Clinical trial results:
An Evaluation of Losmapimod in patients with Chronic Obstructive Pulmonary Disease (COPD) with systemic inflammation stratified using fibrinogen (EVOLUTION)

Summary

EudraCT number	2011-004936-75
Trial protocol	GB
Global end of trial date	06 August 2014

Results information

Result version number	v1 (current)
This version publication date	02 March 2016
First version publication date	02 March 2016
Summary attachment (see zip file)	EVOLUTION SAE Listing (EVOLUTION EudraCT 2011-004936-75.docx)

Trial information

Trial identification

Sponsor protocol code	EVOLUTION

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01541852
WHO universal trial number (UTN)	-
Other trial identifiers	R&D Number: A092519

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust & the University of Cambridge
Sponsor organisation address	Addenbrookes Hospital, Hills Road, Cambridge , United Kingdom, CB2 0QQ
Public contact	Dr Katan Patel , "Cambridge Clinical Trials Unit (Box 111), Addenbrookes Hospital, Hills Road Cambridge" , 01223 349243, katan.patel@addenbrookes.nhs.uk
Scientific contact	Professor Ian Wilkinson , Experimental Medicine & Immunotherapeutics (EMIT) , 01223 296006, ibw20@cam.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	27 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 August 2014
Global end of trial reached?	Yes
Global end of trial date	06 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

"The primary research question is to determine the effect of losmapimod in COPD patients on vascular structure and function as assessed by
1. Vascular inflammation
2. Endothelial function
3. Arterial structure and plaque characteristics"

Protection of trial subjects:

"During participant recruitment, any medical history or clinically relevant abnormality that is deemed by the principal investigator and/or medical monitor to be a safety concern, will make the patient ineligible for inclusion .The safety and tolerability of protocol-specified treatments will be assessed by physical exam findings, 12-lead ECGs recordings, vital signs (blood pressure and heart rate) measurements, clinical laboratory tests (including liver function tests, LFTs), clinical monitoring /observation and spontaneous and elicited adverse event reporting. Methodology for safety assessments will be on file at the clinical research unit.
There will also be overall supervision for the trial provided by the Trial Steering Committee (TSC), to ensure that it is conducted in accordance with the protocol and GCP and to provide advice through its independent chairman.
Participants will be withdrawn from the trial if they experience a SUSAR. At the discretion of the PI/CI, participants will be withdrawn if they experience a SAE, which would affect their ability to participate in the trial. "

Background therapy:

Losmapimod 7.5mg BD (twice daily): 1 x 7.5mg tablet each morning and each evening for 16 weeks.
Placebo: one Placebo tablet to match Losmapimod each morning and each evening, for 16 weeks

Evidence for comparator:

The placebo product visually matches the GW856553(Losmapimod) Tablets 7.5 mg and all placebo batches have been formulated to comply with the test for absence of GW856553X (active ingredient) if tested. The film coat used for the placebo product, Opadry white OY-S-28876, is identical to that used for the active tablets. The placebo product is manufactured using commonly used and recognised tablet excipients that are also employed in the active tablets and are packed into high-density polyethylene (HDPE) bottles.

Actual start date of recruitment	01 April 2012
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: 73
Worldwide total number of subjects	73
EEA total number of subjects	73

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)	21
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

There were 2 sites taking part namely Cambridge University Hospitals NHS Foundation Trust and Royal Brompton & Harefield Foundation NHS Trust. A sufficient number of participants were recruited to complete approximately 60 participant data sets suitable for the primary statistical analysis (approximately 30 per arm).

Pre-assignment

Screening details:

"There is a screening visit within 45 days prior to administration of the first dose of trial medication (V3). Written informed consent must be obtained prior to performance of any protocol specific procedures. The following procedures will be performed:
• Medical history including smoking history.
• Current medication history prior to the screen

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

Blinding implementation details:

The placebo tablets will be manufactured to appear identical to the Losmapimod tablets. Packaging and labelling at point of supply to the patient will be blinded against the active preparation. The site pharmacy will be unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental

Arm description:

Experimental Arm who receive Losmapimod

Arm type	Experimental
Investigational medicinal product name	Losmapimod
Investigational medicinal product code	GW856553
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Losmapimod 7.5mg BD (twice daily): 1 x 7.5mg tablet each morning and each evening for 16 weeks.Placebo: one Placebo tablet to match Losmapimod each morning and each evening, for 16 weeks. Dispensing of IMP will be on Visits 3, 5, 6 and 7. At the point of initial dispensation, the bottles will contain 70 tablets. Participants will be expected to bring their trial medication in with them every visit. Participants will be required to swallow each tablet with approximately 240mL of water.

Arm title	Control

Arm description:

Control arm who receive placebo

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:

Losmapimod 7.5mg BD (twice daily): 1 x 7.5mg tablet each morning and each evening for 16 weeks.Placebo: one Placebo tablet to match Losmapimod each morning and each evening, for 16 weeks. Dispensing of IMP will be on Visits 3, 5, 6 and 7. At the point of initial dispensation, the bottles will contain 70 tablets. Participants will be expected to bring their trial medication in with them every visit. Participants will be required to swallow each tablet with approximately 240mL of water.

Number of subjects in period 1	Experimental	Control
Started	36	37
Completed	29	34
Not completed	7	3
Adverse event, serious fatal	2	-
Consent withdrawn by subject	2	1
Physician decision	3	-
Adverse event, non-fatal	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Experimental
Reporting group description:	
Experimental Arm who receive Losmapimod	
Reporting group title	Control
Reporting group description:	
Control arm who receive placebo	

Reporting group values	Experimental	Control	Total
Number of subjects	36	37	73
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)	11	10	21
From 65-84 years	25	27	52
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	67.3	68.4	
standard deviation	± 8.27	± 7.37	-
Gender categorical Units: Subjects			
Female	11	11	22
Male	25	26	51

End points

End points reporting groups

Reporting group title	Experimental
Reporting group description: Experimental Arm who receive Losmapimod	
Reporting group title	Control
Reporting group description: Control arm who receive placebo	

Primary: Vascular inflammation as measured by FDG/PET scan

End point title	Vascular inflammation as measured by FDG/PET scan

End point description:

Change in mean TBR-max in the index vessel. (The index vessel is the vessel segment with highest mean TBR-max at baseline, excluding the aortic arch. TBR is the tissue to blood ratio; the ratio of FDG uptake in the tissue to the background blood.)

End point type	Primary

End point timeframe:

Visit 3 scan and Visit 9 scan

End point values	Experimental	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	30		
Units: ratio (unit-less)				
arithmetic mean (standard deviation)	-0.258 (± 0.309)	-0.144 (± 0.24)		

Statistical analyses

Statistical analysis title	Change in mean TBR-max in the index vessel

Statistical analysis description:

Linear regression analysis with the change from baseline as the dependent variable, the treatment as the independent variable, and the baseline value, and treatment site as covariates

Comparison groups	Control v Experimental
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.525
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-0.0462

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.191
upper limit	0.0968

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

AEs will be recorded from the start of IMP dosing V3 (Day1), V4, V5, V6, V7 (Days 14/28/56/84 (All 96h)), V8 (Days 105-111), V9 (Days 109-112) and until the follow-up V10 (Days 120-126).
SAEs will be collected over the same time period as stated above fo

Assessment type	Non-systematic

Dictionary used

Dictionary name	None
Dictionary version	1

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: A listing of serious adverse events has been uploaded.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 July 2012	Minor amendment. Reason for amendment: A registration form was created for IMANOVA (non-NHS site 12-EE-0135/0180 SSA) involved in the EVOLUTION clinical trial.
10 August 2012	"1) The telephone number (for information on the product, trial and emergency unblinding) on the Annex 13 dispensing label originally submitted to the MHRA as part of CTA is that of the CI's secretary and not, therefore, available 24-hours. This telephone number is not the label on the unblinded/QP'd product. Since CTA submission, a 24-hour emergency contact number has been put into place for each site (different numbers for each site). This telephone number will appear on a patient card which trial subjects will be provided with at the point of enrolment into the trial (informed consent) and instructed to keep in their possession at all times. To avoid confusion, the telephone number will be removed from the Annex 13 dispensing label. 2) The original Annex 13 label submission to the MHRA listed 'Batch No:' on the label. Now the exact process has been clarified, the label of the final dispensed product will have the addition of 'Bottle No:'. Therefore the Annex 13 label has been clarified by changing 'Batch No:' to 'Batch/Bottle No:'. Please note that the 'Batch No' is exactly the same number as the 'Bottle No:', therefore there is no reconciliation required. The amended Annex 13 label (v2 - 'Batch/Bottle No:') has been further clarified by changing 'Batch/Bottle No:' to 'Bottle No:'. The reason for the change is to avoid any pharmacy staff potentially using the source (original IMP/Placebo) product batch number on the label which could inadvertently unblind the study. This change should minimize any confusion (v2.1). "
01 June 2014	"1) The MRI primary endpoint, which is an optional assessment, requires further clarification (as below from the protocol). Wording has now been added to explain that the MRI primary endpoint analysis will be dependent on a sufficient number of MRI datasets otherwise the endpoint will not be analysed. Page 19 - Change in atheromatous plaque and vessel wall characterisation using MRI and/or FDG-PET/CT, following 16 weeks of treatment. MRI Analysis will be dependent on a sufficient number of datasets. In the case of insufficient datasets the MRI primary endpoint will not be analysed and reported. Page 45 - Change in atheromatous plaque and vessel wall characteristic using MRI and/or FDG-PET/CT, following 16 weeks of treatment. MRI Analysis will be dependent on a sufficient number of datasets. In the case of insufficient datasets the MRI primary endpoint will not be analysed and reported. "

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported