Clinical trial results:
TRANSFORM-UK: A Therapeutic Open Label Study of Tocilizumab in the Treatment of Pulmonary Arterial Hypertension

Summary

EudraCT number	2015-002799-26
Trial protocol	GB
Global end of trial date	09 February 2018

Results information

Result version number	v1 (current)
This version publication date	14 April 2019
First version publication date	14 April 2019
Summary attachment (see zip file)	Final Report (Final Report.pdf)

Trial information

Trial identification

Sponsor protocol code	PO2060

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02676947
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Royal Papworth Hospital NHS Trust
Sponsor organisation address	Papworth Everard, Cambridge, United Kingdom, CB233RE
Public contact	Emily Knightbridge, Royal Papworth Hospital NHS Trust, 44 01223 639694 , e.knightbridge@nhs.net
Scientific contact	Emily Knightbridge, Royal Papworth Hospital NHS Trust, 44 01223 639694 , e.knightbridge@nhs.net

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	17 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2018
Global end of trial reached?	Yes
Global end of trial date	09 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Can blocking the effects of the protein interleukin-6 with the drug tocilizumab safely reduce blood pressure in the lungs of patients with pulmonary arterial hypertension.

Protection of trial subjects:

Strict withdrawal criteria were put in place to protect all subjects, they were as follows: • Development of an Adverse Event (AE) where continuation of the subject's participation in the study is thought by the Investigator to be inappropriate.
- Subject meets liver stopping criteria.
- Subject begins treatment with a prohibited concomitant therapy.
- Subject adjudged by investigator to have a clinically significant neutropaenia or thrombocytopaenia.

Reference ranges for the above laboratory tests were detailed in the protocol.

Monthly blood tests and urine pregnancy tests on women of childbearing potential were performed as a drug safety measure at all clinic visits. These were performed at the subjects local laboratory to ensure timely reporting.

Background therapy:

Tocilizumab is an IL-6 receptor antagonist established as safe, well tolerated and effective, primarily in rheumatoid arthritis, and has shown promise in scleroderma. In uncommon cases, where the underlying cause of PAH is an established inflammatory process such as SLE, mixed connective tissue disease and Castleman's disease, there have been case reports of regression of PAH with tocilizumab. We therefore propose a phase II open-label proof of concept study of tocilizumab in group I PAH.

Evidence for comparator:

n/a as the study was open label and all patients received study drug.

Actual start date of recruitment	01 October 2015
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: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

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)	20
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects will be identified using data collected during their routine outpatient appointments.
Recruitment began on the 23rd December 2015 and Papworth Hospital was the first site to be opened.
The first patient was screened on the 6th of January 2016.
The final patient was recruited on the 7th April 2017.

Pre-assignment

Screening details:

The screening visit will include the following:
Obtain Informed Consent

- Medical History
- Demographics
- Urine pregnancy test (if applicable)
- Physical Exam and WHO class assessment
- Vital signs
- Pulmonary Function tests
- Six minute walk test
- Borg assessment pre and post 6MWT
- PH medication
- Routine Bloods

Pre-assignment period milestones

Number of subjects started	29
Number of subjects completed	29

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

n/a open label.

Arms

Arm title	Tocilizumab

Arm description:

Study drug - open label

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	Ro4877533-000
Other name	RoActemra, Actemra, MRA, Atlizumab
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

8mg/kg of Tocilizumab

Number of subjects in period 1	Tocilizumab
Started	29
Completed	19
Not completed	10
Physician decision	4
Consent withdrawn by subject	1
Adverse event, non-fatal	1
suspected unexpected serious adverse reaction	1
Serious adverse event	3

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description:

In this multi-centre open label single-arm study, patients were recruited across 8 centres in the UK. Twenty-nine patients (M/F 10/19; mean age 54.9) were recruited in total between January 2016 to April 2017. Fifteen patients had idiopathic PAH, ten connective tissue disease associated PAH (CTD-PAH), and four heritable/ BMPR2 associated PAH. Six patients were withdrawn prior to drug administration; one chest infection, one exacerbation of co-morbid disease, four at baseline RHC. Twenty-three patients received study drug. Drug was discontinued in 4 patients due to serious adverse events. There were no deaths in the trial.

Reporting group values	Treatment period	Total	
Number of subjects	29	29	
Age categorical			
Patients on stable therapy aged 18-70 were enrolled with a diagnosis of group 1 PAH: Idiopathic or Heritable PAH, PAH associated with connective tissue disease excluding SLE, RA and mixed CTD.			
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)	20	20	
From 65-84 years	9	9	
85 years and over	0	0	
Gender categorical			
Both male and female participants are eligible for this study. However Female subjects of childbearing potential, if sexually active, must agree to use 2 reliable methods of contraception, from the Screening Visit until at least 4 months following the last dose of Investigational Product. Subjects who have had a Copper T 380A IUD or LNg 20 IUD inserted are not required to use additional methods of contraception. Urine pregnancy tests were performed at each visit is a female subject was of childbearing potential. All of this information was collected on the electronic CRF OpenClinica.			
Units: Subjects			
Female	19	19	
Male	10	10	
Type of Pulmonary Hypertension			
This trial was looking at group 1 pulmonary arterial hypertension (PAH)- this group can then be subdivided further as below : 1. Idiopathic or Heritable PAH 2. PAH associated with connective tissue disease excluding SLE, RA, mixed CTD 3. Drug or toxins induced PAH			
Units: Subjects			
Idiopathic PAH	15	15	
Heritable PAH	4	4	
PAH associated with connective tissue disease	10	10	
Drug or toxins induced PAH	0	0	

End points

End points reporting groups

Reporting group title	Tocilizumab
Reporting group description: Study drug - open label	

Primary: Pulmonary vascular resistance measured using invasive haemodynamic assessment by right heart catheter

End point title	Pulmonary vascular resistance measured using invasive haemodynamic assessment by right heart catheter[1]

End point description:

Pulmonary Vascular resistance as measured by invasive haemodynamic assessment via fluid-filled right heart catheter using cardiac output measured by thermodilution technique. This endpoint is looking for a reduction in Pulmonary Vascular resistance at the end of study right heart catheter.

End point type	Primary

End point timeframe:

The subject had a right heart catheter at baseline (unless they had had one in the last 30 days prior to baseline as this one could be used) and one at the end of study visit.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: I have uploaded a summary chart with the analysis that has been completed in it. It was not analysed in such a way that we had any of the values that were required in the statistical analysis field.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	19[2]			
Units: dynes×s×cm-5				
number (not applicable)	19			

Notes:

[2] - only completed for those subjects who had a RHC pre and post treatment

Attachments (see zip file)	Summary- PVR/End point summary- Pulmonary vascular

Statistical analyses

No statistical analyses for this end point

Primary: Safety as defined by the incidence and severity of adverse events

End point title	Safety as defined by the incidence and severity of adverse events[3]

End point description:

End point type	Primary

End point timeframe:

Safety as defined by the incidence and severity of adverse events. adjudged respectively on the occurrence of adverse events and serious adverse events as classified by use of the Medical Dictionary for Regulatory Activities.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: I have uploaded a summary chart with the analysis that has been completed in it. It was not analysed in such a way that we had any of the values that were required in the statistical analysis field. Descriptive statistics were used only for this endpoint.

End point values	Tocilizumab			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: subject cases	29			

Attachments (see zip file)	Summary/Safety as defined by the incidence and severity of

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the moment the subject had signed the informed consent form to the safety follow up 4 months post end of study.
For serious adverse events they were required to be reported in 24 hours of knowledge of the event.

Adverse event reporting additional description:

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Some of the SAEs and SUSARS are broken down into event for MedDRA coding and to ensure everything is captured. So while there were 7 SAEs/SUSARs there are 10 events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	All subjects who recieved at least one dose of study drug

Reporting group description:

All subjects who recieved at least one dose of study drug.

Serious adverse events	All subjects who recieved at least one dose of study drug		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 23 (30.43%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Femoral artery occlusion	Additional description: Left femoral (common) artery occlusion - critical ischaemia		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension aggravated	Additional description: SUSAR		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Drenching sweats	Additional description: other part of combination SAE Chest Tightness and sweats.		

subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain	Additional description: SUSAR- combination with Vomiting and Diarrhoea		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea	Additional description: SUSAR- combination with Vomiting and abdominal pain.		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting	Additional description: SUSAR- combination with Abdominal pain and Diarrhoea		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chest Tightness	Additional description: This is a combination SAE- Chest Tightness and sweats. the two have been separated for coding purposes.		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnea exacerbated			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urosepsis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia	Additional description: Admitted to local hospital with community acquired pneumonia		

subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All subjects who recieved at least one dose of study drug		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 23 (82.61%)		
Vascular disorders			
Multiple	Additional description: Dizziness Hyperaemia Hypertension Hypotension Pulmonary hypertension		
subjects affected / exposed	6 / 23 (26.09%)		
occurrences (all)	6		
Surgical and medical procedures			
Nasal operation, Tooth extraction			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	2		
General disorders and administration site conditions			
Multiple	Additional description: Chest pain, Decreased appetite, Disease progression, Fatigue, Feeling cold, Flushing, Hernia, Influenza like illness, Injection site mass, Malaise		
subjects affected / exposed	10 / 23 (43.48%)		
occurrences (all)	22		
Respiratory, thoracic and mediastinal disorders			
Multiple	Additional description: Chest pain Cough Dry throat Dyspnoea Nasal congestion Oropharyngeal pain Productive cough Sinusitis Sneezing Upper respiratory tract infection		
subjects affected / exposed	13 / 23 (56.52%)		
occurrences (all)	23		
Psychiatric disorders			

Multiple	Additional description: Anxiety Depressed mood Depression Insomnia Panic attack Tearfulness		
subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	7		
Investigations			
Multiple	Additional description: Blood cholesterol abnormal Blood cholesterol increased Blood creatine phosphokinase increased Blood iron decreased Blood potassium decreased Blood triglycerides abnormal Body temperature increased C-reactive protein increased ….		
subjects affected / exposed	9 / 23 (39.13%)		
occurrences (all)	25		
Injury, poisoning and procedural complications			
Multiple	Additional description: Contusion Corneal abrasion Drug-induced liver injury Fall Neurological and psychiatric procedural complications Tendonitis		
subjects affected / exposed	7 / 23 (30.43%)		
occurrences (all)	12		
Cardiac disorders			
Multiple	Additional description: Cardiac failure, Dizziness Dizziness exertional Dizziness postural Haemoptysis Oedema peripheral Palpitations Presyncope Ventricular extrasystoles Cardiac signs and symptoms NEC Peripheral swelling		
subjects affected / exposed	12 / 23 (52.17%)		
occurrences (all)	27		
Nervous system disorders			
Multiple	Additional description: Dysgeusia Headache Hypoaesthesia Optic ischaemic neuropathy Sensory disturbance Tremor		
subjects affected / exposed	7 / 23 (30.43%)		
occurrences (all)	10		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Gastrointestinal disorders			
Multiple	Additional description: Abdominal discomfort Abdominal distension Abdominal pain Abdominal pain upper Colitis Diarrhoea Diverticulitis Diverticulum Dyspepsia Flatulence Gastric dilatation Gastroenteritis Gingival pain Haematochezia Mouth ulceration Nausea ..		
subjects affected / exposed	12 / 23 (52.17%)		
occurrences (all)	26		
Skin and subcutaneous tissue disorders			
Multiple	Additional description: Increased tendency to bruise Papule Rash Rash pruritic scleroderma flare up		
subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Multiple	Additional description: Arthralgia Back pain Musculoskeletal chest pain Musculoskeletal pain Musculoskeletal stiffness Pain in extremity		
subjects affected / exposed	7 / 23 (30.43%)		
occurrences (all)	11		
Infections and infestations			
Multiple	Additional description: Candida infection, Lower respiratory tract infection Nasopharyngitis, Rhinitis Tooth abscess Urinary tract infection Viral infection		
subjects affected / exposed	13 / 23 (56.52%)		
occurrences (all)	27		

Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	 1 / 23 (4.35%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2015	Amendment done due to the MHRA requesting some changes to the protocol summarised below: extending the use of contraceptive methods to at least 3 months post last dose of study drug adding in an exclusion criteria of active severe infection safety follow up moved from 30 days to 4 months post end of study Telephone follow up added at 30 days post end of study visit Temperature added to vital signs CRP added to safety blood tests clarification of study drug continuation and general formatting
12 July 2016	Addition of trial Website Trial Poster for sites to display to aid recruitment Addition of a new site -Royal United Hospitals Bath Updated patient information sheet: change of working about possible overnight stays. From you will be asked to you may be asked/ may be required.
31 October 2016	Update to the protocol: • Increase recruitment from 21 to 26 • Removal of 6MWD upper limit • 30 day RHC can be used at baseline • Clarification of process for abnormal blood results (platelets, neutrophils and LFTs) in line with the Summary of Product Characteristics (SPC) • Removal of Ophthalmic exclusion • Addition of Diverticulitis exclusion • Extension of termination visit from within 7 days to 14 days Addition of a Principle investigator from the Bath site

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 final publication is being worked on currently and once published will be disseminated to all trial participants who expressed an interest via their consent form and all participating sites.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28956500