Clinical trial results:
COBALT: Coversin Global Study: An Open-Label, Safety and Efficacy Trial in PNH Patients

Summary

EudraCT number	2016-002067-33
Trial protocol	GB
Global end of trial date	21 December 2017

Results information

Result version number	v1 (current)
This version publication date	06 January 2019
First version publication date	06 January 2019
Summary attachment (see zip file)	AK579 Synopsis (CLINICAL STUDY REPORT v 1.0 - 20Dec2018 Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	AK579

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Akari Therapeutics plc
Sponsor organisation address	75-75 Wimpole Street, London, United Kingdom, W1G 9RT
Public contact	Medical Director, Akari Therapeutics Plc, +44 0208004 0261, wwd@akaritx.com
Scientific contact	Medical Director, Akari Therapeutics Plc, +44 0208004 0261, wwd@akaritx.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	13 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2017
Global end of trial reached?	Yes
Global end of trial date	21 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of the study are:
• To assess the safety and tolerability of Coversin for all patients for the duration of the study.
• To assess efficacy of the dosage regimen to reduce haemolysis and control the signs and symptoms thereof, in PNH subjects as manifested by:
i. Serum lactic dehydrogenase (LDH) change from baseline (day 1) to day 28
ii. Haemoglobin (Hb) at day 28 and day 90, absolute and change from baseline
iii. Number of blood transfusions
iv. Quality of Life - EORTC QLQ-C30 at day 1 (baseline), 7, 14, 21, 29, 60 and 90 days
v. Quality of Life – EQ-5D-5L at baseline day 1 (baseline) up to day 60 and then at day 90.

• To determine whether self-injection by subjects with PNH is well-accepted and the home care nursing supervision period sufficient using a (non validated) questionnaire at day 29 and day 90.

Protection of trial subjects:

There were no specific measures put in place for the protection of trial subjects - normal GCP procedures were utilised

Background therapy:

Normal standard of care excluding treatment with other complement C5 inhibitors

Evidence for comparator:

No comparator

Actual start date of recruitment	25 August 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	Poland: 5
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	5
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between 13 December 2016 and last patient last visit was 21 December 2017. The study was opened up for recruitment in both UK and Poland with the first patient being recruited in the UK and also the last patient.

Pre-assignment

Screening details:

Nine patients were screened with 8 being recruited. One patient was screened but withdrew consent at this point. They subsequently decided to take part in the study,

Period 1

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

Blinding implementation details:

Not applicable

Arms

Arm title	Intent to Treat

Arm description:

All patients received the IMP treatment

Arm type	Experimental
Investigational medicinal product name	rVA576 (Coversin)
Investigational medicinal product code	rVA576
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The product is packaged as a lyophilised powder for solution for injection in a vail containing 18 mg/Vial. The product is reconstituted prior to use with 0.6mL WFI giving a concentration of 30mg/mL.
Protocol version 3 used an ablating dosage scheme of 60 mg followed by three times 30 mg every 12 hours. Patients then received 15 mg every 12 hours up to Day 28 and then 30 mg once daily every 24 hours to the end of the study. Patients doses could be amended on response and patients would be dosed either every 24 hours or every 12 hours.
Protocol version 4 used an refined ablating scheme of 60 mg followed by 30 mg 12 hours later and then from Days 2 -28 a dose of 22.5 mg every 12 hours. From Day 29 to the end of the study patients received 45 mg once daily. If control of CH50 was not maintained patients could have their 45 mg dose split into 22.5 mg every 12 hours.

Number of subjects in period 1	Intent to Treat
Started	8
Completed	7
Not completed	1
Physician decision	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	8	8	
Age categorical			
The patients recruited were adults over the age of 18			
Units: Subjects			
Adults (18-64 years)	5	5	
From 65-84 years	3	3	
Gender categorical			
Patients could be male or female			
Units: Subjects			
Female	4	4	
Male	4	4	

End points

End points reporting groups

Reporting group title	Intent to Treat
Reporting group description:	
All patients received the IMP treatment	

Primary: Reduction in serum LDH to <=1.8 x upper limit of Normal from Day 1 to Day 29

End point title	Reduction in serum LDH to <=1.8 x upper limit of Normal from Day 1 to Day 29[1]
End point description:	
The number of patients who achieved a reduction in serum LDH to <= to 1.8 times the upper limit of normal (ULN) by Day 29. There was a drop in LDH over time with median LDH <= 1.8 x ULN reached by Day 29 and maintained throughout the remainder of the study. The number of patients who successfully achieved the primary endpoint was five out of eight.	
End point type	Primary
End point timeframe:	
Day 1 to Day 29	

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: Descriptive statistics were the only statistics performed on the results

End point values	Intent to Treat			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Number of patients	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in LDH at Day 29 to 50% or less of mean of all pre-dose measurements

End point title	Reduction in LDH at Day 29 to 50% or less of mean of all pre-dose measurements
End point description:	
Reduction of LDH at Day 29 to 50% or less of the mean of all pre-dose measurements taken within 14 days of commencing Coversin treatment	
End point type	Secondary
End point timeframe:	
Day 29	

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in CH50 from Day 1 pre-dose to Days 7, 14, 21, 29, 60 and 90

End point title	Reduction in CH50 from Day 1 pre-dose to Days 7, 14, 21, 29, 60 and 90

End point description:

The derived average CH50 level obtained from the Day 1 pre-dose evaluation will be regarded as baseline. Changes and percentage changes from baseline to each post-baseline CH50 average assessment will be derived.

End point type	Secondary

End point timeframe:

Day 1 pre-dose to Day 7, 14, 21, 29, 60 and 90

End point values	Intent to Treat			
Subject group type	Reporting group			
Number of subjects analysed	8[2]			
Units: Change and percentage	7			

Notes:

[2] - One patient was withdrawn at Day 43 so no Day 60 and 90 values available

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in serum LDH to <= 1.8 times the ULN for the Investigators' Reference Laboratory at Day 60

End point title	Reduction in serum LDH to <= 1.8 times the ULN for the Investigators' Reference Laboratory at Day 60

End point description:

The number of patients who achieved a reduction in serum LDH to <= 1.8 times the ULN for the Investigator's reference laboratory at Day 60 and Day 90

End point type	Secondary

End point timeframe:

From Day 1 pre-dose to Day 60

End point values	Intent to Treat			
Subject group type	Reporting group			
Number of subjects analysed	7[3]			
Units: Number	4			

Notes:

[3] - One patient was withdrawn at Day 43

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in serum LDH to < = 1.8 times the ULN for the Investigator's reference laboratory at Day 90

End point title	Reduction in serum LDH to < = 1.8 times the ULN for the Investigator's reference laboratory at Day 90

End point description:

The number of patients with a reduction in serum LDH to <=1.8 times the ULN for the Investigator's reference laboratory at Day 90

End point type	Secondary

End point timeframe:

From Day 1 pre-dose to Day 90

End point values	Intent to Treat			
Subject group type	Reporting group			
Number of subjects analysed	7[4]			
Units: Number	3			

Notes:

[4] - One patient was withdrawn at Day 43

Statistical analyses

No statistical analyses for this end point

Secondary: Increase in haemoglobin from Day 1 to Day 29 to Day 90

End point title	Increase in haemoglobin from Day 1 to Day 29 to Day 90

End point description:

Mean Hb started at approximately 0.8x the LLN and remained at a mean of 0.8 x the LLN though out the trial

End point type	Secondary

End point timeframe:

Day 1 predose to Day 90

End point values	Intent to Treat			
Subject group type	Reporting group			
Number of subjects analysed	7[5]			
Units: Mean	7			

Notes:

[5] - One patient was withdrawn at Day 43

Statistical analyses

No statistical analyses for this end point

Secondary: Number of blood transfusions during study period

End point title	Number of blood transfusions during study period

End point description:

The number of patients who did not require transfusions by the end of the study

End point type	Secondary

End point timeframe:

Day 1 pre-dose to Day 90

End point values	Intent to Treat			
Subject group type	Reporting group			
Number of subjects analysed	6[6]			
Units: Number	3			

Notes:

[6] - Only 6 received transfusions prior to joining the study

Statistical analyses

No statistical analyses for this end point

Secondary: Change in EORTC QLQ-C30 Score from Day 1 (baseline) to Days 7, 14, 21, 29, 60 and 90

End point title	Change in EORTC QLQ-C30 Score from Day 1 (baseline) to Days 7, 14, 21, 29, 60 and 90

End point description:

Patients were to complete the EORTC QLQ-C30 prior to start of Coversin Administration on Day 1 and repeat on Day 7 (+/- 1), Days 14, 21, 29, 36, 60 and Days 90 (+/- 2).
QLQ-C30 comprises of 30 questions on daily quality of life with each question having a response score on a scale of 1-4 or 1-7. QLQ-C30 incorporates a global health status, five functional scales, three symptom scales and six single items.
THE EORTC-QLQ-C30 showed a general improvement in most aspects.

End point type	Secondary

End point timeframe:

Day 1 baseline to Days 7, 14, 21, 29,, 60 and 90

End point values	Intent to Treat			
Subject group type	Reporting group			
Number of subjects analysed	7[7]			
Units: Response score	7			

Notes:

[7] - One patient was withdrawn on Day 43

Statistical analyses

No statistical analyses for this end point

Secondary: Change in EQ-5D-5L from Baseline Day 1 to Day 60 and Day 90

End point title	Change in EQ-5D-5L from Baseline Day 1 to Day 60 and Day 90

End point description:

Patients were to complete the EQ-5D-5L prior to start of Coversin administration on Day 1 and every day up to Day 60 then at Day 90. EQ-5D-5L comprises of 5 questions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each with five levels plus the EQ Visual Analogue scale. A general improvement in all five scales was observed in all EQ-5D-5L.

End point type	Secondary

End point timeframe:

From Day 1 predose to Day 60 and Day 90

End point values	Intent to Treat			
Subject group type	Reporting group			
Number of subjects analysed	7[8]			
Units: Percentage change	7			

Notes:

[8] - One patient was withdrawn at Day 43

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study medication to end of study (approximately 90 days of treatment). All patients except one entered the separate long-term safety study

Adverse event reporting additional description:

Reporting was a mixture of systematic and non-systematic through the use of diary cards

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Safety Analysis Set

Reporting group description:

All subjects who received at least one dose of Coversin

Serious adverse events	Safety Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Angina pectoris			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Lethargy			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Infections and infestations			
Staphylococcal infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)		
Investigations			
Neutrophil count decreased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
White blood cell count decreased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	40		
Injection site pruritus			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	14		

Injection site pain subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 24		
Injection site bruising subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 8		
Injection site discharge subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 8		
Injection site haematoma subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Injection site hypersensitivity subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Injection site induration subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Injection site swelling subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 12		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Lymphadenopathy alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Gastrointestinal disorders Abdominal discomfort alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Diarrhoea			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypophosphataemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Hypoproteinaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2016	Protocol amendment 2 dated 27 June 2016 was updated at the request of the MHRA during their assessment of the initial CTA. The changes included the addition of a discussion on C5 polymorphisms and the need to monitor patients for complete inhibition of CH50 in accordance with the information in the IB. To include information on the fact that the phototoxicity potential of Coversin was unknown and that patients should avoid excessive exposure to sunlight or UV light. The addition of a new exclusion criteria to exclude patients with a known sensitivity to the excipients of meningococcal vaccines, ciprofloxacin or any other antibiotic being administered for the purpose of meningococcal prophylaxis.
12 September 2016	Change in ablating dose from four times 30 mg every 12 hours over to days to an initial ablating dose of 60 mg followed by three times 30 mg every 12 hours for 2 days. There was also a change in the proposed dosing scheme from 30 mg every 24 hours from Day 3 to Day 88 to the initial ablating dose would be followed by 15 mg every 12 hours from Day 3 to Day 28 and then a switch to 30 mg once daily until the end of the trial. The addition of text to state that the dose could be changed from Day 7 onwards in the case of an ineffective dose (e.g. 30 mg once daily) to either an increased dose of 45 mg once daily for example or by dividing the single dose into two doses administered 12 hours apart (e.g. 15 mg or 22.5 mg). An additional secondary endpoint was added to capture the reduction in serum LDH to <= 1.8 times the upper limit of normal (ULN) for the Investigator's reference laboratory or 500 I U/L whichever is the lower at Day 60 and at Day 90. There were other changes made throughout the protocol to reflect these updates to the dosing schedule including the frequency of blood draws and visits.
28 July 2017	The main changes to protocol amendment 4 dated 19 June 2017 was a change to the ablating dose from 60 mg followed by three times 30 mg over 12 hours for 2 days to 60 mg followed by 30 mg 12 hours later all in the first day. The initiation phase dosing was changed from 15 mg every 12 hours for 26 days to 22.5 mg every 12 hours for 27 days. The maintenance phase dosing was changed from a single dose of 30 mg every 24 hours to a single dose of 45 mg every 24 hours. Dose increases were no longer permitted but the dose could be split to 12 hourly. There was the removal of some of the homecare visits. Additional safety assessments were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported