Clinical trial results:
Effect of the CRTH2 antagonist OC459 on the response to rhinovirus challenge in asthma

Summary

EudraCT number	2015-002555-10
Trial protocol	GB
Global end of trial date	24 January 2018

Results information

Result version number	v1 (current)
This version publication date	13 November 2019
First version publication date	13 November 2019

Trial information

Trial identification

Sponsor protocol code	ORCA2015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02660489
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College
Sponsor organisation address	St Mary's Medical School Building, Norfolk Place, London, United Kingdom, W2 1PG
Public contact	Professor Sebastian Johnston, Imperial College, +44 20 7594 3849, s.johnston@imperial.ac.uk
Scientific contact	Professor Sebastian Johnston, Imperial College, +44 20 7594 3849, s.johnston@imperial.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	22 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 January 2018
Global end of trial reached?	Yes
Global end of trial date	24 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall aim of this study is to assess the effectiveness of the study drug (OC459) in preventing or attenuating the worsening of asthma symptoms (an asthma exacerbation) that occurs when asthma sufferers catch a cold (defined as an infection with the virus rhinovirus). The study drug will be compared with a placebo to find out the extent of any improvement in the condition of the participants. A placebo is a medically noneffective copy of the drug being tested; it looks and tastes the same as the treatment drug (it can be seen as a dummy drug).

In healthy subjects, rhinovirus infection causes symptoms of a cold e.g. sneezing, runny nose. In patients with asthma, rhinovirus infection causes a worsening of their asthma symptoms (e.g. breathlessness, wheeze) because of the way the immune system reacts to the virus. The study drug OC459 blocks activation of receptor cells found in the immune system and by blocking that activation may prevent an exacerbation of symptoms.

Protection of trial subjects:

There were 11 scheduled visits for trial subjects, with seven of these scheduled during the period when subjects had a cold.

In addition subjects had access to the study team via mobile and email 24/7.

A procedure for unblinding was also available 24/7.

Background therapy:

Subjects were told to continue their usual medication as prescribed. This included inhaled corticosteriods ('preventers') and inhaled short-acting beta agonists ('relievers').

Evidence for comparator:

A placebo was given in the comparator arm.

Actual start date of recruitment	18 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	44
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment ran from 18 January 2016 until completion (November 2018; the last subjects were enrolled on 15 November 2018). This was a single site study.

Pre-assignment

Screening details:

Volunteers who were potentially eligible for inclusion were screened by an Asthma Control Questionnaire, skin prick test, bronchoprovocation testing (using histamine) and rhinovirus serology (looking for evidence of antibodies to rhinovirus serotype 16).

Period 1

Period 1 title	Randomisation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The unblinded randomisation list was generated by a statistician working independently of the trial and entered into the study database. The unblinded randomisation list was also provided to the drug manufacturer in order to label the drug/placebo appropriately prior to dispensing to pharmacy. In this way the subjects, investigators, pharmacy, trial statisticians and study monitors were all blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	OC459

Arm description:

Subjects randomised to treatment with OC459 50mg once daily.

Arm type	Experimental
Investigational medicinal product name	OC459
Investigational medicinal product code	
Other name	Timapiprant
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50mg once daily for five weeks

Arm title	Placebo

Arm description:

Subjects randomised to treatment with placebo once daily.

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:

One tablet once daily for five weeks

Number of subjects in period 1	OC459	Placebo
Started	22	22
Completed	20	18
Not completed	2	4
Incidental respiratory tract infection	-	3
Non-attendance at study visit	1	1
Incidental respiratory viral infection	1	-

Period 2

Period 2 title	Rhinovirus infection
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

(as per previous period)

Arms

Are arms mutually exclusive?	Yes
Arm title	OC459 - confirmed rhinovirus infection

Arm description:

Subjects randomised to treatment with OC459 in whom infection with rhinovirus-16 was confirmed.

Arm type	Experimental
Investigational medicinal product name	OC459
Investigational medicinal product code	
Other name	Timapiprant
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50mg once daily for five weeks

Arm title	Placebo - confirmed rhinovirus infection

Arm description:

Subjects randomised to treatment with placebo in whom infection with rhinovirus-16 was confirmed.

