µm			
Average retinal nerve fibre layer, worst eye only			
Units: µm			
arithmetic mean	152	158.4	
standard deviation	± 68.7	± 83	-
OCT, thickness in µm			
Maximum retinal nerve fibre, worst eye only			
Units: µm			
arithmetic mean	320.2	290	
standard deviation	± 117.2	± 102.4	-
Average Frisén grading			
Worst eye only			
Units: Frisén grading			
arithmetic mean	2.19	2.27	
standard deviation	± 1.17	± 0.9	-

End points

End points reporting groups

Reporting group title	AZD4017
Reporting group description:	
An oral selective 11β-HSD1 inhibitor, AZD4017, at 400mg twice daily for 12 weeks.	
Reporting group title	Placebo arm
Reporting group description:	
A matched placebo 400mg twice daily for 12 weeks.	

Primary: Primary clinical outcome, mean ICP at 12 weeks

End point title	Primary clinical outcome, mean ICP at 12 weeks
End point description:	
End point type	Primary
End point timeframe:	
Baseline to 12 weeks	

End point values	AZD4017	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[1]	12[2]		
Units: cmCSF				
arithmetic mean (standard deviation)	29.7 (± 5.2)	31.3 (± 6.7)		

Notes:

[1] - 1 participant unable to complete LP for ICP at week 12

[2] - 2 participants withdrawn before timepoint

Statistical analyses

Statistical analysis title	Primary outcome
Statistical analysis description:	
The primary outcome is to examine the effect of AZD4017 on ICP, as measured by lumbar puncture in cmCSF, from baseline to 12 weeks. The primary outcome measure is the difference in ICP at 12 weeks. Analysis is by intention-to-treat. A linear regression model will be used to compare the ICP at 12 weeks between the two arms, adjusting for baseline ICP.	
Comparison groups	Placebo arm v AZD4017
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.2
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	1.5
Variability estimate	Standard deviation

Notes:

[3] - Negative values in the adjusted mean difference between treatment arms favour AZD4017.

Secondary: Secondary clinical outcome: Log Visual Acuity

End point title	Secondary clinical outcome: Log Visual Acuity
End point description: Worst eye only	
End point type	Secondary
End point timeframe: Baseline to 12 weeks	

End point values	AZD4017	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	12		
Units: LogMAR				
arithmetic mean (standard deviation)	0.06 (± 0.15)	0.09 (± 0.18)		

Statistical analyses

Statistical analysis title	Visual acuity
Comparison groups	AZD4017 v Placebo arm
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.5
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.07
Variability estimate	Standard deviation

Notes:

[4] - Negative values in the adjusted mean difference between treatment arms favour AZD4017.

Secondary: Secondary clinical outcome: Log contrast sensitivity

End point title	Secondary clinical outcome: Log contrast sensitivity

End point description: worst eye only	
End point type	Secondary
End point timeframe: Baseline to 12 weeks	

End point values	AZD4017	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: LCS				
arithmetic mean (standard deviation)	1.65 (± 0.15)	1.66 (± 0.12)		

Statistical analyses

Statistical analysis title	Log Contrast Sensitivity
Comparison groups	AZD4017 v Placebo arm
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.7
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.11
Variability estimate	Standard deviation

Notes:

[5] - Negative values in the adjusted mean difference between treatment arms favour AZD4017.

Secondary: Secondary clinical outcome: Perimetric mean deviation

End point title	Secondary clinical outcome: Perimetric mean deviation
End point description: worst eye only	
End point type	Secondary
End point timeframe: Baseline to 12 weeks	

End point values	AZD4017	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	12		
Units: dB				
arithmetic mean (standard deviation)	-3.4 (± 3.2)	-2.2 (± 3.1)		

Statistical analyses

Statistical analysis title	Perimetric mean deviation
Comparison groups	AZD4017 v Placebo arm
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.8
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	2.7
Variability estimate	Standard deviation

Notes:

[6] - Negative values in the adjusted mean difference between treatment arms favour AZD4017.

Secondary: Secondary clinical outcome: OCT retinal nerve fibre layer average

End point title	Secondary clinical outcome: OCT retinal nerve fibre layer average
End point description:	
Worst eye only	
End point type	Secondary
End point timeframe:	
Baseline to 12 weeks	

End point values	AZD4017	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	11		
Units: µm				
arithmetic mean (standard deviation)	139.7 (± 56.3)	143.2 (± 78.7)		

Statistical analyses

Statistical analysis title	OCT RNFL average
Comparison groups	AZD4017 v Placebo arm
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 1
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34
upper limit	34.1
Variability estimate	Standard deviation

Notes:

[7] - Negative values in the adjusted mean difference between treatment arms favour AZD4017.

Secondary: Secondary clinical outcome: OCT retinal nerve fibre layer maxium	
End point title	Secondary clinical outcome: OCT retinal nerve fibre layer maxium
End point description: Worst eye only	
End point type	Secondary
End point timeframe: Baseline to 12 weeks	

End point values	AZD4017	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	11		
Units: µm				
arithmetic mean (standard deviation)	305.5 (± 122.3)	277 (± 133.1)		

Statistical analyses

Statistical analysis title	OCT RNFL maximum
Comparison groups	AZD4017 v Placebo arm
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.9
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-4.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-68.1
upper limit	59.1
Variability estimate	Standard deviation

Notes:

[8] - Negative values in the adjusted mean difference between treatment arms favour AZD4017.

Secondary: Secondary clinical outcome: Average Frisén grading

End point title	Secondary clinical outcome: Average Frisén grading
End point description:	
Worst eye only	
End point type	Secondary
End point timeframe:	
Baseline to 12 weeks	

End point values	AZD4017	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	12		
Units: Frisén grading				
arithmetic mean (standard deviation)	1.56 (± 0.96)	2.25 (± 0.87)		

Statistical analyses

Statistical analysis title	Average Frisén grading
Statistical analysis description:	
Negative values in the adjusted mean difference between treatment arms favour AZD4017.	
Comparison groups	AZD4017 v Placebo arm
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.06
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.03
Variability estimate	Standard deviation

Notes:

[9] - Negative values in the adjusted mean difference between treatment arms favour AZD4017.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs and SAEs were reported from the signing of the consent form to the end of the follow-up period at week 16. SAEs were to be reported within 24 hours of the site becoming aware of it.

Adverse event reporting additional description:

AEs were collected whether or not related to the IMP.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	AZD4017

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	AZD4017	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Deterioration of IIH symptoms	Additional description: Expected progression of condition		
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	AZD4017	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 17 (94.12%)	11 / 14 (78.57%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Cardiac disorders			

Cardiovascular			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Nervous system disorders			
Neurological			
subjects affected / exposed	7 / 17 (41.18%)	3 / 14 (21.43%)	
occurrences (all)	18	6	
General disorders and administration site conditions			
Genito-urinary			
subjects affected / exposed	2 / 17 (11.76%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
Allergies			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Other	Additional description: Reasons for other included: tiredness, hot sweats, flu like symptoms, disrupted sleep, toothache/infection, breast pain, mentrual problems for more than 3 weeks, mouth ulcers, a cold, transient nausea, and height headaches.		
subjects affected / exposed	7 / 17 (41.18%)	5 / 14 (35.71%)	
occurrences (all)	9	6	
Ear and labyrinth disorders			
Eyes, ear, nose, Throat			
subjects affected / exposed	12 / 17 (70.59%)	6 / 14 (42.86%)	
occurrences (all)	22	14	
Immune system disorders			
Immunological			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Gastrointestinal			
subjects affected / exposed	8 / 17 (47.06%)	3 / 14 (21.43%)	
occurrences (all)	22	3	
Respiratory, thoracic and mediastinal disorders			
Respiratory			
subjects affected / exposed	4 / 17 (23.53%)	3 / 14 (21.43%)	
occurrences (all)	4	3	
Skin and subcutaneous tissue disorders			
Dermatological			

subjects affected / exposed	2 / 17 (11.76%)	5 / 14 (35.71%)	
occurrences (all)	4	8	
Psychiatric disorders			
Psychological			
subjects affected / exposed	4 / 17 (23.53%)	4 / 14 (28.57%)	
occurrences (all)	8	8	
Endocrine disorders			
Endocrine			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal			
subjects affected / exposed	6 / 17 (35.29%)	7 / 14 (50.00%)	
occurrences (all)	13	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2014	Substantial Amendment 1: To improve recruitment: Introducing patient compensation; switching subset of follow up visits to telephone visits to ease patient burden.
13 August 2015	Substantial Amendment 2: Change from single- to multi-centre trial; Removal of eligibility criteria requiring patients to be within 6 months of confirmed IIH diagnosis.
26 October 2015	Substantial Amendment 3: Correction of stratification text in randomisation section of protocol to reflect changing from single- to multi-centre trial.
17 November 2015	Substantial Amendment 4: Clarification of safety bloods required and their reporting/review timelines
07 July 2016	Substantial Amendment 5: Clarification to IIH symptom recording
04 January 2017	Substantial Amendment 6: Change to statistical analysis proposed in protocol (from change over 12 weeks to mean difference between arms)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The pre-print of the results has not been peer-reviewed as of July 2019.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28923789