Clinical trial results:
Coversin in Paroxysmal Nocturnal Haemoglobulinuria (PNH) in patients with resistance to Eculizumab due to complement C5 Polymorphisms

Summary

EudraCT number	2015-003778-34
Trial protocol	NL
Global end of trial date	20 March 2018

Results information

Result version number	v1 (current)
This version publication date	18 November 2021
First version publication date	18 November 2021

Trial information

Trial identification

Sponsor protocol code	AK578

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02591862
WHO universal trial number (UTN)	-
Other trial identifiers	Coversin VIP578: Coversin VIP578

Notes:

Sponsors

Sponsor organisation name	Akari Therapeutics plc
Sponsor organisation address	75-76 Wimpole Street, London, United Kingdom, W1G 9RT
Public contact	Chief Scientific Officer, Akari Therapeutics Plc, +44 (0)2080040261, miles.nunn@akaritx.com
Scientific contact	Chief Scientific Officer, Akari Therapeutics Plc, +44 (0)2080040261, miles.nunn@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	20 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 March 2018
Global end of trial reached?	Yes
Global end of trial date	20 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective: Safety and tolerability of Nomacopan

Protection of trial subjects:

The study was performed in accordance with the current version of the declaration of Helsinki. The trial was conducted in agreement with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) E6(R1) which were current at the time of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 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	Netherlands: 1
Worldwide total number of subjects	1
EEA total number of subjects	1

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)	1
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were screened up to 14 days prior to study treatment to confirm eligibility for the study. A total of 1 patient was screened and enrolled onto the study.

Period 1

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

Arms

Arm title	Nomacopan (Coversin)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Nomacopan
Investigational medicinal product code	rVA576
Other name	Coversin, rEV576
Pharmaceutical forms	Powder for solution for injection, Solution for injection in vial
Routes of administration	Solution for injection , Subcutaneous use

Dosage and administration details:

Patient will be given a single ablating dose of 0.57mg/kg per subject followed by daily repeat maintenance doses. The initial repeat dose will be 25% of the ablating dose. If this is insufficient to maintain complement inhibition at ≤10% of baseline (pre-treatment) level after 5 days of treatment the daily dose will be increased by doubling until that level of inhibition is achieved. In the event of 100% inhibition being achieved the dose may be titrated downwards at the PI’s discretion until a satisfactory clinical result is obtained. If at any point in treatment complement inhibition falls to less than 50% of baseline a further ablating dose of 0.57mg/kg should be given. Nomacopan lyophilised powder in each vial was diluted with 0.6 mL water for injection prior to use.

Number of subjects in period 1	Nomacopan (Coversin)
Started	1
Completed	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description: Results from 1 enrolled patient.	

Reporting group values	Overall Trial	Total	
Number of subjects	1	1	
Age categorical 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)	1	1	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	1	1	
Race Units: Subjects			
white	1	1	
Region of enrolment Units: Subjects			
Netherlands	1	1	
Dependency on blood transfusion Units: Subjects			
Dependent on blood transfusion	0	0	
Not dependent on blood transfusion	1	1	
Weight Units: kilogram(s)			
arithmetic mean	67.8		
standard deviation	± 0	-	
Height Units: centimeter			
arithmetic mean	172		
standard deviation	± 0	-	
Serum Lactate Dehydrogenase Units: U/L			
arithmetic mean	1391		
standard deviation	± 0	-	
Haemoglobin concentration (Hb)			

Units: Millimole(s)/litre			
arithmetic mean	8.2		
standard deviation	± 0	-	
Haptoglobin (Hp) concentration			
Units: grams(s)/litre			
arithmetic mean	0.0		
standard deviation	± 0	-	

End points

End points reporting groups

Reporting group title	Nomacopan (Coversin)

Reporting group description: -

Primary: Measurement of Serum lactate dehydrogenase (LDH) from Day 0 (pre-dose) to Day 28 (AUC) compared with 28 days pre-treatment

End point title	Measurement of Serum lactate dehydrogenase (LDH) from Day 0 (pre-dose) to Day 28 (AUC) compared with 28 days pre-treatment[1]

End point description:

LDH is an indicator of disease progression in patients with PNH and is expected to fall to within 2x upper limit of normal (ULN) within 28 days in successfully treated patients. Units are measured in ratio of LDH:ULN, where the ULN is 250 U/L.

End point type	Primary

End point timeframe:

Day 0 and Day 28

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: This was an open-label study in which just one patient was recruited. Simple descriptive statistics were therefore used.

End point values	Nomacopan (Coversin)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: ratio of LDH:ULN (250 U/L)				
number (not applicable)				
Day 0	5.6			
Day 28	1.9			

Statistical analyses

No statistical analyses for this end point

Primary: Number and Type of Adverse Events (AE)

End point title	Number and Type of Adverse Events (AE)[2]

End point description:

The number and type of reported AEs will be recorded as well as the opinion of the Principle Investigator (PI) as to their possible relationship to the study drug.

End point type	Primary

End point timeframe:

2 years

Notes:

[2] - 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: This was an open-label study in which just one patient was recruited. Simple descriptive

statistics were therefore used.

End point values	Nomacopan (Coversin)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Events				
Serious Adverse Events (SAE)	2			
Adverse Event (AE) (Total)	20			
Treatment Emergent Adverse Event (TAEA)	13			
AE- moderate	1			
AE- severe	1			
AE- mild	18			

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of Haemoglobin (Hb) at Days 28, 90 and 180, absolute and change from baseline

End point title	Measurement of Haemoglobin (Hb) at Days 28, 90 and 180, absolute and change from baseline
End point description:	
Measuring change in mean Hb from Day 28, Day 90 and Day 180 (absolute and change from baseline)	
End point type	Secondary
End point timeframe:	
Baseline, Day 28, Day 90 and 180	

End point values	Nomacopan (Coversin)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: millimole(s)/litre				
number (not applicable)				
Baseline	8.2			
Day 28 (absolute)	7.8			
Day 28 (change from baseline)	-0.7			
Day 90 (absolute)	7.8			
Day 90 (change from baseline)	-0.4			
Day 180 (absolute)	8.0			
Day 180 (change from baseline)	-0.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of Lactate Dehydrogenase (LDH) at Baseline, day 90 and 180

End point title	Measurement of Lactate Dehydrogenase (LDH) at Baseline, day 90 and 180

End point description:

Measuring the change in LDH at Baseline, Day 90 and Day 180. LDH is an indicator of disease progression in patients with PNH and is expected to fall to within 2x upper limit of normal (ULN) within 28 days in successfully treated patients. Units are measured in ratio of LDH:ULN, where the ULN is 250 U/L.

End point type	Secondary

End point timeframe:

Baseline, Day 90 and Day 180

End point values	Nomacopan (Coversin)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: ratio of LDH:ULN (250 U/L)				
number (not applicable)				
Day 0	5.6			
Day 90	1.6			
Day 180	1.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of Haptoglobin (Hp) at Days 28, 90 and 180, Absolute and Change From Baseline

End point title	Measurement of Haptoglobin (Hp) at Days 28, 90 and 180, Absolute and Change From Baseline

End point description:

Measuring change in mean Hp from Day 28, Day 90 and Day 180 (absolute and change from baseline)

End point type	Secondary

End point timeframe:

Baseline, Day 28, Day 90 and Day 180

End point values	Nomacopan (Coversin)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: gram(s)/litre				
number (not applicable)				
Baseline	0.0			
Day 28	0.0			
Day 90	0.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Dependency on blood transfusion

End point title	Dependency on blood transfusion

End point description:

Number of participants depending on blood transfusion prior to starting the study compared to during the study.

End point type	Secondary

End point timeframe:

Day 0 through to study completion (2 years)

End point values	Nomacopan (Coversin)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Participants				
Transfusion dependent prior to starting trial	0			
Transfusion dependent during trial	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Functional Assessment of Chronic Illness Therapy (FACIT) Score at Days 0, 28, 90 and 180

End point title	Change in Functional Assessment of Chronic Illness Therapy (FACIT) Score at Days 0, 28, 90 and 180

End point description:

Functional Assessment of Chronic Illness Therapy – fatigue (FACIT-F) is a 13 item instrument designed to assess fatigue/tiredness and it's impact on daily activities and functioning in a chronic disease setting. The scale for each question in relation to quality of life ranges from 0-4 where 0= not at all, 1= a little bit, 2= somewhat, 3 = quite a bit and 4= very much. An increase in the scale score indicates an improvement in quality of life (less fatigue). A maximum score of 52 is interpreted as no fatigue . Baseline is assumed as 0.0 to demonstrate the change in units. The subscale score (as presented) is

determined as per FACIT-f guidance, by multiplying the sum of the item scores by the number of items in the subscale, then divide by the number of items answered.

End point type	Secondary

End point timeframe:

Day 28, 90 and 180

End point values	Nomacopan (Coversin)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: FACIT-f scale (Change from Baseline)				
number (not applicable)				
Day 28	13.0			
Day 90	13.3			
Day 180	11.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Quality Of Life Questionnaire (QOQ) Score at Days 0, 28, 90 and 180

End point title	Change in Quality Of Life Questionnaire (QOQ) Score at Days 0, 28, 90 and 180

End point description:

The European Organization for Research and Treatment of Cancer (EORTC) QOQ C30 instrument measures the change in the quality of of life of patients in the trial. Quality of Life Questionnaire (QLQ)-C30 comprises 30 questions on daily quality of life and incorporates a global health status, five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, nausea/vomiting, pain), and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties). Higher score for the functioning scales and global health status denote a better level of functioning (i.e. a better state of the patient), while higher scores on the symptom and single-item scales indicate a higher level of symptoms (i.e. a worse state of the patient). Baseline is assumed as 0.0 to demonstrate the change in units.

End point type	Secondary

End point timeframe:

Day 28, 90 and 180

End point values	Nomacopan (Coversin)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: QLQ-C30 scale (Change from baseline)				
number (not applicable)				
Global Health Status/ QOL (day 28)	16.7			

Global Health Status/ QOL (day 90)	16.7			
Global Health Status/ QOL (day 180)	16.7			
Physical Functioning (day 28)	6.6			
Physical Functioning (day 90)	0.0			
Physical Functioning (day 180)	6.6			
Role functioning (day 28)	33.4			
Role functioning (day 90)	33.4			
Role functioning (day 180)	16.7			
Emotional functioning (day 28)	16.6			
Emotional functioning (day 90)	8.3			
Emotional functioning (day 180)	8.3			
Cognitive functioning (day 28)	33.3			
Cognitive functioning (day 90)	16.7			
Cognitive functioning (day 180)	16.7			
Social functioning (day 28)	0.0			
Social functioning (day 90)	0.0			
Social functioning (day 180)	0.0			
Fatigue symptom scale (day 28)	-11.1			
Fatigue symptom scale (day 90)	0.0			
Fatigue symptom scale (day 180)	0.0			
Nausea and vomiting symptom scale (day 28)	0.0			
Nausea and vomiting symptom scale (day 90)	0.0			
Nausea and vomiting symptom scale (day 180)	0.0			
Pain symptom scale (day 28)	0.0			
Pain symptom scale (day 90)	16.7			
Pain symptom scale (day 180)	0.0			
Symptom: Dyspnoea (day 28)	0.0			
Symptom: Dyspnoea (day 90)	0.0			
Symptom: Dyspnoea (day 180)	0.0			
Symptom: Insomnia (day 28)	-33.3			
Symptom: Insomnia (day 90)	0.0			
Symptom: Insomnia (day 180)	0.0			
Symptom: Appetite loss (day 28)	0.0			
Symptom: Appetite loss (day 90)	0.0			
Symptom: Appetite loss (day 180)	0.0			
Symptom: constipation (day 28)	0.0			
Symptom: constipation (day 90)	0.0			
Symptom: constipation (day 180)	0.0			
Symptom: diarrhoea (day 28)	-33.3			
Symptom: diarrhoea (day 90)	-33.3			
Symptom: diarrhoea (day 180)	-33.3			
Symptom: financial difficulties (day 28)	0.0			
Symptom: financial difficulties (day 90)	0.0			
Symptom: financial difficulties (day 180)	0.0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Duration of the study (2 years)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0
Reporting groups	
Reporting group title	nomacopan (coversin)

Reporting group description: -

Serious adverse events	nomacopan (coversin)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Breakthrough haemolysis			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	nomacopan (coversin)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Vascular disorders			
Cold fingers and toes			

subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	6		
Insomnia			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Cough			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Flu like symptoms			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	5		
Injection site reaction			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	13		
Malaise			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Non-cardiac chest pain			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Coughing subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Sore throat subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1 1 / 1 (100.00%) 1 1 / 1 (100.00%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) Haemoglobinuria subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1 1 / 1 (100.00%) 1		
Infections and infestations Papulopustular rash subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 November 2015	- Volution Immuno Pharmaceuticals changes to Akari Therapeutics Plc - primary efficacy endpoint - Significant Reduction in serum LDH from day 0 – Day 28 (AUC) compared with 28 days pre treatment - secondary endpoint change of timepoints, and wording clarification - clarity over patient discharge before day 7 - addition of prohibited drugs - addition to clarity over patient comparisons - change to concentration of drug product for first treatment (8.9 mg/ml to 7.2 mg/ml) - addition to have vaccination against meningococci type ACW135Y as a requirement for the study - addition of patients being required to be admitted to hospital for a minimum of 2 days at the start of treatment - If an ablating dose is repeated , PK/PD and other assessment will be performed as indicated in Appendix 1 at 1hr, day 2 and day 5 - Extra samples for PK/PD may be taken at the discretion of the investigators during illness or infection - clarification over statistical approach - clarity over storage of biological samples

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported