Clinical trial results:
A study of the effect of OC000459 on signs & symptoms in subjects with moderate to severe atopic dermatitis: A randomised double blind placebo controlled parallel group study

Summary

EudraCT number	2013-001924-20
Trial protocol	GB DE FI AT CZ SK PL
Global end of trial date	24 September 2015

Results information

Result version number	v1 (current)
This version publication date	19 August 2016
First version publication date	19 August 2016

Trial information

Trial identification

Sponsor protocol code	OC000459/017/13

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Atopix Therapeutics Ltd
Sponsor organisation address	99 Park Drive, Milton Park, Abingdon, United Kingdom, OX14 4RY
Public contact	Timothy Edwards, Atopix Therapeutics Ltd, 44 1235841522, atopix@atopixtherapeutics.com
Scientific contact	Michael Hunter, Atopix Therapeutics Ltd, 44 1235841522, atopix@atopixtherapeutics.com

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	14 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 September 2015
Global end of trial reached?	Yes
Global end of trial date	24 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of OC000459 50 mg given once a day orally in comparison to placebo on the severity and extent of atopic dermatitis using the Eczema Area and Severity Index (EASI) after a 16 week treatment period in subjects with active moderate to severe atopic dermatitis (AD) requiring treatment.

Protection of trial subjects:

Rescue medication was provided to patients. Patients were permitted to withdraw from trial at their own request.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Czech Republic: 25
Country: Number of subjects enrolled	Finland: 17
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 38
Worldwide total number of subjects	139
EEA total number of subjects	139

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	139
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Sixty study centres were initiated in Austria, Czech Republic, Finland, France, Germany, Poland, Slovakia and United Kingdom. Five of the 60 centres did not screen or randomise any subjects, and 11 centres screened but did not randomise any subjects.
Date of first enrolment: 30 October 2013
Date of last completed: 24 September 2015

Pre-assignment

Screening details:

This was a randomised, double-blind, placebo-controlled, parallel-group evaluation of OC000459 50 mg given once a day orally for 16 weeks. Eligible subjects were randomised to treatment with either OC000459 or matching placebo. There were two follow-up visits at 2 and 4 weeks after the final dose of OC000459 or placebo.

Period 1

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

Blinding implementation details:

Active compared with matching placebo

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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

Dosage and administration details:

50 mg once daily

Arm title	OC000459

Arm description: -

Arm type	Experimental
Investigational medicinal product name	OC000459
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50mg once daily

Number of subjects in period 1	Placebo	OC000459
Started	70	69
Completed	32	30
Not completed	38	39
Physician decision	38	39

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	OC000459
Reporting group description: -	

Reporting group values	Placebo	OC000459	Total
Number of subjects	70	69	139
Age categorical Units: Subjects			
Adults (18-64 years)	70	69	139
Gender categorical Units: Subjects			
Female	31	29	60
Male	39	40	79

Subject analysis sets	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description: All subjects who received at least one dose of double-blind study treatment, irrespective of compliance with eligibility and other protocol criteria. Used for baseline and safety and tolerability analyses.	
Subject analysis set title	OC000459
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set	

Reporting group values	Placebo	OC000459	
Number of subjects	70	69	
Age categorical Units: Subjects			
Adults (18-64 years)	139		
Gender categorical Units: Subjects			
Female	61		
Male	80		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	OC000459
Reporting group description: -	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who received at least one dose of double-blind study treatment, irrespective of compliance with eligibility and other protocol criteria. Used for baseline and safety and tolerability analyses.	
Subject analysis set title	OC000459
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set	

Primary: Eczema Area and Severity Index (EASI)

End point title	Eczema Area and Severity Index (EASI)
End point description:	
End point type	Primary
End point timeframe:	
Measured at week 16 of treatment	

End point values	Placebo	OC000459	Placebo	OC000459
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	70	69	70	69
Units: Score				
arithmetic mean (standard deviation)	-3.7 (± 15.2)	-1.7 (± 13.9)	-3.7 (± 15.2)	-1.7 (± 13.9)

Statistical analyses

Statistical analysis title	EASI Statistical analysis
Comparison groups	Placebo v OC000459
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)

Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessed at randomisation, weeks 2, 4, 8, 12 and 16 of the study and at follow-up at 2 or 4 weeks after last dose.

Adverse event reporting additional description:

The safety population consisted of all randomised subjects who received at least one dose of double-blind study treatment, irrespective of compliance with eligibility and other protocol criteria. Used for baseline and safety and tolerability analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects who received placebo treatment.

Reporting group title	OC000459

Reporting group description:

Subjects who received OC000459

Serious adverse events	Placebo	OC000459	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 71 (8.45%)	1 / 70 (1.43%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
ECG abnormality			
subjects affected / exposed	1 / 71 (1.41%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction	Additional description: Anaphylaxis due to peanut allergy		
subjects affected / exposed	1 / 71 (1.41%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroenteritis			

subjects affected / exposed	1 / 71 (1.41%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema	Additional description: Worsening of eczema		
subjects affected / exposed	6 / 71 (8.45%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	6 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema infected	Additional description: Staphylococcal infection		
subjects affected / exposed	1 / 71 (1.41%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	OC000459	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 71 (67.61%)	44 / 70 (62.86%)	
General disorders and administration site conditions			
Headache			
subjects affected / exposed	15 / 71 (21.13%)	15 / 70 (21.43%)	
occurrences (all)	15	15	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 71 (5.63%)	3 / 70 (4.29%)	
occurrences (all)	4	3	
Respiratory, thoracic and mediastinal disorders			
Nasopharangitis			
subjects affected / exposed	15 / 71 (21.13%)	9 / 70 (12.86%)	
occurrences (all)	15	9	
Skin and subcutaneous tissue disorders			
Atopic dermatitis			
subjects affected / exposed	8 / 71 (11.27%)	7 / 70 (10.00%)	
occurrences (all)	8	7	
Pruritis			

subjects affected / exposed occurrences (all)	4 / 71 (5.63%) 4	6 / 70 (8.57%) 6	
Infections and infestations Herpes simplex subjects affected / exposed occurrences (all)	 2 / 71 (2.82%) 2	 4 / 70 (5.71%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2013	Protocol Amendment 1, dated 16 August 2013, was applicable to all sites that were open at the time (United Kingdom, Germany, Finland, France) and made a number of changes. Hydrocortisone cream was added to the list of rescue medications provided, as hydrocortisone acetate was not available in all countries, so an equivalent medication was required as an alternative. This amendment also stated that the prescribed creams for each subject should not change during the course of the study. Subjects with a known allergy to hydrocortisone or hydrocortisone acetate were added to the exclusion criterion on allergies to hydrocortisone preparations. For serology, hepatitis B surface antigen was measured instead of hepatitis B antibodies. Important/significant medical events were also defined. In addition, minor corrections and clarifications were made. At the request of the French competent authority, glycated haemoglobin testing was added to the protocol and subjects with diabetes mellitus were excluded from the study; therefore, a country-specific amendment was issued to include these additional changes for sites in France only.
24 October 2013	Protocol Amendment 2, dated 24 October 2013, was applicable to all sites open at the time, and was a non-substantial amendment. This amendment added a new country, Austria, along with additional sites in the United Kingdom and Germany. This was because projections indicated that there were insufficient sites recruiting subjects into the study to complete recruitment in the required timelines. The number of planned sites was increased from approximately 20 to up to 40. The estimated number of subjects to be screened was changed from approximately 250 to at least 250.
30 January 2014	Protocol Amendment 3, dated 30 January 2014 (08 February 2014 in France), was applicable to all sites open at that time. The changes were designed to improve recruitment and to reduce the number of subjects needed. Data from a study with dupilumab reported a significant effect on EASI score after 4 weeks of treatment. Dupilumab, an interleukin-4 receptor alpha subunit inhibitor which attenuates Th2-mediated inflammation, represented a relevant comparison for OC000459 and indicated that a significant effect on EASI could be achieved with fewer patients within a shorter treatment period than the 26 weeks defined in the protocol. The treatment period was thus reduced from 26 to 16 weeks. The estimated number of subjects to be screened was decreased from at least 250 to approximately 200, and the number of subjects in each treatment arm was reduced from approximately 100 (90 evaluable) to at least 70 (64 evaluable). The upper age limit was increased from 40 to 48 years. An inclusion criterion on AD and co-morbid conditions was removed (subjects must meet at least one of: diagnosed with AD below 2 years of age; co-existing asthma and/or allergic rhinoconjunctivitis; or a history of these conditions). Recruitment criteria for blood eosinophil results, systemic corticosteroid use and use of NSAIDs were relaxed. Short-term use of NSAIDs was added to the list of permitted medications. The following secondary objectives (and corresponding endpoints) were also added: EASI at 4, 8 and 12 weeks; subject withdrawal due to treatment failure. The number of flares was added to the list of secondary endpoints. Unnecessary pregnancy tests were reduced and the number of blood draws for plasma drug levels was decreased. Minor clarifications were also made.

09 October 2014	Protocol Amendment 4, dated 09 October 2014, applied to all sites open at that time. This amendment extended the recruitment timeline, added sites in three new countries (Poland, Czech Republic and Slovakia) and included new sites in Germany, increasing the total number of sites defined in the protocol to 60. On review of screening failures and discussions with some of the investigators a relaxation of some of the permitted medications was permitted, to allow concomitant use of anti-hypertensives, antidepressants, anti-migraine, anti-epileptics, oral contraceptives, hormone replacement therapies and thyroid medications. As some investigators treat AD with high-dose vitamin D, a washout period for high-dose vitamin D treatment was defined. This amendment also clarified the definition and procedures for flares, and defined visit windows more clearly. Amendment 4 was subsequently withdrawn in Germany.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported