CONFIDENTIAL

AKARI
THERAPEUTICS

STATISTICAL ANALYSIS PLAN

CONSERVE:
rVA576 (Coversin) Long Term Safety and Efficacy Surveillance Study

Drug Name:	**Coversin, nomacopan, OmCI, rVA576, rEV576**
Study Number:	**AK581**
EudraCT Number:	**2016-004129-18**
Name of Sponsor:	**Akari Therapeutics Plc**
Address:	[redacted]
Protocol Version (Date):	**Protocol Version 3.0 (11 Januray 2019)**
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SAP SIGNATURE PAGE

STUDY TITLE: CONSERVE: Coversin Long Term Safety and Efficacy Surveillance Study

We, the undersigned, have reviewed and approve this statistical analysis plan.

Signature	Date
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LIST OF ABBREVIATIONS

ADA	Anti-drug Antibodies
ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BP	Blood Pressure
CH50	Classical haemolytic 50% lysis
CH50 U Eq/ml	Classical haemolytic 50% lysis units equivalent / ml
CI	Confidence Interval
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5 dimensional 5 level
ET	Early termination
FAS	Full Analysis Set
FLAER	Fluorescein-labelled proaerolysin
Hb	Haemoglobin
ICF	Informed consent form
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetics
PNH	Paroxysmal Nocturnal Haemoglobinuria
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
TE	Treatment-emergent
ULN	Upper limit of normal
ULOQ	Upper limit of quantification

1 Introduction

This document provides a description of the statistical methods and procedures to be implemented for the analysis and reporting of data from the Akari Therapeutics study with protocol number AK581. Any deviations from this statistical analysis plan (SAP) after database lock will be clearly documented in the final clinical study report (CSR).

This SAP is based on the Clinical Study Protocol Version 3.0, dated 11 January 2019. A previous version had been developed between June and December 2017 but was not finalised or approved. Therefore this document is considered version 1.0.

This SAP only describes the analyses that will be performed for PNH patients given that the aHUS trial has been terminated due to inability to recruit. Therefore as no aHUS patients will enter AK581, all references to objectives and analyses related to aHUS patients have been removed from this SAP.

2 Study Objectives and Study Design

The objective of the trial is to provide a database of information regarding long-term administration of rVA576 (Coversin) to show that it remains safe for long periods and is acceptable to patients and show that the effect observed in the previous clinical trial is maintained. It also provides the opportunity to adjust an individual patient's dose or dose frequency should it be considered desirable. All patients enrolled into the CONSERVE study will have transitioned from a parent clinical trial.

2.1 Study Objectives

The specific objectives of the study are:

- To observe the long term safety and efficacy of rVA576 (Coversin)
- To assess the long term patient acceptability of rVA576 (Coversin) using the EORTC QLQ-C30 (for some PNH only), EQ-5D-5L & FACIT-F instruments and the Sponsor non validated questionnaire.
- To observe the changes, if any, in the production of anti-drug antibodies (ADA) and whether such antibodies are, or become, neutralising.

2.2 Study Design

The trial is an open-label, non-comparative study in up to approximately 50 patients, 18 years and above with either PNH or aHUS who have participated in another rVA576 (Coversin) and who wish to remain on the study.

The study population will consist of patients with diseases requiring complement inhibition who have previously taken part in Akari clinical trials and who wish to

continue to receive rVA576 (Coversin) after their active participation in the previous trial has completed and patients treated under compassionate use or named patient arrangements who wish to continue on rVA576 (Coversin) therapy.

The study visit schedule and procedures intended to be performed at each visit are displayed in the study protocol Tables 8 and 9.

2.3 Study Data

All patients enrolled into the CONSERVE study will have transitioned from a parent clinical trial and all will have been previously treated with rVA576.

Parent trial data used to assess patient safety and eligibility for enrollment will be entered into the AK581 database. Where applicable, assessment data collected at the subject's parent trial end of study visit will be captured. Coversin dosing history, parent trial ECG and LDH results, and plasma (blood) transfusion/dialysis history will be available in the AK581 subject casebooks.

Where applicable and where possible, parent trial locked databases will be used and pooled with the AK581 database:

- Raw data from AK578 CONSENT
- Study Data Tabulation Model (SDTM) and/or Analysis Data Model (ADaM) datasets from AK579 COBALT
- SDTM and/or ADaM datasets from AK580 CAPSTONE

See section 3.1, for the definitions of baseline (study entry) and parent trial baseline.

2.4 Study Endpoints

2.4.1 Primary Endpoint

Long term safety of rVA576 (Coversin) therapy as assessed by AEs, serious adverse events (SAEs), vital signs, results of standard laboratory tests (clinical chemistry, haematology and urinalysis), and results of electrocardiograms (ECGs).

2.4.2 Secondary Endpoints

1. Proportion of subjects with thrombotic and haemolytic event-free status during each 3 month time period since the start of the study.

2. Time to thrombotic or haemolytic event since the start of the study.

3. Proportion of subjects who require PRBC transfusion during each 3-month period since the start of the study and over the entire period of the study, with analysis of i) subjects who were transfusion-dependent when they started receiving rVA576 (Coversin), ii) subjects who were transfusion-independent when they started receiving rVA576 (Coversin), and iii) all subjects, and further stratification of these proportions by a) patients who were complement inhibitor-naïve prior to treatment with rVA576 (Coversin), and b) patients who received treatment with another complement inhibitor before switching to rVA576 (Coversin).

4. Time to first transfusion since joining the study.

5. Proportion of subjects with no adverse change in overall scores of Quality of Life using the EORTC QLQ-C30, the EQ-5D-5L and FACIT-F instruments at each 3-month time period since the start of the study.

6. Proportion of subjects with serum Lactate Dehydrogenase (LDH) <1.8, >1.8 to 2.4, >2.4 to 3, and >3 times the upper limit of normal (ULN) at each 3-month time period since the start of the study.

7. Proportion of subjects with median serum Lactate Dehydrogenase (LDH) <1.8, >1.8 to 2.4, >2.4 to 3, and >3 times the upper limit of normal (ULN) over the entire duration of the study.

8. Proportion of transfusion-independent subjects at each 3-month time point, with haemoglobin (g/L) above the baseline haemoglobin value they had at the start of the trial from which they entered CONSERVE. With baseline for CAPSTONE (AK580) defined as the haemoglobin value at which they received their qualifying transfusion (the set point) or for COBALT (AK579) and CONSENT (AK578) the haemoglobin value at which patients entered those trials. With separate analysis of subjects who were i) transfusion-independent prior to receiving rVA576 (Coversin) and remain transfusion-independent and ii) transfusion-dependent prior to receiving rVA576 (Coversin).

9. Proportion of transfusion-independent subjects over the entire duration of the study with mean haemoglobin (g/L) above the baseline haemoglobin value they had at the start of the trial from which they entered CONSERVE. With baseline haemoglobin defined as for the previous secondary endpoint (#8). With separate analysis of subjects who were i) transfusion-independent prior to receiving rVA576 (Coversin) and remain transfusion-independent and ii) transfusion-dependent prior to receiving rVA576 (Coversin).

10. Proportion of patients experiencing Major Adverse Vascular Events (MAVE) over the entire period of the study.

11. Time to first Major Adverse Vascular Event (MAVE) for each subject since joining the study.

12. Number of Major Adverse Vascular Events (MAVE) over the entire period of the study.

2.5 Additional Endpoints:

PK and PD parameters during treatment, to include terminal complement activity measured by CH50 ELISA, unbound nomacopan concentration measured by ELISA and total C5 concentration measured by ELISA.

3 Efficacy and Safety Variables

3.1 Baseline (study entry) and Parent trial Baseline

In order to describe changes over time, and compare values to the pre-Coversin dosing value (historical baseline), some parameters (LDH, CH50, quality of life scores, haemoglobin) may have both parent trial baseline values and CONSERVE baseline values used in analyses. To avoid any confusion the term "baseline" will always refer to CONSERVE baseline, while 'Parent trial baseline' will be used otherwise.

Baseline will therefore be defined as the last measurement prior to CONSERVE study entry.

Parent trial baseline will be defined as :

- Baseline for CAPSTONE (AK580) defined as the value at which they received their qualifying transfusion (the set point)
- Baseline for COBALT (AK579) or CONSENT (AK578) the value at which patients entered those trials.

3.2 Entry

Written informed consent will be obtained before any study procedures are performed. The following procedures will be performed exclusively at the Entry visit.

3.2.1 Medical History

A complete medical history will include an evaluation of the previous medical history from the previous rVA576 (Coversin) trial which will be transferred to the current database.

As all patients enrolled into the CONSERVE study will have transitioned from a parent clinical trial, a full new medical history and examination is not considered necessary unless there has been a lag time in entry into the long term study The investigator responsible for the patient's treatment will decide if there have been significant changes in the patient's condition since being in the previous study to warrant an additional examination and new entries to the medical history page. If there has been development of a new medical condition (with diagnosis) in the previous study this will be considered as part of the patient's medical history for this study.

All medical history data will be coded using the MedDRA dictionary version available at the time of the analysis.

3.2.2 Demographics

Demographic information (date/year of birth, age, sex, ethnicity, race and blood group) will be collected at study entry.

3.2.3 Eligibility

Evaluation of the study inclusion/exclusion criteria (see study AK581 trial Protocol sections 4.1 and 4.2) will be assessed at Entry.

3.2.4 Transfusions and Complement inhibitor history

Patients will be classified in subgroups as follows:

i) Patients who were transfusion-dependent when they started receiving rVA576 (Coversin),

ii) Patients who were transfusion-independent when they started receiving rVA576 (Coversin),

and further groupings will be performed as follows:

a) Patients who were complement inhibitor-naïve prior to treatment with rVA576 (Coversin),

b) Patients who received treatment with another complement inhibitor before of the switching to rVA576 (Coversin).

3.3 Efficacy Measurements and Variables

3.3.1 Blood transfusions

Details of blood transfusions administered during the study will be captured at all visits. Infusion type (PRBC or platelet), date, volume, reason and whether the transfusion was used as a method of PNH treatment will be recorded.

Patients who were transfusion-independent when they started receiving rVA576 (Coversin) and remain transfusion-independent will be identified.

3.3.2 Serum Lactate dehydrogenase (LDH)

Lactate dehydrogenase (LDH) values will be obtained as per the schedule of events. Changes and percent changes from the Parent trial baseline to each assessment of this study will be derived.

To permit the comparison of LDH values from different local laboratories, the ratio of the recorded LDH value to the local laboratory upper limit of normal (ULN) will be derived. Values below the ULN will provide a ratio of less than one; values above the ULN will provide a ratio of greater than one.

Indicators will be derived for each patient at every visit, to identify whether the LDH value ≤1.8, >1.8 to 2.4, >2.4 to 3, and >3 times the ULN.The median serum LDH will also be derived for each patient.

3.3.3 CH50 Levels

Blood samples for CH50 will be collected as per the schedule of events and analysed in the Central Laboratory. The Central Laboratory considers values less than 10 CH50 U Eq/mL as completely inhibited. In previous trials (AK577, AK578 and AK579) with rVA576 (Coversin) the lower limit of quantification (LLOQ) of the CH50 was 8 CH50 EU/mL. The LLOQ has increased because the assay is now being performed using an automated system

for the ELISA. Results recorded as below the LLOQ will be imputed using half of the lower limit of quantification that applies to the sample for the purpose of calculating change from baseline, or percentage change from baseline, for summaries and figures.

The absolute change and percentage change from the parent trial Baseline to each subsequent assessment will be derived.

3.3.4 EORTC QLQ-C30

Patients are to complete the EORTC QLQ-C30 as per the schedule of events.

QLQ-C30 comprises 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 (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). Each scale and single item is derived and scaled to fall in the range 0 to 100, where a high score represents higher response. Table lists the scores to be derived and the items used in their derivation.

Table 1: QLQ-C30 Scales

Derived Scale	Scale	Items	#Items	Range
Global health status	QL	29, 30	2	6
Functional scale – Physical Functioning	PF	1, 2, 3, 4, 5	5	3
Functional scale – Role Functioning	RF	6, 7	2	3
Functional scale – Emotional Functioning	EF	21, 22, 23, 24	4	3
Functional scale – Cognitive Functioning	CF	20, 25	2	3
Functional scale – Social Functioning	SF	26, 27	2	3
Symptom scale – Fatigue	FA	10, 12, 18	3	3
Symptom scale – Nausea and Vomiting	NV	14, 15	2	3
Symptom scale – Pain	PA	9, 19	2	3
Symptom item – Dyspnoea	DY	8	1	3
Symptom item – Insomnia	SL	11	1	3
Symptom item – Appetite Loss	AP	13	1	3
Symptom item – Constipation	CO	16	1	3
Symptom item – Diarrhoea	DI	17	1	3
Symptom item – Financial Difficulties	FI	28	1	3

The following algorithm will be used in deriving the functional and symptom scale scores:

1. Derive the raw score (RS) for each functional and symptom score by deriving the average of the contributing items (I).

$$RS = (I_1 + I_2 + \ldots + I_n)/n$$

2. Derive the standardised score (Score) for each functional and symptom score by mapping the raw score to the range from 0 to 100, where a higher score represents a better level of function or a worse level of symptoms.
   For Function scales:

$$Score = \{1 - (RS-1)/range\} \times 100$$

   For Symptom scales and Global health status:

$$Score = \{(RS-1/range\} \times 100$$

3. For derived scales that include two or more items, a derived value will be calculated if at least half of the items are non-missing. If more than half of the items are missing then the scale will be set to missing.

For each of the standardised function scales, symptom scales, global health status scale and standardised single item scales the Baseline for each patient is parent trial baseline. The absolute change from the parent trial Baseline to each subsequent assessment will be derived for each of the standardised scales and standardised single item scores.

Changes in the global health status will be identified as adverse if the score has decreasd (negative absolute change from the parent trial Baseline) in a 3-month time period.

Patients with no adverse change at each 3-month time period since the start of the study will be identified.

3.3.5 EQ-5D-5L

Patients were to complete the EQ-5D-5L as per the schedule of events .

EQ-5D-5L comprises 5 questions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each with five levels plus the EQ Visual Analogue scale. The patient response to each of the 5 questions will be mapped to the score indicated in Table 2. The five mapped responses, also known as the 5L profile, will then be used to obtain a normalised score for each patient assessment by obtaining the country-specific normalised value from the Crosswalk Index Value Calculator.

Table 2: EQ-5D-5L Response Scores

Question	Response	Score
Q1: Mobility	I have no problems in walking	1
	I have slight problems in walking	2
	I have moderate problems in walking	3
	I have severe problems in walking	4
	I am unable to walk	5
Q2: Self-Care	I have no problems washing or dressing myself	1
	I have slight problems washing or dressing myself	2
	I have moderate problems washing or dressing myself	3
	I have severe problems washing or dressing myself	4
	I am unable to wash or dress myself	5
Q3: Usual Activities	I have no problems doing my usual activities	1
	I have slight problems doing my usual activities	2
	I have moderate problems doing my usual activities	3
	I have severe problems doing my usual activities	4
	I am unable to do my usual activities	5
Q4: Pain/Discomfort	I have no pain or discomfort	1
	I have slight pain or discomfort	2
	I have moderate pain or discomfort	3
	I have severe pain or discomfort	4
	I have extreme pain or discomfort	5
Q5: Anxiety/Depression	I am not anxious or depressed	1
	I am slightly anxious or depressed	2
	I am moderately anxious or depressed	3
	I am severely anxious or depressed	4
	I am extremely anxious or depressed	5

The absolute change from the Parent trial baseline to each subsequent assessment will be derived.

Changes in the normalised score will be identified as adverse if the score has decreasd (negative absolute change from the parent trial Baseline) in a 3-month time period.

Patients with no adverse change at each 3-month time period since the start of the study will be identified.

3.3.6 FACIT-F

The FACIT-F (functional assessment of chronic illness therapy - fatigue) version 4 comprises 41 items measuring an individual's level of fatigue during their usual daily activities. The level of fatigue is measured on 5 subscales (Physical Well-Being subscale, Social/Family Well-Being subscale, Emotional Well-Being subscale, Functional Well-Being subscale and additional concerns).

Where applicable, item variables will be reverse coded for the purpose of generating the scale scores as per the FACIT-F scoring guidelines. For each patient, at each visit, the FACT-G Total Score, FACIT-F Total Score and FACIT-F Trial Outcome Index will be calculated. For guidelines on handling missing data and scoring options, the administration and scoring guidelines in the manual or on-line at www.facit.org will be used.

Changes in the FACIT-F Total score will be identified as adverse if the score has decreased (negative absolute change from Baseline) in a 3-month time period.

Patients with no adverse change at each 3-month time period since the start of the study will be identified.

Where possible, the change from the Parent Baseline may also be described. Parent trials AK580, AK585 and AK578 used version 4 of the FACIT questionnaire, while AK579 did not collect this data.

3.3.7 Self-Injection Questionnaire

Patients will complete a non-validated questionnaire at every visit to determine whether self-injection by patients is well-accepted and the support provided sufficient. Each question was to be answered using one of the available categorical scores.

No derivations will be performed on this data. This data will only be listed.

3.4 Safety Measurements and Variables

3.4.1 Major Adverse Vascular Event (MAVE) Assessment

The MAVE will be used to collect information on large and small vessel thrombosis as well as micro thrombosis and will be recorded always pre-dose at each clinic visit.

MAVE will be recorded as part of the AEs and the following details will be reported:

- MAVE location:

  - Limbs
  - Lungs
  - Brain
  - Heart
  - Kidneys
  - Intestines
  - Liver
  - Other
- Method of diagnosis:
  - MRI
  - Ultrasound
  - Angiogram
  - Other

3.4.2 Thrombotic and Haemolytic Events

Thrombotic and Haemolytic Events will include, but are not limited to, the following: haemolytic anaemia, thrombocytopenia, red blood cell hemolysis indicated by dark urine, Budd-Chiara syndrome, any other thrombotic or hemolytic event deemed to be associated with PNH.

A haemolytic event will be defined as a rise in LDH or other biochemical evidence of haemolysis (eg increasing serum bilirubin or liver enzymes) accompanied by an increase in symptoms (eg myalgia, erectile dysfunction, fatigue) and/or frank haemoglobinuria. Increased symptoms without objective haematological or biochemical evidence of haemolysis will not be counted as haemolytic events.

In addition, the following signs and symptoms may be reviewed and classified as Thrombotic/Haemolytic events if appropriate:

- Acute kidney failure
- Hypertension
- Myocardial infarction
- Stroke
- Lung complications (e.g. Pulmonary embolism)
- Pancreatitis
- Liver necrosis
- Encephalopathy (brain dysfunction
- Seizure
- Coma
- Premature death (secondary to neurologic, cardiac, kidney, and gastrointestinal organ dysfunction)

3.4.3 Adverse Events (AEs)

All AEs, which occurred at any time after signing the informed consent form (ICF), will be recorded in the electronic Case Report Form (eCRF). The following details will be reported for each adverse event:

- Start and stop dates
- Severity, using CTCAE grading 1 to 5
- Relationship to study treatment:
  - Unrelated
  - Possibly Related
  - Related
- Serious:
  - Yes
  - No
- Action taken with study treatment:
  - Dose increased
  - Dose not changed
  - Dose reduced
  - Drug interrupted
  - Drug withdrawn
  - Not applicable
  - Unknown
  - Other
- Outcome
  - Fatal
  - Not recovered/not resolved
  - Recovered/resolved
  - Recovered/resolved with sequelae
  - Recovering/resolving
  - Unknown

Other action taken, whether the AE caused discontinuation, details of death, hospitalisation, last dose before the event and other information reated to the AE will be collected and listed.

Treatment emergent adverse events are defined as any AE with a recorded start date/time on or after the date/time of start of study medication. All patients enrolled into the CONSERVE study will have transitioned from a parent clinical trial and all will have been previously treated with rVA576, therefore all AEs recorded under protocol AK581 will be considered treatment-emergent.

3.4.4 Safety Clinical Laboratory Measurements

A blood and urine sample will be collected for clinical laboratory measurements (haematology, biochemistry and urinalysis) as per the schedule of events. The following laboratory parameters for haematology, chemistry and urinalysis will be evaluated at each clinical site's local laboratory:

Haematology

- Haemoglobin [g/L]

- Haematocrit [%]
- Mean cell haemoglobin [pg]
- Mean cell haemoglobin concentration [g/L]
- Mean cell volume [fL]
- Red blood cell count [10^12/L]
- Erythrocyte sedimentation rate [mm/h]
- Platelets [10^9/L]
- White blood cell count [10^9/L]
- Neutrophils absolute [10^9/L]
- Lymphocytes absolute [10^9/L]
- Monocytes absolute [10^9/L]
- Eosinophils absolute [10^9/L]
- Basophils absolute [10^9/L]
- Reticulocytes [10^9/L]

Chemistry

- Lactate dehydrogenase [U/L]
- Sodium [mmol/L]
- Potassium [mmol/L]
- Bicarbonate [mmol/L]
- Urea [mmol/L]
- Creatinine [µmol/L]
- Chloride [mmol/L]
- Albumin [g/L]
- Calcium [mmol/L]
- Gamma-glutamyl transpeptidase [U/L]
- Glucose (random) [mmol/L]
- Alkaline phosphatase [U/L]
- Alanine aminotransferase [U/L]
- Aspartate aminotransferase [U/L]
- Creatine kinase [U/L]
- Total Bilirubin [µmol/L]
- Bilirubin (Direct) (only if Total is elevated) [µmol/L]
- Phosphate (Inorganic) [mmol/L]
- Protein (Total) [g/L]

For each of the haematology and chemistry parameters, values from the locally reported laboratory will be converted to the standardised units shown in parenthesis during statistical programming of the SDTM datasets.

Urinalysis

- Leukocytes
- Protein
- Bilirubin
- Glucose
- pH
- Ketones

- Nitrates
- Blood
- hCG (female patients)
- Specific gravity

At the discretion of the Investigator:

- Microbiology
- Urine microscopy
- Pregnancy testing
- Urobilinogen

Central Laboratory Testing

The following parameters may also be evaluated at the Central Laboratory but are not mandatory:

- LTB4
- Total LDH and LDH Isoenzyme
- Total bound and unbound C5

Out-of-range laboratory data will be flagged as low or high according to gender and laboratory specific normal ranges.

The absolute change from Baseline to each subsequent assessment will be derived for each of the continuous laboratory parameters.

Haemoglobin

For Haemoglobin, the Parent trial baseline will be used. Patients with an haemoglobin above the baseline haemoglobin value they had in the parent trial will be flagged.

The mean haemoglobin value post study entry will be calculated for each patient.

3.4.5 Vital Signs

Blood pressure and pulse rate will be measured in the supine position after the patient has rested comfortably as per the schedule of events.

The change from Baseline to each subsequent assessment will be derived for each vital signs parameter.

3.4.6 Weight

Patient's weight will be recorded as per the schedule of events.

Changes from Baseline to each post baseline assessment will derived.

3.4.7 Electrocardiogram

Routine ECG will be performed at entry and then annually during the study. The following ECG parameters will be recorded in the eCRF:

- Heart rate (beats/min)
- PR interval (msec)

- QRS duration (msec)
- QT interval (msec)
- QTc interval (msec)
- RR interval (msec)
- Overall interpretation

Interpretation of the ECG will be performed by the investigator and reported as normal, abnormal, inderterminate, and if deemed abnormal, whether the abnormality is clinically significant or not clinically significant.

Changes in each ECG parameter from Baseline or any additional unscheduled ECGs, will be derived.

3.4.8 Anti-drug Antibodies (ADA)

Serum samples will be analysed for ADA formation to rVA576 (Coversin) as per the schedule of events. ADA analyses may be performed at a later stage and results reported separately from the main CSR.

3.4.9 Physical Examination

A physical examination, covering the following aspects, will be performed as per the schedule of events:

- General appearance
- Dermatological/skin
- Haematologic/lymphatic
- Heart/cardiovascular
- Respiratory
- Vein and injection site inspection

No derivations will be performed on this data. This data will only be listed.

3.4.10 Pharmacokinetic Coversin Levels

A blood sample for unbound rVA576 Coversin levels will be collected as per the schedule of events.

Unbound nomacopan, total C5 and serum LTB4 levels will be summarised overtime and spaghetti plot of concentrations through time will be produced.

Additional exploratory figures may be produced in order to investigate threshold levels that should be exceeded to ensure >90% inhibition of terminal complement activity. Additional PK analyses may be performed at a later stage and results reported separately from the main CSR.

3.4.11 Fluorescein-labelled proaerolysin FLAER / Flow Cytometry

A blood sample will be collected for flow cytometry measurements at study entry, Month 3, 15, 24, 33 and 48. The following parameters will be evaluated at each clinical site's local laboratory:

- Red blood cells and neutrophils: % cells negative for CD55, CD59, and both CD55 and CD59 and/or

- Granulocytes: % cells negative for CD24, CD16, CD24 and FLAER, CD16 and FLAER and/or
- Granulocytes, monocytes: % cells negative for FLAER and/or Monocytes: % cells negative for CD14, and both CD14 and FLAER

No derivations will be performed on this data. This data will only be listed.

3.5 Compliance and Exposure

Exposure will be derived as the number of days between the first and last dose of study medication in this study.

Study medication compliance will be derived as the proportion of doses that the patient received during the exposure period.

The overall patient compliance (%) will be derived as:

= 1 - (Total number of missed doses / Total number of planned doses)

This derived compliance will be categorised:

- <95%
- 95% to <99%
- 99% to 100%
- >100%

3.6 Concomitant Medications

All medications recorded on the Concomitant Medications eCRF will be considered as used during the treatment period (i.e., concomitant).

All concomitant medication will be coded with Anatomical Therapeutic Chemical (ATC) class and preferred term.

3.7 Presentation

Statistical analyses will be performed using SAS® (Version 9.3 or later). All available data will be presented in patient data listings, which will be sorted by site number, patient identifier and where appropriate, visit and/or visit date.

Descriptive statistics (n, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum) will be used to summarise the continuous efficacy and safety data. Discrete measures will be summarised using count and percentage. Unless otherwise stated, descriptive statistics showing the mean or median will be displayed to one decimal place more than the original data; the standard deviation will be displayed to two decimal places more than the original data; minimum and maximum will be displayed to the same number of decimal places as the original data.

Any significance tests or confidence intervals will be exploratory.

Unless otherwise stated, all data will be listed.

4 Statistical Methods Planned

4.1 Changes from Protocol

- ADA analyses may be performed at a later stage and results will be reported separately from the main CSR.
- The LDH categories referenced in the protocol were < 1.8, >1.8 to 2.4, >2.4 to 3, and >3 times the upper limit of normal (ULN), given that these do not cover LDH equal to 1.8ULN, the following categories will be used serum LDH ≤ 1.8, >1.8 to 2.4, >2.4 to 3, and >3 ULN

4.2 Analysis Sets

4.2.1 Screened Set

The Screened Set will include all patients screened for participation in the study.

4.2.2 Full Analysis Set

The primary analysis will be intention to treat and all patients who entered and signed informed consent will be included. The Full Analysis Set (FAS) will therefore include all enrolled patients.

All patients will be included in the safety analysis, whether completing the trial according to the protocol or not. Analyses of efficacy at various time points (6 months 12 months, 2, 3, 4 and 5 years) will be made for all patients reaching those points. The FAS will be the population used for assessing safety and efficacy and will be used for all outputs with the exception of patient disposition summary and data listings.

4.3 Review of Data and SAP Finalisation

Patient data will be reviewed for major protocol deviations by the Study Monitor during site visits and the entire team will review the database at timed intervals prior to the database lock.

Missing data that cannot be retrieved from source records or other repositories will be recorded as such in the eCRFs and will not be entered into the statistical analysis. Spurious data will be examined by the Sponsor's monitor, medical or statistical advisors and a decision made as to how it should be handled. If there is an obvious transcription or data entry error, such as a misplaced decimal point in a biochemical parameter, this will be discussed with the CRO or the laboratory and, if all parties agree, it will be corrected and endorsed by both the PI and the Sponsor.

Unused data (e.g. superfluous blood pressure recordings or haematological results in addition to those required by the protocol) will remain part of the source documentation and only be incorporated into the trial documents and analysis if there is reason for them to be (e.g. an unexpected fall in blood pressure that might constitute an AE).

The final analysis will be performed using data collected up to the end of the study. This data will be presented in the CSR.

4.4 Statistical Methods, definitions

4.5 General Data Handling Rules

Values from the locally reported laboratory will be converted to the standardised units at the SDTM level.

Laboratory values recorded as below the LLOQ or above the upper limit of quantification (ULOQ) will be handled as follows: results recorded as below will be imputed using half of the LLOQ for the purpose of calculating change from baseline, or percentage change from baseline, for summaries and figures. Measurements recorded as above the ULOQ will be imputed using the quantification limit. The raw data will be displayed in the listings.

The data may be log transformed, this will be guided by the degree of skewness and variability in the data within and between subjects across time.

4.6 Patient Disposition

Patient disposition will be provided for all screened patients, showing the number and percentage of patients who received study drug, completed the study visit schedule or withdrew early. For patients who withdraw from the study, the primary reason for the withdrawal will also be summarized.

The total number of patients who were screened and the number who failed screening will be tabulated. Screen failures and screen failure reasons will be listed in a data listing.

The number of patients Screened and the number and percentage of patients included in the FAS will be presented.

4.7 Demographics and Baseline Characteristics

Demographic characteristics will be summarized.

4.8 Medical History

Medical history findings at study entry will be summarized.

4.9 Study Drug Exposure and Compliance

Exposure to study medication, defined as the number of days between first and last dose (see section 3.5), will be summarized using descriptive statistics. In addition, a table will be provided to display the number and percentage of patients with exposure in the following categories:

- 1-182 days
- 183-365 days
- 366-730 days
- 731-1095 days

Study medication percentage compliance will be summarised using descriptive statistics. The count and percentage of patients with overall compliance will also be tabulated:

- <95%
- 95% to <99%

- 99% to 100%
- >100%

4.10 Concomitant Medications

The numbers and percentages of patients taking concomitant medications will be summarised by ATC and preferred term.

4.11 Analysis of Efficacy

All presentations and analyses of efficacy data will be conducted on the FAS. All efficacy data will be listed.

4.11.1 Blood Transfusions

The proportion of subjects who require PRBC transfusion during each 3-month period since the start of the study and over the entire period of the study will be summarised. This summary will also be produced by subgroup of patients based on their transfusions and complement inhibitor history as defined in section 3.2.4.

The number of RBC or platelet transfusions per patient during the study will be summarised using descriptive statistics. Patients with no recorded transfusions will be included with an imputed count of zero.

The time (days) to first transfusion for each patient will be summarized using Kaplan-Meier methodology. Kaplan-Meier estimates of the proportion of patients receiving at least one transfusion during the study will be displayed with 95% two-sided confidence limits. The median, 95% Confidence Interval of the median, 25th and 75th percentiles of the time to first transfusion will be produced.

4.11.2 LDH

The derived LDH ratio of reported:ULN values over time will be presented as a (spaghetti) line plot for all patients. Observed values and change from baseline will be summarised. Boxplots over time will also be presented to provide an indication of how the mean and median LDH ratio changes over the course of the study.

The number and percentage of patients with serum LDH ≤ 1.8, >1.8 to 2.4, >2.4 to 3, and >3 times the upper limit of normal (ULN) at each 3-month time period since the start of the study will be summarised

The number and percentage of patients with median serum LDH ≤ 1.8, >1.8 to 2.4, >2.4 to 3, and >3 times the upper limit of normal (ULN) over the entire duration of the study will also be summarised.

4.11.3 Transfusion-independence and Haemoglobin

The proportion of transfusion-independent subjects with haemoglobin (g/L) above the baseline haemoglobin value as defined in section 3.3.4 will be summarised at each 3-month time point.

The proportion of transfusion-independent subjects over the entire duration of the study with mean haemoglobin (g/L) above the baseline haemoglobin value as defined in section 3.3.4 will be summarised.

These summaries will be repeated separately for patients :

i) transfusion-independent prior to receiving rVA576 (Coversin) and remain transfusion-independent
ii) transfusion-dependent prior to receiving rVA576 (Coversin).

4.11.4 CH50

Observed values, change from baseline, and ratio to baseline expressed as a percentage (also called % activity) in CH50 will be summarised at each applicable study visit.

4.11.5 EORTC QLQ-C30

Observed values and change from baseline of the standardised function scales, symptom scales, global health status scale and standardised single item scales will be summarised at each applicable study visit.

The proportion of patients with no adverse change in the global health status scale will be summarised for each 3-month time period since the start of the study.

4.11.6 EQ-5D-5L

Observed values and change from baseline of the EQ-5D-5L Crosswalk normalised score will be summarised at each applicable study visit.

The proportion of patients with no adverse change in the normalised score will be summarised for each 3-month time period since the start of the study.

4.11.7 FACIT-F

Observed values and change from baseline of the FACT-G Total Score, FACIT-F Total Score and FACIT-F Trial Outcome Index will be summarised at each applicable study visit.

The proportion of patients with no adverse change in the FACIT-F Total Score will be summarised for each 3-month time period since the start of the study.

4.12 Analysis of Safety

All presentations and analyses of safety data will be conducted on the FAS. All safety data will be listed.

4.12.1 Adverse Events

A summary overview of adverse events will be provided, which presents the number and percentage of patients from the FAS satisfying each of the following categories:

- Any AEs
- Serious AEs (SAEs)
- Drug-related AEs
- SAEs leading to death
- AEs leading to discontinuation

The number and percentage of patients with AEs, and number of AEs will be summarised by MedDRA System Organ Class, High Level Term, and Preferred Term. In this summary, any patient reporting multiple episodes of the same AE (i.e. same preferred term), will be counted once. The incidence of SAE will also be summarised. The listings will contain all data available.

The number and percentage of patients with AEs will be summarised by reported severity within each preferred term within system organ class. In this summary, any patients reporting multiple episodes of the same AE (i.e. same preferred term), will be counted once against the most severely reported category.

A list of patients reporting any SAEs and a list of patients reporting any AEs that led to an interruption or withdrawal of the study medication will be provided.

4.12.2 Clinical Laboratory Assessments

Observed values and change from baseline will be summarised at each applicable study visit for the parameters listed in Section 3.3.4. Counts and percentages of patients in each category will be used to summarise categorical urinalysis parameters for the baseline visit and each post-baseline assessment.

Counts and percentages of patients with haematology and chemistry observations that are below (<LLN) or above (>ULN) the limit of normal at any post baseline visit will be summarised. Patients with haematology or chemistry observations that are below (<LLN) or above (>ULN) the limit of normal at *any* post baseline visit will be listed, as well as patients with markedly abnormal values.

4.12.3 Vital Signs

Observed values and change from baseline of Vitals signs measurements will be summarised at each applicable study visit.

Subjects with markedly abnormal values for vital signs will be listed.

4.12.4 Electrocardiogram

The number and percentage of patients who have an ECG post-baseline Overall interpretation that falls within each category ('Normal'; 'Abnormal, Not Clinically Significant'; 'Abnormal, Clinically Significant') will be tabulated.

Observed values and change from baseline of ECG measurements will be summarised at each applicable study visit.

4.12.5 Thrombotic and Haemolytic Events

The number and percentage of patients

i) without a thrombotic event,
ii) without a haemolytic event,
iii) without either a thrombotic or haemolytic event,

will be summarized at each visit. The time (days) to first event for each patient will be summarized using Kaplan-Meier methodology. Kaplan-Meier estimates of the proportion of patients achieving each event during the study will be displayed with 95% two-sided

confidence limits. The median, 95% Confidence Interval of the median, 25th and 75th percentiles of the time to achieving event will be produced.

4.12.6 Major Adverse Vascular Event (MAVE)

The number and percentage of patients with MAVEs, and number of MAVEs will be summarised by MedDRA System Organ Class, High Level Term, and Preferred Term. In this summary, any patient reporting multiple episodes of the same MAVE (i.e. same preferred term), will be counted once. The listings will contain all data available.

The time (days) to first MAVE for each patient will be summarized using Kaplan-Meier methodology. Kaplan-Meier estimates of the proportion of patients experiencing MAVE events during the study will be displayed with 95% two-sided confidence limits. The median, 95% Confidence Interval of the median, 25th and 75th percentiles of the time to experiencing event will be produced.

4.13 Interim Analysis

The Sponsor reserves the right to review accruing safety and efficacy data from the study as a management aid to assist in the design of future studies.

4.14 Data Safety Monitoring Board (DSMB)

Not applicable

5 Sample Size Determination

This is an open-label study to evaluate the safety experience of long term rVA576 (Coversin) treatment in up to approximately 50 patients.

6 Programming Specifications

The programming specification, including the mock-up analysis tables, figures, and data listings, as well as the derived database specification, will be prepared in a stand-alone documents.

7 APPENDIX 1

7.1 Tables

Table 14.1.1	Patient Disposition – Screened Set
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7.2 Listings

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7.3 Figures