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:

One tablet once daily for five weeks

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: As per the Protocol and Statistical Analysis Plan, the full analysis set includes only subjects who have been randomised and in addition have confirmed rhinovirus-16 infection and completed at

least 14 days post inoculation with rhinovirus-16. The baseline characteristics are provided for the Full Analysis Set, not the subjects enrolled, given the outcome analyses are performed on the Full Analysis Set.

Number of subjects in period 2[2][3]	OC459 - confirmed rhinovirus infection	Placebo - confirmed rhinovirus infection
Started	16	14
Completed	16	14

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: As per the Protocol and Statistical Analysis Plan, the full analysis set includes only subjects who have been randomised and in addition have confirmed rhinovirus-16 infection and completed at least 14 days post inoculation with rhinovirus-16.

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: As per the Protocol and Statistical Analysis Plan, the full analysis set includes only subjects who have been randomised and in addition have confirmed rhinovirus-16 infection and completed at least 14 days post inoculation with rhinovirus-16.

Baseline characteristics

Reporting groups	
Reporting group title	OC459 - confirmed rhinovirus infection
Reporting group description:	
Subjects randomised to treatment with OC459 in whom infection with rhinovirus-16 was confirmed.	
Reporting group title	Placebo - confirmed rhinovirus infection
Reporting group description:	
Subjects randomised to treatment with placebo in whom infection with rhinovirus-16 was confirmed.	

Reporting group values	OC459 - confirmed rhinovirus infection	Placebo - confirmed rhinovirus infection	Total
Number of subjects	16	14	30
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	25.1	24.8	
standard deviation	± 9.0	± 3.8	-
Gender categorical Units: Subjects			
Female	9	9	18
Male	7	5	12

End points

End points reporting groups

Reporting group title	OC459
Reporting group description:	
Subjects randomised to treatment with OC459 50mg once daily.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomised to treatment with placebo once daily.	
Reporting group title	OC459 - confirmed rhinovirus infection
Reporting group description:	
Subjects randomised to treatment with OC459 in whom infection with rhinovirus-16 was confirmed.	
Reporting group title	Placebo - confirmed rhinovirus infection
Reporting group description:	
Subjects randomised to treatment with placebo in whom infection with rhinovirus-16 was confirmed.	

Primary: Total Lower Respiratory Symptom score

End point title	Total Lower Respiratory Symptom score
End point description:	
End point type	Primary
End point timeframe:	
Sum of daily scores for 14 days after rhinovirus inoculation	

End point values	OC459 - confirmed rhinovirus infection	Placebo - confirmed rhinovirus infection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: score on a scale				
median (inter-quartile range (Q1-Q3))	21 (13.3 to 46.5)	18 (4 to 121)		

Statistical analyses

Statistical analysis title	Mann-Whitney test
Comparison groups	OC459 - confirmed rhinovirus infection v Placebo - confirmed rhinovirus infection

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Wilcoxon (Mann-Whitney)

Secondary: Asthma Control Questionnaire (ACQ)-6 score

End point title	Asthma Control Questionnaire (ACQ)-6 score

End point description:

End point type	Secondary

End point timeframe:

Change from baseline (rhinovirus inoculation, day 0) to day 10

End point values	OC459 - confirmed rhinovirus infection	Placebo - confirmed rhinovirus infection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.01 (± 0.68)	0.17 (± 0.71)		

Statistical analyses

Statistical analysis title	Unpaired T-test
Comparison groups	OC459 - confirmed rhinovirus infection v Placebo - confirmed rhinovirus infection
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49
Method	t-test, 2-sided

Secondary: Peak Expiratory Flow Rate

End point title	Peak Expiratory Flow Rate

End point description:

End point type	Secondary

End point timeframe:

Percentage change from baseline (rhinovirus inoculation, day 0) to trough during infection (up to day 14)

End point values	OC459 - confirmed rhinovirus infection	Placebo - confirmed rhinovirus infection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: percentage change				
arithmetic mean (standard deviation)	-16.9 (± 10.2)	-13.1 (± 12.8)		

Statistical analyses

Statistical analysis title	Unpaired T-test
Comparison groups	OC459 - confirmed rhinovirus infection v Placebo - confirmed rhinovirus infection
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	t-test, 2-sided

Secondary: Forced Expiratory Volume in 1 Second (FEV1)

End point title	Forced Expiratory Volume in 1 Second (FEV1)

End point description:

End point type	Secondary

End point timeframe:

Percentage change from baseline (rhinovirus inoculation, day 0) to trough during infection (up to day 14)

End point values	OC459 - confirmed rhinovirus infection	Placebo - confirmed rhinovirus infection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: percentage change				
arithmetic mean (standard deviation)	-18.5 (± 11.3)	-12.7 (± 14.0)		

Statistical analyses

Statistical analysis title	Unpaired T-test
Comparison groups	OC459 - confirmed rhinovirus infection v Placebo - confirmed rhinovirus infection
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	t-test, 2-sided

Secondary: Exhaled nitric oxide (FeNO)

End point title	Exhaled nitric oxide (FeNO)

End point description:

End point type	Secondary

End point timeframe:

Percentage change from baseline (rhinovirus inoculation, day 0) to peak during infection (measured on days 3, 5, 7, 10 post inoculation)

End point values	OC459 - confirmed rhinovirus infection	Placebo - confirmed rhinovirus infection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: percentage change				
median (inter-quartile range (Q1-Q3))	58 (27 to 101)	23 (0 to 77)		

Statistical analyses

Statistical analysis title	Mann-Whitney test
Comparison groups	Placebo - confirmed rhinovirus infection v OC459 - confirmed rhinovirus infection
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Wilcoxon (Mann-Whitney)

Secondary: Airway Hyperresponsiveness (Assessed as the Provocation Concentration of Histamine Producing a 20% Fall in FEV1, or PC20)

End point title	Airway Hyperresponsiveness (Assessed as the Provocation Concentration of Histamine Producing a 20% Fall in FEV1, or PC20)

End point description:

End point type	Secondary

End point timeframe:

Change from baseline (rhinovirus inoculation, day 0) to day 7

End point values	OC459 - confirmed rhinovirus infection	Placebo - confirmed rhinovirus infection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[1]	13[2]		
Units: mg/mL histamine				
median (inter-quartile range (Q1-Q3))	-0.1 (-0.77 to 0.21)	-0.64 (-2.19 to -0.31)		

Notes:

[1] - One subject could not complete one of the two measurements owing to logistical issues.

[2] - One subject could not complete one of the two measurements owing to logistical issues.

Statistical analyses

Statistical analysis title	Mann-Whitney test
Comparison groups	OC459 - confirmed rhinovirus infection v Placebo - confirmed rhinovirus infection
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Wilcoxon (Mann-Whitney)

Secondary: Viral Load (in Nasal Lavage Samples)

End point title	Viral Load (in Nasal Lavage Samples)

End point description:

End point type	Secondary

End point timeframe:

Peak during infection (up to day 14)

End point values	OC459 - confirmed rhinovirus infection	Placebo - confirmed rhinovirus infection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: viral copies / mL				
median (full range (min-max))	445861 (0 to	215782 (0 to		

9025667)	25240371)

Statistical analyses

Statistical analysis title	Mann-Whitney test
Comparison groups	OC459 - confirmed rhinovirus infection v Placebo - confirmed rhinovirus infection
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.75
Method	Wilcoxon (Mann-Whitney)

Secondary: Total Upper Respiratory Symptom Score

End point title	Total Upper Respiratory Symptom Score

End point description:

End point type	Secondary

End point timeframe:

Sum of daily scores for 14 days after rhinovirus inoculation

End point values	OC459 - confirmed rhinovirus infection	Placebo - confirmed rhinovirus infection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: score on a scale				
median (inter-quartile range (Q1-Q3))	33 (20.5 to 63.3)	41 (18.5 to 63.8)		

Statistical analyses

Statistical analysis title	Mann-Whitney test
Comparison groups	OC459 - confirmed rhinovirus infection v Placebo - confirmed rhinovirus infection

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Nine weeks' study duration, including the first five weeks during which subjects were treated with OC459/placebo.	
Assessment type	Systematic

Dictionary used	
Dictionary name	none used
Dictionary version	n/a

Reporting groups	
Reporting group title	OC459
Reporting group description: All subjects randomised to OC459	
Reporting group title	Placebo
Reporting group description: All subjects randomised to placebo	

Serious adverse events	OC459	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	OC459	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 22 (18.18%)	2 / 22 (9.09%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 22 (18.18%)	2 / 22 (9.09%)	
occurrences (all)	17	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 January 2017	Increase in recruitment target owing to lower infection rate and higher number of drop outs than anticipated.
11 July 2017	Increase in recruitment target as subjects enrolled had fewer asthma symptoms than anticipated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported