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

PROTOCOL NUMBER:	**AK581**
DATE:	11 January 2019
VERSION NUMBER:	3.0
SPONSOR:	**Akari Therapeutics Plc**
EudraCT number	**2016-004129-18**

SPONSOR ADDRESS:	Akari Therapeutics Plc. [redacted]
AUTHORISED SIGNATORIES:	[redacted]
SPONSOR'S MEDICAL EXPERT:	[redacted] Akari Therapeutics Plc. [redacted]
24 HOUR MEDICAL CONTACT:	[redacted]
CENTRAL LAB	[redacted]

List of Abbreviations

Abbreviation	Definition/Term
ADR	Adverse Drug Reaction
AE	Adverse Event
aHUS	Atypical Haemolytic Uraemic Syndrome
AD	Ablating Dose
CH50 U q/mL	Classical haemolytic 50% lysis Units Equivalent/mL
CRO	Contract Research Organisation
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
EORTC	European Organisation for Research and Treatment of Cancer
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GvHD	Graft versus host disease
HED	Human Equivalent Dose
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
IMP	Investigational Medical Product
IRB	Institutional Review Board (or equivalent, e.g. Ethics Committee)
ITT	Intention to Treat
LDH	lactate dehydrogenase
LEC	Local Ethics Committee
MAC	Membrane Attack Complex
MG	Myasthenia gravis
MW	Molecular Weight
NHP	Non-human Primate
NOAEL	No Observable Adverse Event Level
OmCI	*Ornithodoros moubata* Complement Inhibitor
PBS	Phosphate-buffered Saline
PEX	Plasma Exchange
PI	Principal Investigator
PK	Pharmacokinetic(s)
PNH	Paroxysmal Nocturnal Haemoglobinuria
PP	Per Protocol
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
s.c.	Subcutaneous
SAE	Serious Adverse Event

Abbreviation	Definition/Term
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedures
STEC	Shiga toxin-producing *Escherichia coli*
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCA	Terminal Complement Activation
TMA	Thrombotic microangiopathy
TTP	Thrombotic Thrombocytopaenic Purpura
ULN	Upper limit of normal
WFI	Water for Injection

Protocol Signature Page

Protocol Title:	CONSERVE: rVA576 (Coversin) Long Term Safety and Efficacy Surveillance Study
Protocol Number:	AK581

Authorized Sponsor Representative Signature:

Signature: [redacted] Date: 11 JAN 2019

[redacted]

Signature: [redacted] Date: 11 JAN 2019.

[redacted]

Principal Investigators Signatures:

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practice, applicable laws and regulations and the Declaration of Helsinki.

Signature: _____ Date: _____

Contents

Protocol Title:	CONSERVE: **rVA576** (**Co**versi**n)** Long Term **S**afety and **E**fficacy Su**rve**illance Study		
Protocol Number:	AK581		
Sponsor:	Akari Therapeutics Plc [redacted]		
Investigational Product(s):	rVA576 (Coversin) powder for solution for subcutaneous injection, 18mg/vial		
Phase of Development:	III	**Indication:**	Long term management of patients with diseases including PNH and aHUS
Study Center(s):	Multi-centre		
Objectives:	**Primary Objective:** To determine the safety profile of long-term rVA576 (Coversin) treatment.		
Study Design:	Open-label, non-comparative		
Planned Number of Subjects:	Approximately 50 patients		
Subject Population:	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.		
Criteria for Inclusion:	**Inclusion Criteria:** 1) Patients 18 years and above treated with rVA576 (Coversin) under other Akari clinical trial protocols and wish to remain on rVA576 (Coversin) at the conclusion of that trial. 2) In the opinion of the treating responsible clinician patient is receiving clinical benefit from continued treatment with study drug. 3) Evidence of sustained complement inhibition by CH50 assay. 4) Women of childbearing potential (WOCBP) must agree to use effective contraception consistently throughout the study and have a negative pregnancy test at screening.Women are considered post-menopausal and not of childbearing potential if they have had 12 months of amenorrhea and considered sterile if they have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks previously. 5) Males with a childbearing potential partner must agree to use effective contraception consistently OR have had a vasectomy. 6) Weight $\geq$50kg.		

	7) Received appropriate prophylaxis against *Neisseria meningitidis* infection, by both immunisation and continuous or intermittent antibiotics. 8) Patient is willing to give voluntary written informed consent. 9) The patient is willing in the process of preparation and self-administration of the study drug.
Criteria for Exclusion:	**Exclusion Criteria:** 1. Patient experienced any safety event in the previous study protocol, which puts the patient at unacceptable risk in the current protocol in the clinical judgement of the investigator and sponsor. 2. Patient is unwilling to complete the Quality of Life instruments and diary cards. 3. Active meningococcal infection (section 4.3.2 for additional information). 4. Any other reason for which, in the opinion of the Investigator, it would not be in the interests of the patient to remain on rVA576 (Coversin). 5. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 90 days after last dose; or intending to donate ova during such period. 6. If male, the subject intends to donate sperm during this study or for 90 days after last dose. 7. Failure to satisfy the Investigator of fitness to participate for any other reason or any condition which, in the opinion of the investigator, could increase the subject's risk from participating in the study or confound the outcome of the study. 8. Use of prohibited medication (e.g. Eculizumab (Soliris®), Chemotherapeutic agents, any other drug acting directly on the complement system). 9. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within one year prior to screening. 10. Participation in other clinical trials with investigational product.
Concurrent control	None
Treatment Regimen:	Test Product, Dose and Mode of Administration: rVA576 (Coversin) 18 mg/vial powder for solution for injection. When the contents of one vial are reconstituted with 0.6 mL Water for Injection (WFI) and drawn up according to the instruction manual the resulting solution consists of rVA576 (Coversin) 30mg/mL in an extractable volume of greater than or equal to 0.5mL phosphate-buffered saline (PBS), pH 7.2. The product is administered subcutaneously. It is expected that all patients being treated under this protocol will have been on a stable dose of rVA576 (Coversin) prior to entering the study and will remain on that dose initially. Should a change in dose or dose

frequency become desirable, the responsible investigator will have discretion to alter the treatment regime in consultation with the Sponsor's medical representative. During any such changes careful monitoring of complement inhibition is mandatory and this should include regular assessment of haematological/biochemical parameters (e.g. serum LDH) and CH50 as well as the patient's clinical status.

In the event of an increase of dose or dose frequency, an ablating dose (AD) may be given to ensure complete complement inhibition before the new dose is started. It is assumed that a reduction of dose or dose frequency would only be considered if the patient's prior complement control was adequate and so no AD need be given before commencing the new dose.

The ablating dose (AD) consists of 2 doses; an initial dose of 60mg followed 12 hours later by 1 dose of 30mg. A suggested regimen to be followed in the event of an inadequate response to rVA576 (Coversin) treatment is given below:

PNH patients

Ablating Doses (if required)	
Dose	*Interval*
60mg	Single dose
30mg	1 x 12 hourly dose
Inadequate Response	

Existing		**Switch to**	
Dose	*Interval*	*Dose*	*Interval*
15mg	12 hourly	22.5mg	12 hourly
22.5mg	12 hourly	45mg	24 hourly
30mg	24 hourly	45mg	24 hourly
45mg	24 hourly	22.5mg	12 hourly

aHUS patients

Ablating Doses (if required)	
Dose	*Interval*
60mg	Single dose
30mg	1 x 12 hourly dose
Inadequate Response	

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<tr><td></td><td>
<table>
<tr><th colspan="2">Existing</th><th colspan="2">Switch to</th></tr>
<tr><td>Dose</td><td>Interval</td><td>Dose</td><td>Interval</td></tr>
<tr><td>30mg</td><td>12 hourly</td><td colspan="2">After assessment decision will be made in collaboration with the Sponsor and PI.</td></tr>
<tr><td>45mg</td><td>24 hourly</td><td>30mg</td><td>12 hourly</td></tr>
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<tr><td>Duration of Treatment:</td><td>Up to 4 years

Patients for whom rVA576 (Coversin) was found to be effective in this clinical trial and who wish to continue on the drug following conclusion of this trial, will continue to receive rVA576 (Coversin), subject to approval of the applicable governmental agency, until rVA576 (Coversin) receives marketing approval or another treatment of benefit becomes available. If Akari encounters any issues with the availability of the drug, it will allocate available drug to such patients in a manner which is fair and consistent with ethical requirements.</td></tr>
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1. Introduction

rVA576 (Coversin) is a small protein complement C5 inhibitor which prevents the cleavage of C5 by C5 convertase into C5a and C5b and thereby inhibits generation of the membrane attack complex, C5b-9 (MAC). It is effective in inhibiting terminal complement activity irrespective of the activating pathway. [redacted]

1.1. PNH

PNH is an acquired genetic haemolytic anaemia, in which failure to synthesise GPI-anchored proteins prevents affected blood cells from attaching the complement regulatory proteins CD55 and CD59 to their surface, making them vulnerable to attack by normal background complement activity. The resulting intravascular haemolysis of affected red blood cells (RBC) causes free haemoglobin to be released into the bloodstream. Some lysis of RBC may also be extravascular caused by complement deposition on cell surfaces and subsequent phagocytosis via the reticulo-endothelial system, in particular Kupfer cells and splenic phagocytes [Brodsky et al, 2014]. In the bloodstream, free haemoglobin causes depletion of nitric oxide with resultant smooth muscle spasm causing or contributing to symptoms such as dysphagia, erectile dysfunction, abdominal pain and, possibly, pulmonary hypertension.

PNH is characterised by red blood cell haemolysis, large vessel thrombosis particularly affecting the hepatic, visceral, cerebral and dermal veins and impaired haematopoiesis. The relationship between aplastic anaemia and PNH is not fully understood, however there is a greater incidence of PNH in patients with a history of aplastic anaemia, possibly because PNH clones have a higher rate of proliferation in this condition than normal stem cells. Treatment of aplastic anaemia with immunosuppressants is known to increase PNH clone size but whether the cells so produced are more or less susceptible to haemolysis than other PNH cells remains controversial. PNH patients with bone marrow aplasia are more likely to require blood transfusion because of the impaired production of normal red cells.

Treatment of PNH is by bone marrow allograft or, where available, by terminal complement blockade with the only approved complement C5 inhibitor, the monoclonal antibody eculizumab. Untreated, patients with PNH have a reduced life expectancy, principally because of major thrombotic events. Side effects of repeated blood transfusion, such as iron accumulation, also contribute to the morbidity of the disease.

1.2. **aHUS**

Atypical HUS is caused by a disorder in complement regulation, which leads to leukocyte and platelet activation, thrombotic microangiopathy, and subsequent end-organ damage [Thomson & Ulrickson, 2016]. Atypical HUS is distinguished from other more common causes of haemolytic uraemic syndrome, the commonest being Shigatoxin-producing Escherichia coli (STEC) and *Streptococcus pneumoniae*. The most common causes of atypical HUS are specific complement gene mutations that predispose towards development of the disease, while antibodies to complement factor H have also been implicated in a smaller subset of patients. Classic laboratory findings include haemolytic anaemia, thrombocytopenia, and acute kidney injury. Atypical HUS is distinguished from thrombotic thrombocytopenic purpura (TTP) by its lack of reduction in activity of ADAMTS13 (A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13).

Untreated aHUS is associated with permanent renal dysfunction, high recurrence rate, and high mortality. Historically, prognosis was poor: studies showed that 33–40% of patients progressed to end stage renal disease (ESRD) or death during the first clinical manifestation. Plasma therapy in the form of plasma exchange or infusion has remained the standard treatment for aHUS. However, many patients do not respond to plasma therapy and some require prolonged treatment. Within 1 year of diagnosis, up to 65% of patients managed with plasma exchange (PEX) suffered permanent renal damage, progressed to ESRD, or died. The elucidation of the pathogenesis from uncontrolled activation of the alternative complement pathway, resulting in formation of the MAC C5b-9 has ultimately led to approval in EU and in USA for treatment with eculizumab, a monoclonal IgG antibody that binds to C5 and prevents subsequent formation of terminal complement.

Patients being admitted to this study will have previously received treatment with rVA576 (Coversin) under different investigational protocols for PNH , for eculizumab resistance or aHUS.

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Table 1: aHUS Recommended Vial Usage

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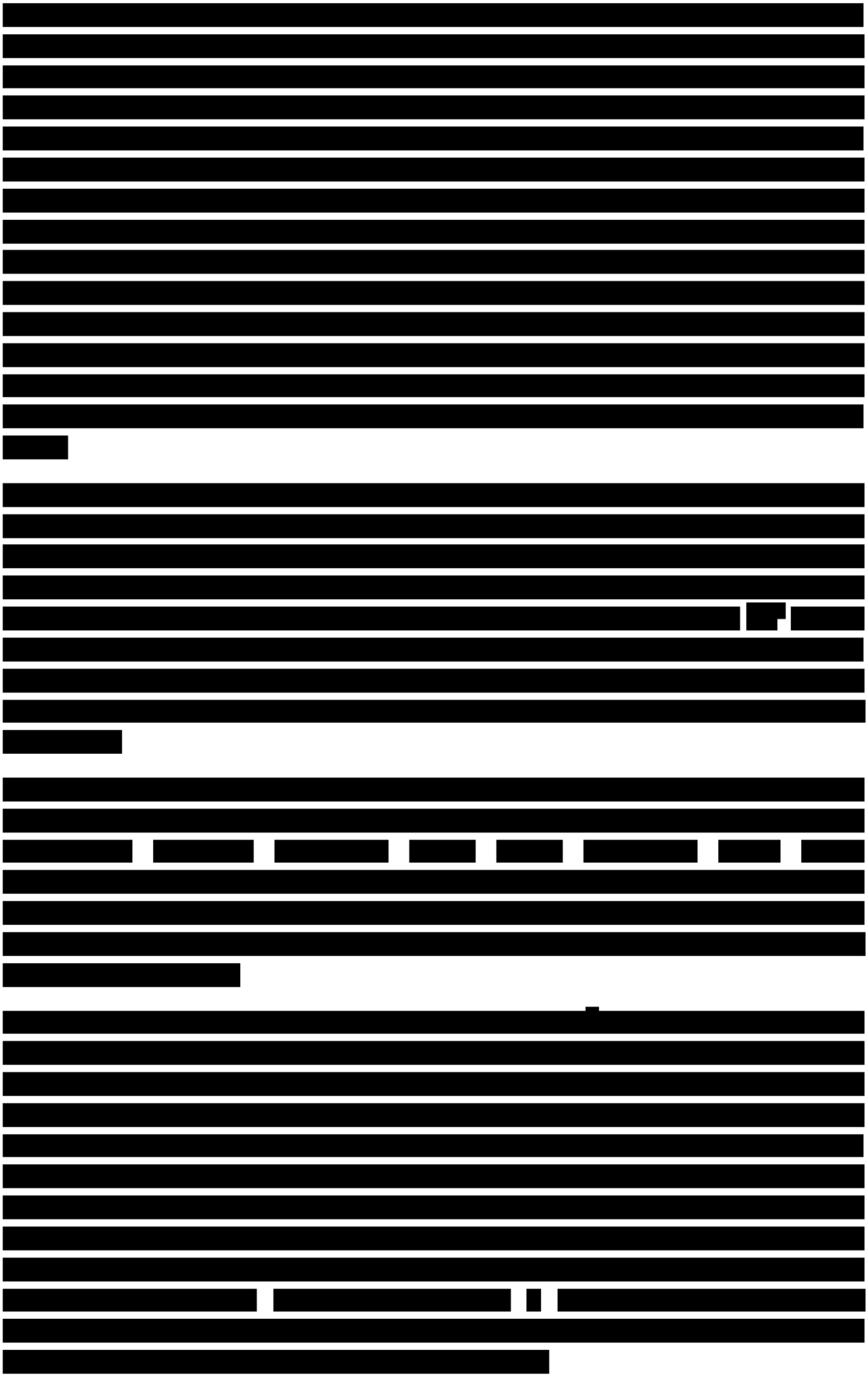

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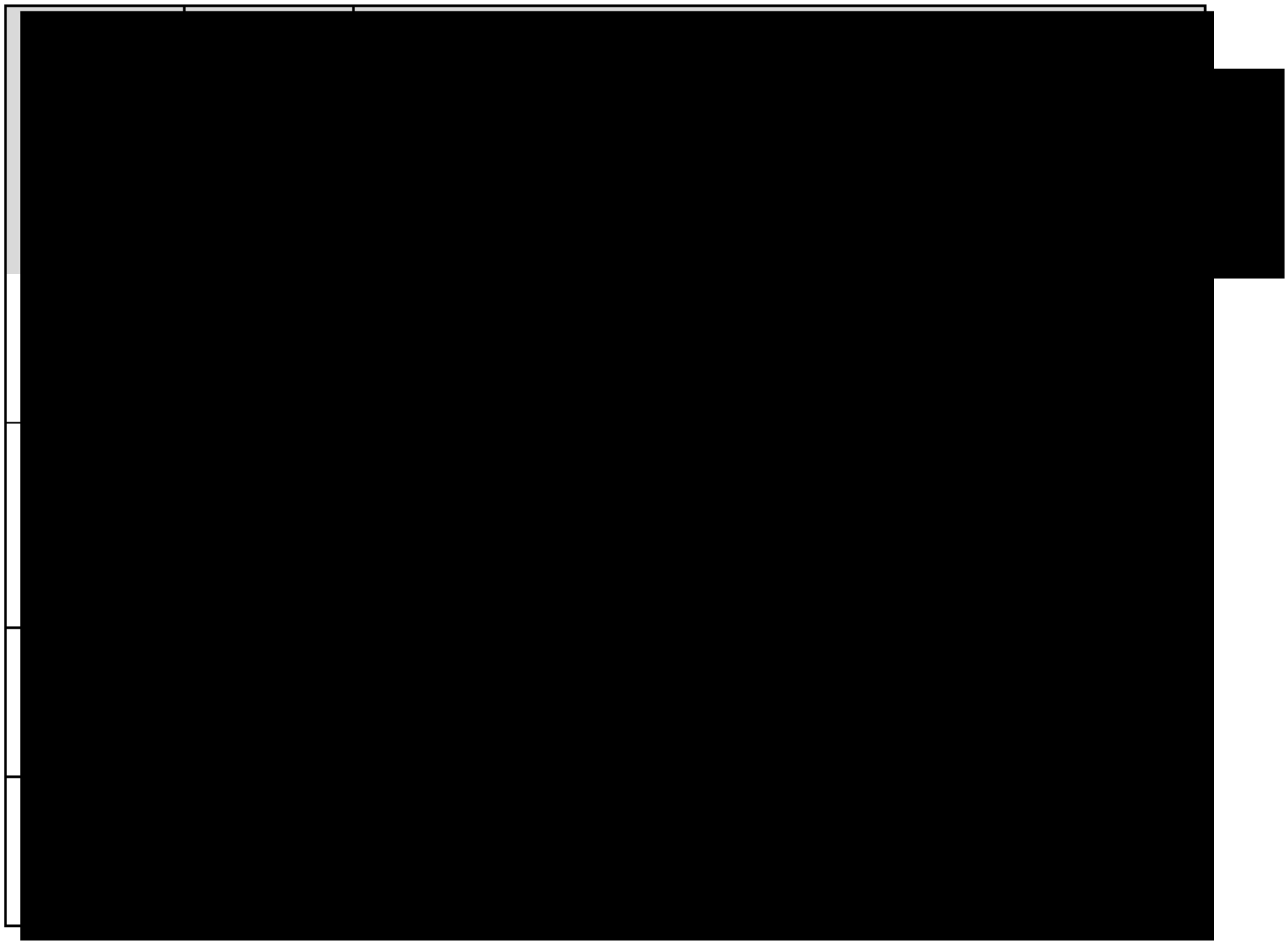

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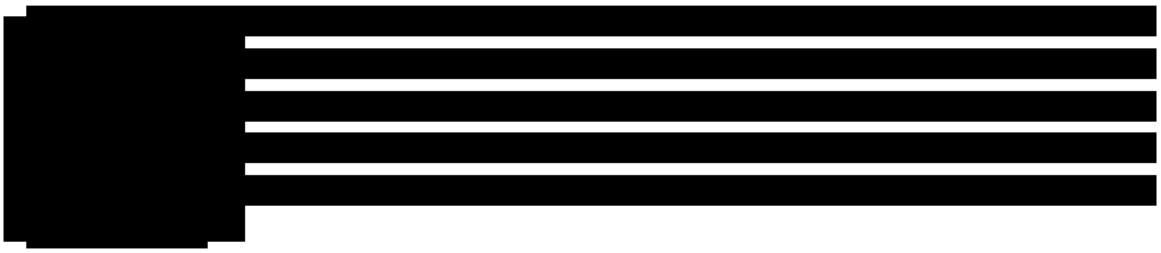

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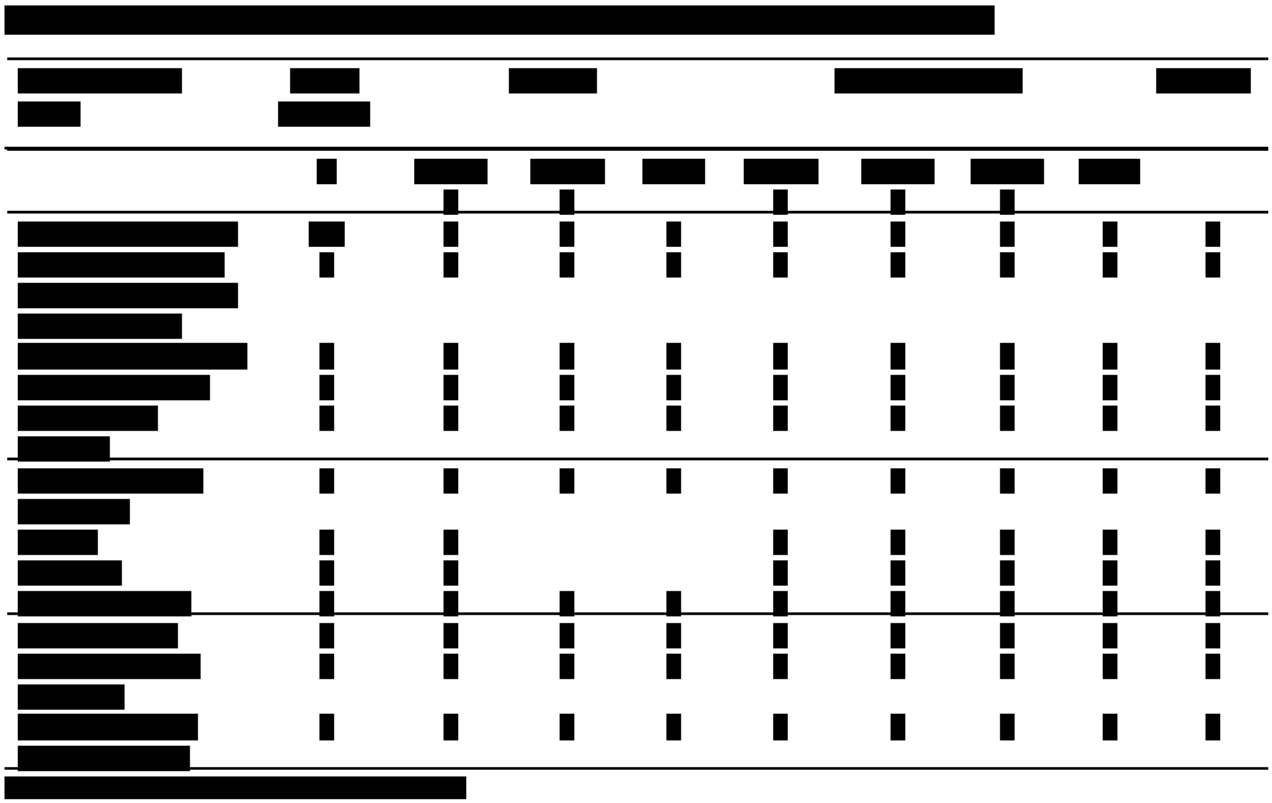

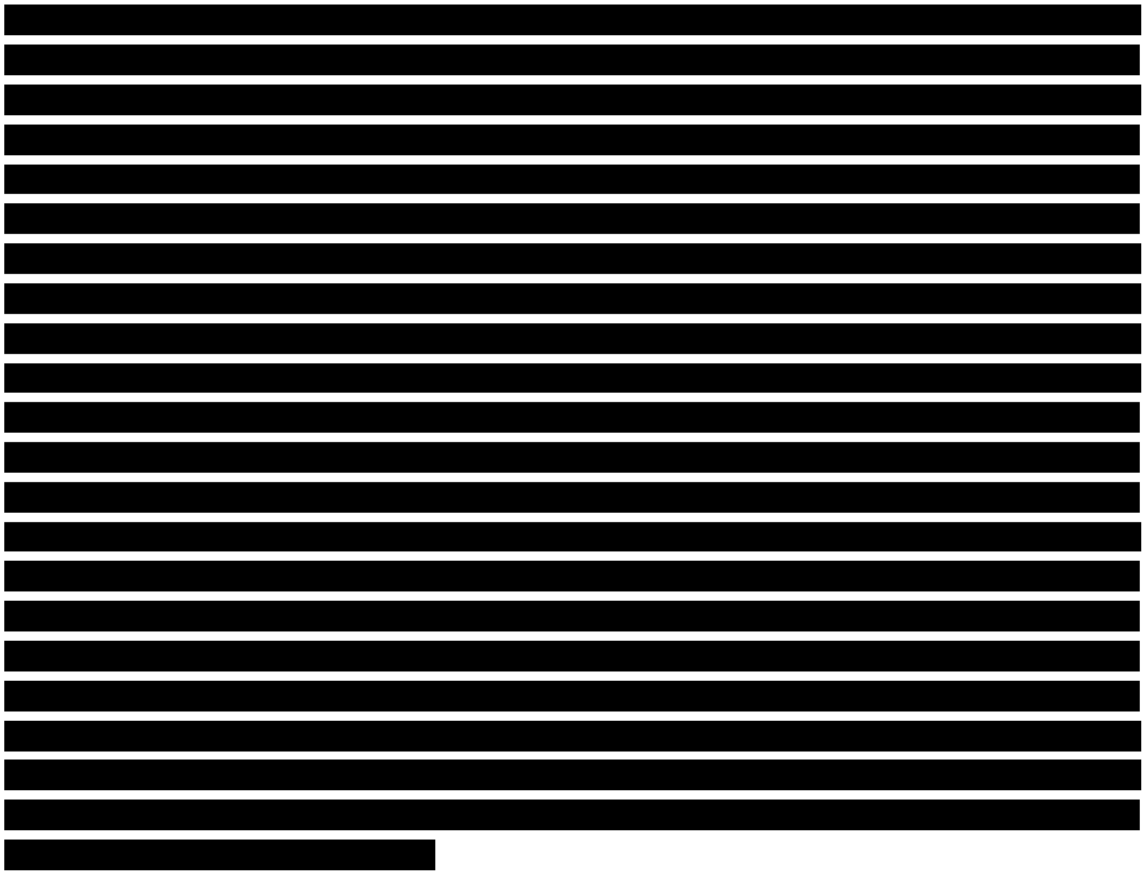

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2.5. Description of and justification of route of administration, dosage regimen and treatment period(s)

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3. Trial Purpose, Objectives and Endpoints

3.1. **Trial purpose & Objectives**

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

[redacted]

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.

The specific objectives of the study are:

- To observe the long term safety and efficacy of rVA576 (Coversin) in a period exceeding the 6 months of treatment.
- To assess the long term patient acceptability of rVA576 (Coversin) using the EORTC QLQ-C30 (for some PNH only), EQ-5D-5L & FACIT-F (both PNH & aHUS) 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

3.2. **Endpoints**

3.2.1. *Safety & Efficacy Endpoints:*

Primary:

- 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).

PNH Secondary:

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) $\leq$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.

aHUS Secondary:

1. Proportion of subjects with Normal Platelet count [defined as Platelet count ≥ 150 x10^9/L] at each 3-month time point since the start of the study and over the entire period of the study.
2. Proportion of subjects entering study with complete TMA response who continue to exhibit complete TMA response with preserved renal function, defined as hematologic normalization (platelet count ≥150 X 10^9/L and LDH ≤ ULN) and preservation of kidney function (<25% increase in SCr from baseline of previous study), during each 3-month time period since the start of this study.
3. Proportion of subjects with complete TMA response with improved renal function defined as normalization of haematological parameters (normalisation of platelet count and LDH≤ULN) and ≥ 25% decrease in SCr from baseline of previous study during each 3-month time period since the start of the study.
4. Proportion of subjects who exhibit haematological normalisation (platelet count ≥150 X 10^9/L and LDH ≤ ULN) during each 3-month time period since the start of this study.

5. Proportion of subjects with improvement in renal function defined as a decrease in SCr over three consecutive measurements from baseline of previous study without the need for dialysis even if not within the normal range.
6. Proportion of subjects who are TMA event-free during each 3-month time period since the start of the study.
7. Platelet mean count change at each 3-month time period since the start of the study.
8. Quality of Life measures from baseline at 3 monthly intervals up to the end of study in FACIT-F instrument and the EQ-5D-5L instrument.

Additional Endpoints:

- PK and PD parameters during treatment.

4. Trial population

The study population will consist of patients who have completed participation in clinical trials under other Akari protocols and who wish to continue to receive rVA576 (Coversin). Patients may be male or non-pregnant females using adequate methods of contraception if of childbearing potential. All patients will enter the trial on the same dose and dose frequency as they were receiving at the end of the previous trial.

4.1. Inclusion criteria

1) Patients 18 years and above treated with rVA576 (Coversin) under other Akari clinical trial protocols and wish to remain on rVA576 (Coversin) at the conclusion of that trial.
2) In the opinion of the treating responsible clinician patient is receiving clinical benefit from continued treatment with study drug.
3) Evidence of sustained complement inhibition by CH50 assay.
4) Women of childbearing potential (WOCBP) must agree to use effective contraception consistently throughout the study and have a negative pregnancy test at screening. Women are considered post-menopausal and not of childbearing potential if they have had 12 months of amenorrhea and considered sterile if they have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks previously.
5) Males with a childbearing potential partner must agree to use effective contraception consistently OR have had a vasectomy.
6) Weight ≥50kg.
7) Received appropriate prophylaxis against *Neisseria meningitidis* infection, by both immunisation and continuous or intermittent antibiotics.
8) The patient is willing to give voluntary written informed consent.
9) The patient is willing in the process of preparation and self-administration of the study drug.

4.2. **Exclusion criteria**

1. Patient experienced any safety event in the previous study protocol, which puts the patient at unacceptable risk in current protocol as judged by the investigator and sponsor.
2. Patient is unwilling to complete the Quality of Life instruments and diary card.
3. Active meningococcal infection (section 4.3.2 for additional information).
4. Any other reason for which, in the opinion of the Investigator, it would not be in the interests of the patient to remain on rVA576 (Coversin).
5. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 90 days after last dose; or intending to donate ova during such time period.
6. If male, the subject intends to donate sperm during this study or for 90 days after last dose.
7. Failure to satisfy the Investigator of fitness to participate for any other reason or any other condition which, in the opinion of the investigator, could increase the subject's risk from participating in the study or confound the outcome of the study.
8. Use of prohibited medication (e.g. Eculizumab (Soliris®), Chemotherapeutic agents, any other drug acting directly on the complement system).
9. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within one year prior to screening.
10. Participation in other clinical trials with investigational product.

4.3. **Meningitis**

4.3.1. ***Meningitis prophylaxis***

It is known that the products of C5 complement activation are important in protection against infection by gram negative bacteria especially *Neisseria sp.* [Ram et al, 2010]. This is believed to be the only known hazard of blocking this stage of the complement cascade and subjects taking part in previous trials of complement C5 inhibitors were found to be at greater risk of Neisseria infection, particularly meningococcal infection [Dymtrijuk et al, 2008].

Prophylaxis against *Neisseria Meningitis*. will be mandatory in this study and may consist of either or both active immunisation against meningitis A, C, W and Y (and B in countries where the *Bexsero*® vaccine is approved) and prophylactic antibiotics. The exact nature of meningococcal prophylaxis during complement inhibitor therapy will be according to local practice/guidelines and will be recorded in the eCRFs.

The patient would have been vaccinated for prophylaxis against meningitis during the previous study and similar vaccination is not required to be repeated at the beginning of this study.The patient's history of meningococcal vaccines will be transferred from the previous study they participated in.

In this study the anti-meningococcal measures employed in individual cases will be at the discretion of the Investigators and in accordance with local practice. In limited duration toxicological studies, with both eculizumab and rVA576 (Coversin), no adverse events or findings attributable to C5 blockade have been reported but

Investigators are advised to be alert for possible infectious events even in subjects who have received meningococcal immunisation.

4.3.2. *Active Meningococcal Infection*

The patient with active meningococcal or other significant infection at screening will undergo risk benefit assessment by the investigator and sponsor for continuing to receive AK581 study treatment. On risk-benefit assessment, if the treatment with rVA576 (Coversin did not continue, the eligibility for enrolment in AK581 study will be evaluated after treatment of infection.

4.4. **Concomitant Therapy**

At screening, the PI will ask the patient about any medication that is currently ongoing. During the course of the study, patients should be reminded to record any concomitant medications in their patient diaries and the PI should discuss medications at each visit. All concomitant medications, including herbal and vitamin supplements, must be recorded in the diary card/patient medical records and captured in electronic case report form (eCRF).

4.5. **Prohibited Medications**

The following medications are not permitted whilst the patient is taking part in this study. The PI should discuss at each visit with the patient.

- Eculizumab (Soliris®)
- Chemotherapeutic agents
- Any other drug acting directly on the complement system

4.6. **Contraception**

There are no specific, identified risks to mother or foetus from rVA576 (Coversin) therapy. A segment 1 reproductive toxicology study has been undertaken in mice (YUU0001) to assess the effects of 0, 0.5, 5 and 10 mg/kg/day rVA576 (Coversin) on the fertility and early embryonic development of the mouse when administered for at least 14 days before and during pairing, and then to Day 6 of gestation in females and until the day before necropsy for males. The study reported no deaths or clinical signs considered to be associated with the doses of rVA576 (Coversin) test; the causes of death for 1 male and 1 female found dead during the study were considered to be unrelated to test item administration. There was no effect of rVA576 (Coversin) on body weight, food intake, mating activity, fertility and pregnancy or uterine implantation. There were no findings at necropsy considered to be related to rVA576 (Coversin) and group mean ovary and testes weights for animals given the test item were similar to Controls. Segment 2 and 3 reproductive toxicology studies will be undertaken prior to seeking market approval. Until the results from reproductive toxicology studies are completed, patients being treated with rVA576 (Coversin) should be advised to use the following precautions against sexual exposure and pregnancy.

Patients who are or become sexually active during the course of the study must use, with their partner, approved methods of highly effective contraception from the time of signing the Informed Consent Form (ICF) until 90 days after the last dose of rVA576 (Coversin).

Women of childbearing potential (WOCBP) are considered those women who have menarche and until becoming post-menopausal unless permanently sterilised. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative cause.

Two or more of the following methods are acceptable and must include one barrier method:

- Surgical sterilisation (i.e. bilateral tubal removal, bilateral overay removal, hysterectomy for female partners; vasectomy for males)
- Placement of an intrauterine device or intrauterine system
- Hormonal contraception associated with the inhibition of ovulation (implantable, patch, oral)
- Barrier methods (for male patients, this must be a condom; for female patients, either their partner's use of a condom or the patient's use of an occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository). Barrier methods must be used in conjunction with another method.

Alternatively, true abstinence is acceptable when consistent with the patient's preferred and usual lifestyle. If a patient is usually not sexually active but becomes active during the course of study, they and their partner should use two of the contraceptive methods listed above. Any female patient who becomes pregnant during the course of the trial will be withdrawn from the trial unless she consents to a termination of the pregnancy.

Male patients who have been sterilised are required to use one barrier method of contraception (condom).

4.6.1. *Exposure of partners during the study*

There is a risk of drug exposure through ejaculate (which also applies to vasectomised males) which might be harmful to the sexual partners, including pregnant partners, of male patients. Barrier contraception should be used throughout the study and for 90 days after the last day of IMP administration.

Fathering a child through samples before IMP exposure is acceptable. Similarly, a surrogacy through frozen eggs collected before IMP exposure is acceptable i.e. prior to previous study participation.

4.6.2. *Sperm Donation*

Male patients should not donate sperm for the duration of the study and for at least 90 days after the last day of IMP administration.

4.6.3. ***Egg Donation***

Female patients should not donate eggs whilst on the study and for at least 90 days after the last day of IMP administration.

4.6.4. ***Breast Feeding***

Female patients must agree not to breastfeed whilst on the trial and for at least 90 days after the last day of IMP administration.

5. Trial Design and Procedures

5.1. Trial Design:

The trial is an open-label, non-comparative study in 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.

5.2. Dose Changes:

If the Investigator considers that a change in dose or dose frequency is necessary, it is suggested that the schedule shown in **Table *7*** is followed. Please note that Ablating Doses may only be needed if the change is to a higher dose or dose frequency. A change to an increased dose is mandated by an inadequate response (see definition below) but may also occur at the discretion of the Investigator in consultation with the Sponsor.

Table 7: Dose Decision Table: Suggested schedule for changing dose/dose interval in case of inadequate response

PNH patients

Ablating Doses (if required)			
Dose	*Interval*		
60mg	Single dose		
30mg	1 x 12 hourly dose		
Inadequate Response			
Existing		**Switch to**	
Dose	*Interval*	*Dose*	*Interval*
15mg	12 hourly	22.5mg	12 hourly
22.5mg	12 hourly	45mg	24 hourly
30mg	24 hourly	45mg	24 hourly
45mg	24 hourly	22.5mg	12 hourly

aHUS patients

Note: aHUS pts from the parent study will rollover to AK581 with the dosing regimen (taken) on the last dosing day of the parent study

Ablating Doses (if required)			
Dose	*Interval*		
60mg	Single dose		
30mg	1 x 12 hourly dose		
Inadequate Response			
Existing		**Switch to**	
Dose	*Interval*	*Dose*	*Interval*
30mg	12 hourly	After assessment decision will be made in collaboration with the Sponsor and PI.	
45mg	24 hourly	30mg	12 hourly

5.3 Duration of trial

Up to 4 years

Patients for whom rVA576 (Coversin) was found to be effective in this clinical trial and who wish to continue on the drug following conclusion of the trial, will continue to receive rVA576 (Coversin), subject to approval of the applicable governmental agency, until rVA576 (Coversin) receives marketing approval. If Akari encounters any issues with the availability of the drug, it will allocate available drug to such patients in a manner which is fair and consistent with ethical requirements.

5.4 Trial procedures

5.4.1 ***Screening***

Patients considered unsuitable for inclusion in this trial should be identified by their Investigator before the end of their participation in the preceding trial (i.e. should the investigator feel participation in the long term safety study is not in the patient's benefit or if the patient declines to participate in AK581) allowing adequate time for any alternative therapy to be implemented. The Investigators should discuss the suitability of patients to enter AK581 with the Sponsor at least four weeks before the likely time of entry in order that documentation, including ICF, can be put in place and continuity of drug supply can be ensured.

Ideally the patient will be entered on the long term safety trial on the last day of dosing of the parent trial on condition that they have provided consent.

*5.4.2 **Dosing period(s)***

Patients will be dispensed drug at suitable timepoints during the trial

*5.4.3 **Exiting the trial***

Patients may choose to leave the trial at any time or may be withdrawn by the Investigator in case of lack of efficacy, adverse reactions to rVA576 (Coversin), lack of compliance or for any other reason which, in the opinion of the Investigator, makes their continued participation no longer in their best interests.

Patients will also leave this trial, or an extended access trial if one is required, once rVA576 (Coversin) is fully approved and reimbursed for their indication in their country and once continuity of supply has been ensured.

*5.4.4 **End of Study/Follow-up***

All patients will have a follow up clinic visit at 1 Month $\pm$ 7 days and all women of child bearing potential (WOCBP) will have a follow up visit at Month 3 $\pm$7 days from last dose.

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Table 8: Schedule of Events for PNH Patients

EVENT (PNH)	**Entry**	**[i]1 Months (±7 days)**	**2 Months (±7 days)**	**3 Months (±7 days)**	**6 Months (±7 days)**	**9 Months (±7 days)**	**12 Months (±7 days)**	**15 Months (±7 days)**	**18 Months (±7 days)**	**21 Months (±7 days)**	**24 Months (±7 days)**
Medical History. Eligibility & Informed Consent & demographics	✓										
[iii]Physical Examination *if not done within 7 days of entry*	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[iv]Vital Signs (including weight) at every visit	✓ [vii]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[xi]ECG	✓ [vii]						✓				✓
Urinalysis (including pregnancy testing)[viii]	✓ [vii]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[ii]Haematology & Chemistry including LDH, FBC and creatinine (local or central labs)	✓ [vii]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[ii]CH50, unbound rVA576 (Coversin) blood level (PK) & LTB4 (Central lab)	✓ [vii]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ADA (Central lab)	✓ [vii]			✓		✓		✓			✓
[ix]Additional blood draws for further indepth analysis (Total LDH and LDH Isoenzymes) (Central lab)	✓ [vii]			✓		✓		✓			✓
Total C5 level (Central lab)	✓ [vii]			✓		✓		✓			✓
FLAER and/or Flow Cytometry (local or central)	✓ [vii]			✓				✓			✓

Table 8: Schedule of Events for PNH Patients (Continued)

EVENT (PNH)	**Entry**	**[i]1 Months (±7 days)**	**2 Months (±7 days)**	**3 Months (±7 days)**	**6 Months (±7 days)**	**9 Months (±7 days)**	**12 Months (±7 days)**	**15 Months (±7 days)**	**18 Months (±7 days)**	**21 Months (±7 days)**	**24 Months (±7 days)**
[v]EORTC-QLQ-C30, EQ-5D-5L & FACIT-F questionnaires (*if not done within 7 days of entry)* & Sponsor non-validated questionnaire	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[vi]Drug Accountability		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AE and Concomitant Medication reporting	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MAVE Assesment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 8: Schedule of Events for PNH Patients (Continued)

EVENT (PNH)	**27 Months (±7 days)**	**30 Months (±7 days)**	**33 Months (±7 days)**	**36 Months (±7 days)**	**39 Months (±7 days)**	**42 Months (±7 days)**	**45 Months (±7 days)**	**48 Months (±7 days) End of study Visit**	**[x]Follow up visit after 1 month (±7 days) (inc 3 month follow up visit for females)**	**Early Termination**
[iii]Physical Examination	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[iv]Vital Signs (including weight) at every visit	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[xi]ECG				✓				✓		✓
Urinalysis (including pregnancy testing)[viii]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[ii]Haematology & Chemistry including LDH, FBC and creatinine (local labs)	✓	✓	✓	✓	✓	✓	✓	✓		✓
[ii]CH50, unbound rVA576 (Coversin) blood level (PK) & LTB4 (Central lab)	✓	✓	✓	✓	✓	✓	✓	✓		✓
ADA (Central lab)			✓			✓		✓		✓
[ix]Additional blood draws for further indepth analysis (Total LDH and LDH Isoenzymes)			✓			✓		✓		✓
Total C5 level			✓			✓		✓		✓
FLAER and/or Flow Cytometry (local or central)			✓					✓		✓
[v]EORTC-QLQ-C30, EQ-5D-5L & FACIT-F questionnaires & Sponsor non-validated questionnaire	✓	✓	✓	✓	✓	✓	✓	✓		✓
[vi]Drug Accountability	✓	✓	✓	✓	✓	✓	✓	✓		✓

Table 8: Schedule of Events for PNH Patients (Continued)

EVENT (PNH)	27 Months (±7 days)	30 Months (±7 days)	33 Months (±7 days)	36 Months (±7 days)	39 Months (±7 days)	42 Months (±7 days)	45 Months (±7 days)	48 Months (±7 days) End of study Visit	[x]Follow up visit after 1 month (±7 days) (inc 3 month follow up visit for females)	Early Termination
AE and Concomitant Medication reporting	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MAVE Assessment	✓	✓	✓	✓	✓	✓	✓	✓		✓

Table 8 Notes (for PNH patients):

i. Investigator visits may take place more frequently if needed or desired (unscheduled visits/testing where needed), but the schedule shown is the minimum permitted
ii. All blood draws will be taken pre-dose. If not possible, a note to that effect must be made in the medical records and captured in the eCRFs
iii. Physical Examination - Inclusive of vein assessment and injection site inspection
iv. Vital Signs – Diastolic and Systolic blood pressure &pulse rate
v. Patients must complete the Quality of Life (QOL) Instruments and sponsor non-validated questionnaire at every clinic visit
vi. Drug accountability will be performed at each visit. Patients are requested to bring in empty vials only and inform the site of unused vials remaining in their fridge.
vii. Test to be conducted at entry if not done within 14 days of entry visit.
viii. Pregnancy tests for women of childbearing potential must be done monthly. The current protocol design requires a pregnancy test at each hospital visit and then every 3 months after Month 3 (Months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48 & ET). In addition Home Pregnancy tests must be repeated every month during the use of rVA576 (Coversin) and up to 90 days after the last dose of rVA576 (Coversin) by the patient.
ix. Total LDH and LDH isoenzymes via a central laboratory maybe required as per the schedule to monitor patient safety (unscheduled visit/test is also permitted)
x. All patients will have a follow up clinic visit at 1 Month $\pm$ 7 days in addition all women of childbearing potential (WCBP) will have a follow up visit at Month 3 $\pm$7 days from last dose whereby urine pregnancy test will be conducted on site.
xi. Routine ECG to be performed at entry and then annually during the study. *(Limb lead or 12 lead ECG machines are acceptable)*

FLAER/Flow Cytometry: Local lab or via Central Lab (if not available locally). **A 7 day window is permitted for each visit.**

Table 9: Schedule of Events for aHUS patients

EVENT (aHUS)	**Entry**	**[i]1 Months (±7 days)**	**2 Months (±7 days)**	**3 Months (±7 days)**	**6 Months (±7 days)**	**9 Months (±7 days)**	**12 Months (±7 days)**	**15 Months (±7 days)**	**18 Months (±7 days)**	**21 Months (±7 days)**	**24 Months (±7 days)**
Medical History. Eligibility, Informed Consent & demographics	✓										
[iii]Physical Examination *if not done within 7 days of entry*	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[iv]Vital Signs (including weight) at every visit	✓ [vii]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[x]ECG	✓ [vii]						✓				✓
Urinalysis (including pregnancy testing)[viii]	✓ [vii]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[ii]CH50, unbound rVA576 (Coversin) blood level (PK) & LTB4 (Central Lab)	✓ [vii]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ADA (Central Lab)	✓ [vii]			✓		✓		✓			✓
[ii]Haematology & Chemistry including LDH, FBC and creatinine (local or Central labs)	✓ [vii]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Total C5 level & C3 (aHUS only)	✓ [vii]			✓		✓		✓			✓

Table 9: Schedule of Events for aHUS patients (Continued)

EVENT (aHUS)	**Entry**	[i]**1 Months (±7 days)**	**2 Months (±7 days)**	**3 Months (±7 days)**	**6 Months (±7 days)**	**9 Months (±7 days)**	**12 Months (±7 days)**	**15 Months (±7 days)**	**18 Months :(±7 days)**	**21 Months :(±7 days)**	**24 Months (±7 days)**
Thrombotic Markers (D-dimer, Prothrombin f1/f2)	✓[vii]			✓		✓		✓			✓
Pro-inflammatory Markers (platelet E and P-selectin, CRP (high-sensitivity)	✓[vii]			✓		✓		✓			✓
Haemolytic Markers (Haptoglobin, Schistocyte count)	✓[vii]			✓		✓		✓			✓
Dialysis Assessment & Plasma Transfer record	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[v]EQ-5D-5L and FACIT -F questionnaires *(if not done within 7 days of entry)* & Sponsor non-validated questionnaire	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[vi]Drug Accountability		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AE and Concomitant Medication reporting	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 9: Schedule of Events for aHUS patients (Continued)

EVENT (aHUS)	**27 Months (±7 days)**	**30 Months (±7 days)**	**33 Months (±7 days)**	**36 Months ((±7 days)**	**39 Months (±7 days)**	**42 Months (±7 days)**	**45 Months (±7 days)**	**48 Months (±7 days) End of study Visit**	**[ix]Follow up visit after 1 month (±7 days) (inc 3 month follow up visit for females)**	**Early Termination**
[iii]Physical Examination *if not done within 7 days of entry*	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[iv]Vital Signs (including weight) at every visit	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[x]ECG				✓				✓		✓
Urinalysis (including pregnancy testing)[viii]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[ii]CH50, unbound rVA576 (Coversin) blood level (PK) & LTB4 (Central Lab)	✓	✓	✓	✓	✓	✓	✓	✓		✓
ADA (Central Lab)			✓			✓		✓		✓
[ii]Haematology & Chemistry including LDH, FBC and creatinine (local labs)	✓	✓	✓	✓	✓	✓	✓	✓		✓
Total C5 level & C3 (aHUS only)			✓			✓		✓		✓
Thrombotic Markers (D-dimer, Prothrombin f1/f2)			✓			✓		✓		✓

Table 9: Schedule of Events for aHUS patients (Continued)

EVENT (aHUS)	**27 Months (±7 days)**	**30 Months (±7 days)**	**33 Months (±7 days)**	**36 Months ((±7 days)**	**39 Months (±7 days)**	**42 Months (±7 days)**	**45 Months (±7 days)**	**48 Months ((±7 days) End of study Visit**	**[ix]Follow up visit after 1 month (±7 days) (inc 3 month follow up visit for females)**	**Early Termination**
Pro-inflammatory Markers (platelet E and P-selectin, CRP (high-sensitivity)			✓			✓		✓		✓
Haemolytic Markers (Haptoglobin, Schistocyte count)			✓			✓		✓		✓
Dialysis Assessment & Plasma Transfer record	✓	✓	✓	✓	✓	✓	✓	✓		✓
[v]EQ-5D-5L and FACIT -F questionnaires & Sponsor non-validated questionnaire	✓	✓	✓	✓	✓	✓	✓	✓		✓
[vi]Drug Accountability	✓	✓	✓	✓	✓	✓	✓	✓		✓
AE and Concomitant Medication reporting	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 9 Notes (for aHUS patients):

i. Investigator visits may take place more frequently if needed or desired (unscheduled visits/testing where needed), but the schedule shown is the minimum permitted
ii. All blood draws will be taken pre-dose. If not possible, a note to that effect must be made in the the medical records and captured in the eCRFs
iii. Physical Examination – Inclusive of vein assessment and injection site inspection
iv. Vital Signs – Diastolic and Systolic blood pressure & pulse rate
v. Patients must complete the Quality of Life (QOL) Instruments and sponsor non-validated questionnaire at every clinic visit
vi. Drug accountability will be performed at each visit. Patients are requested to bring in empty vials only and inform the site of unused vials remaining in their fridge.
vii. Test to be conducted at entry if not done within 14 days of entry visit
viii. Pregnancy tests for women of childbearing potential must be done monthly. The current protocol design requires a pregnancy test at each hospital visit every month, and then every 3 months after Month 3 (Months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42 45, 48 & ET). In addition Home Pregnancy tests must be repeated every month during the use of rVA576 (Coversin) and up to 90 days after the last dose of rVA576 (Coversin) by the patient.
ix. All patients will have a follow up clinic visit at 1 Month $\pm$ 7 days in addition all women of childbearing potential (WCBP) will have a follow up visit at Month 3 $\pm$7 days from last dose whereby urine pregnancy test will be conducted on site
x. Routine ECG to be performed at entry and then annually during the study. *(Limb lead or 12 lead ECG machines are acceptable)*

A 7 day window is permitted for each visit.

5.5 Measurements conducted on blood draws

5.5.1 CH50 assay

It appears that in PNH and aHUS, close to 100% inhibition of CH50 activity is necessary for clinical control of the disease. Serum CH50 assay is currently the most sensitive and quickest means of detecting inadequate control during anti-complement therapy as other indicators, such as LDH lag 24 - 48 hours behind the change in CH50. In practice, the Quidel ELISA assay, which is used to measure complement activity in units of CH50 U Eq/mL has a lower limit of quantification (LLOQ) of 10 CH50 U Eq/mL with individual normal baseline values ranging from 58-156 CH50 U Eq/mL. Thus the assay is insensitive to differences in CH50 when there is <10 CH50 U Eq/mL residual complement activity. Therefore, for practical purposes, the Central Laboratory (which will conduct all CH50 assays during the trial) considers values less than 10 CH50 U Eq/mL as completely inhibited. In previous trials (AK577, AK578 and AK579) with rVA576 (Coversin) the 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.

CH50 samples will be collected as per Schedule of Events.

5.5.2 Antibodies (ADA)

Serum will be analysed for ADA formation to rVA576 (Coversin), as per schedule of events and stored and shipped frozen for analysis.

5.5.3 LTB4

Plasma (EDTA-treated) will be collected as per Schedule of Events and stored and shipped frozen for analysis.

5.5.4 LDH Isoenzymes

The assay determines the absolute LDH value and the proportions of LDH Isoenzymes 1 to 5. The serum sample should be stored and shipped to The Doctors Laboratory (TDL) at ambient temperature immediately. Do not store samples at 2-8°C. Do not use frozen or haemolysed samples.

5.5.5 Total C5 Levels

C5 is the complement protein bound by rVA576 (Coversin). C5 concentration in blood will be measured by ELISA to understand how and if individual subject levels of C5 vary through time. Serum samples used should be stored and shipped frozen prior to analysis.

5.5.6 Fluorescein-labelled proaerolysin FLAER / Flow Cytometry

FLAER accurately determines the number and proportion of white blood cells that lack GPI-anchor and therefore lack the complement regulatory proteins CD55 and CD59.

The whole blood EDTA sample is analysed from an ambient temperature sample. Flow cytometry using anti-CD55 and anti-CD59 antibodies identifies the number and proportion of red blood cells deficient in these GPI-linked proteins. Absence of CD55 and CD59 are

diagnostic for PNH. Clone size (proportion of cells affected) can change through time and with C5 inhibition.

5.5.7 Central Laboratory Testing (if not done within 14 days of entry)

LTB4	Anti-Drug Antibody (ADA)
CH50	rVA576 Level (PK)
C5	LDH Isoenzyme
C3 (aHUS only)	

If any site is unable to use the standard laboratory kits provided by the Central Laboratory, the site needs to inform the Sponsor immediately (providing justification) as it may have an impact on the analysis of samples and ultimately the study results.

5.5.8 Pharmacokinetics (PK) and Pharmacodynamics (PD) (aHUS only)

Blood samples for PK and PD will be collected as detailed in the schedule of events. Samples for PK and PD will be taken 5 – 60 minutes before IMP administration. The date and exact time of collection must be recorded.

The sample for PK/PD (CH50) analysis may be taken prior and/or after plasma exchange and/or dialysis. As the CH50 results are unlikely to be available for some days, the Investigator should be guided by the history, clinical signs or Platelet count and LDH as to whether it is necessary to administer additional Ablating Doses. Clinical signs of intravascular haemolysis following resumption of dosing mandates re-initiation of the Ablating dose schedule. The CRO and the Sponsor should be informed as soon as possible.

5.6 Efficacy Assessments

Measures of clinical efficacy will be assessed by the Investigator. The Sponsor (or designee) will review all eCRFs regulary for all patients in the study.

Details of safety and efficacy endpoints are detailed in section 3.2.1

5.7 Safety Assessments

5.7.1 Medical History and Present Conditions

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.

Plasma Transfer/Dialysis History is also required for aHUS patients.

Relevant data held in databases from previous rVA576 (Coversin) trials will be transferred to the current database in pdf format.

5.7.2 Physical Examination (if not done within 7 days of entry)

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

5.7.3 Vital Signs & Weight

Blood pressure and pulse rate will be measured in the supine position after the patient has rested comfortably. Body weight will be recorded, if not done within 14 days of entry. Measurements will be recorded in the patient's eCRF.

5.7.4 Cardiac Safety

Routine ECG should be performed at entry and then annually during the study. The ECG traces *(using Limb lead or 12 lead ECG depending on what is available at site)* will be reviewed, signed, and dated by a physician and he/she will record on the trace whether whether the ECG is normal or abnormal and if deemed abnormal, whether the abnormality is clinically significant (CS) or not clinically significant (NCS).

5.7.5 Clinical Laboratory Safety Tests (if not done within 14 days of entry)

All samples will be collected in accordance with acceptable laboratory procedures at the time points specified in the Schedule of Events **Table *8*** &**Table *9***. Additional and repeat testing may be performed at the discretion of the Investigator. All clinical laboratory safety tests will be performed locally by each clinical unit unless this is not possible in a participating country.

Baseline haematology, chemistry and urinalysis will be performed at entry unless these investigations have taken place within 14 days of screening.

5.7.6 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.

5.7.7 Pregnancy Test

Pregnancy tests for women of childbearing potential (WOCBP) must be done monthly. The current protocol design requires a urine pregnancy test at entry and at each clinic visit. In addition, home pregnancy tests must be repeated every month during the use of rVA576 (Coversin) and up to 90 days after the last dose of rVA576 (Coversin) by the patient.

5.7.8 Additional Investigational & Safety Testing

Additional, non-genetic testing may be conducted on retained samples if deemed appropriate by the Investigator or should additional research suggest further investigation is required to improve disease evaluation and drug response. Consent for additional, currently undetermined, exploratory analysis will be in place prior to further analysis. The patient may refuse additional testing on their retained samples at any point and this will not influence their participation in the study.

Additional and repeat blood draws considered necessary for safety and well-being of the patient may be performed at the discretion of the Investigator.

Further to the above, the Sponsor and Investigator may request additional blood samples, (not listed in the Schedule of Events), to be taken during the course of the study to support further non-genetic testing, should there be insufficient blood remaining in the retained sample. A maximum study blood draw volume of 800mL per patient will not be exceeded inclusive of additional testing.

Additional, currently undetermined, exploratory analysis is likely to be done for C3, C3a, C5a and sC5b9.

Haematology Parameters

White blood cell count	Neutrophils absolute
Red blood cell count	Lymphocytes absolute
Haemoglobin	Monocytes absolute
Mean Cell Haemoglobin (MCH)	Mean Cell Haemoglobin Concentration (MCHC)
Haematocrit	Eosinophils absolute
Erythrocyte sedimentation rate (ESR)	Basophils absolute
Platelets	Mean Cell Volume (MCV)
Reticulocytes	

Chemistry Parameters

Lactate dehydrogenase & LDH isoenzymes	Glucose (Random)
Sodium	Alkaline phosphatase
Potassium	Alanine Aminotransferase (ALT)
Bicarbonate	Aminotransferase (AST)
Urea	Creatine Kinase (CK)
Creatinine	Total Bilirubin
Chloride	Bilirubin (Direct) (only if Total is elevated)
Albumin	Phosphate (Inorganic)
Calcium	Protein (Total)
Gamma Glutamyl Transpeptidase (GGT)	

Urinalysis Parameters

Leukocytes	Ketones
Protein	Nitrates
Bilirubin	Blood
Glucose	hCG (female WOCBP patient)
pH	Specific gravity
At Discretion of PI Based on Urinalysis Results Microbiology Urine Microscopy Pregnancy testing	Urobilinogen

5.8 Data that can be carried over from previous study to current AK581 study:

If done within 7 days of entry:

- Physical exam & QOL

If done within 14 days of entry:

- CH50 + complement factors and activation markers, rVA567 level (PK), LTB4, Haematology, Chemistry, Urinalysis.

If ECG, vital signs, Pregnancy testing and MAVE are done on the same day as the end of study visit for the previous study as the entry day for the long term safety study, then these procedures do not need to be repeated again.

Note*: laboratory results can only be used if they are from the same reference laboratory in both studies.*

aHUS Parameters

If done within 14 days of entry:

- Thrombotic Markers (D-dimer, prothombin f1/f2)
- Pro-inflammatory Markers (platelet E and P-selectin, CRP (high-sensitivity)
- Haemolytic Markers (Haptoglobin)
- Schistocyte count
- Dialysis Assessment & Plasma Transfer record

5.9 Definition of an inadequate response

If patients show evidence of persistent loss of disease control (on clinical or haematological or biochemical or CH50 parameter), the Investigator may increase the dose or the dose frequency in line with the **table in section 5.10** if they are not already on the maximum permitted dose. This should only be done in consultation with the Sponsor's Medical Director and after other possible causes such as poor compliance have been eliminated. The subject may require additional investigations (including blood tests) to evaluate loss of disease control and dose adjustment.

5.10 Missed doses

For PNH patients:

For a missed dose of more than >24 hours, the sample for PD (CH50) analysis should be taken if possible just prior to the next morning dose of rVA576 (Coversin). As the CH50 results will not be available for some days the Investigator should be guided by the history, clinical signs or platelet count and LDH. In some cases, the PI may feel that an ablating dose is not required and the patient should resume their usual dosing schedule as soon as possible. In PNH, clinical signs of intravascular haemolysis following resumption of dosing mandates re-initiation of the AD schedule. The CRO and the Sponsor should be informed as soon as possible.

<table>
<tr><th>Dose</th><th>Interval</th><th>Missed Dose <4hr</th><th>Missed Dose <24hrs</th><th>Missed dose by day(s)>24hrs</th></tr>
<tr><td>15mg</td><td>12 hourly</td><td rowspan="5">Dose to be taken as soon as patient realizes</td><td>Take 15mg dose immediately and 15mg dose at usual time</td><td rowspan="5">Take ablating dose 60mg/30mg. then take dose as per usual routine</td></tr>
<tr><td>22.5mg</td><td>12 hourly</td><td>Take 22.5mg dose immediately and 22.5 mg dose at usual time</td></tr>
<tr><td>30mg</td><td>12 hourly</td><td>Take 30mg dose immediately and 30mg dose at usual time</td></tr>
<tr><td>30mg</td><td>24 hourly</td><td>Take 45mg dose immediately and 45mg dose at usual time</td></tr>
<tr><td>45mg</td><td>24 hourly</td><td>Take 45mg dose immediately and 45mg dose at usual time</td></tr>
</table>

For aHUS patients:

In the event of one missed dose (defined as a dose not taken within a one-hour time window either side of the specified time) the following procedure should be adopted by the patient:

- Take the appropriate dose as per the day of the protocol as soon as possible and then resume the usual dosing schedule at the specified times

In the event of more than one missed dose the CRO and the Investigator's clinic should be informed as soon as possible and the following procedure should be adopted:

- Take 60 mg Coversin followed by 30 mg 12 hours later and then resume the usual dosing schedule (i.e. between 07:00 and 11:00 hrs daily) at the first time point after the ablation doses.

The Investigator's clinical staff should arrange for a Central laboratory blood draw for PK/PD to be taken 3 days $\pm$ 1 day after first becoming aware of the missed doses in this situation.

The sample for PD (CH50) analysis should be taken just prior to dosing with rVA576 (Coversin).

As the CH50 results are unlikely to be available for some days the Investigator should be guided by the history, clinical signs or platelet count and LDH as to whether it is necessary to administer additional Ablating Doses.

If 3 or more consecutive doses have been missed the patient's ability or willingness to comply with the protocol should be discussed and consideration should be given as to whether that subject should continue in the study.

5.11 Rescue Therapy (aHUS only)

Plasma Transfer or Dialysis/Hemofiltration will be considered Rescue Therapy.

If Rescue Therapy is known to be required on a day during treatment, then the Rescue Therapy should be completed before any rVA576 (Coversin) is given to the subject on that day, if possible.

The following rules should be used when the Investigator administers Rescue Therapy to the subject:

Administer 60 mg rVA576 (Coversin) within 60 minutes after the end of each Rescue therapy.

- If $\leq$ 6hrs to the next scheduled dose:15mg of rVA576 (Coversin) at the next scheduled dose, then resume to dose subject was prior Rescue Therapy.
- If > 6hrs to next scheduled dose: 30 mg of rVA576 (Coversin) at the next scheduled dose, then resume to dose subject was prior Rescue Therapy.

Examples:

Dose/time	**Rescue Therapy (RT) and ablation dose**	**Next Dose/Time**	**Next Dose/Time**
30 mg /9am	RT ends at 4pm then 60 mg of rVA576 (Coversin) (within 1hr after end of PT) ≤6hrs till the next scheduled dose	15mg/9pm	30mg/9am
45mg /8am	RT ends at 12pm then 60 mg of rVA576 (Coversin) (within 1hr after end of PT) >6hrs till the next scheduled dose	Evening dose 8pm 30 mg of rVA576 (Coversin)	45mg/8am

It is the responsibility of the PI to ensure that details regarding the medication, therapy, or procedure are recorded in full in the patient's source/chart and CRF.

Additional PK/PD samples may be required in case of Rescue Therapy.

5.11.1 Plasma Transfer (aHUS only)

The need for Plasma Transfer during the clinical trial should be guided by:

a) A new decrease in platelet counts > 25% below the previous / baseline Platelet Count value and to a level less than 100 x 10^9/L; or
b) A new decrease in platelet count below 40 x 10^9/L; or
c) An emergent and new neurological, renal or another clinical event as prospectively defined for each patient.
d) In the judgement of the Principal Investigator administering Plasma Transfer is required for the best interests of the subject.

If one of these conditions applies, then the Investigator may, at his or her discretion, precribe Plasma Transfer treatment based on the clinical assessment of the subject. The investigator should inform the CRA if Plasma Transfer is required during the clinical trial.

If Plasma Transfer treatment is required, the following details need to be recorded in the subject medical records for each event:

Start and end date; Total number of sessions; Fresh Frozen Plasma volume used for each session (ml/kg/session); and Adverse reactions.

5.11.2 Dialysis / Haemofiltration

Subjects will not be generally permitted to receive new Dialysis unless there is compelling medical need, for example due to:

a) Hypervolaemia unresponsive to diuretics
b) Refractory electrolyte imbalance, or

c) New-onset uraemic encephalopathy, and after discussion with the Sponsor that details regarding the medication, therapy, or procedure are recorded in full in the patient's source/chart and CRF.
d) It is deemed necessary by the PI in the best interests of the subject

If dialysis treatment is administered, the following details need to be recorded in the subject medical records for each event: Start and end date; Serum creatinine value at the start and end of dialysis; Total number of sessions; Type of dialysis membrane used; Type of generator used; Type of dialysis; Adverse reactions

5.12 Quality of life questionnaires (EORTC QLQ C30 , EQ-5D-5L & FACIT-F)

The subject will complete the EORTC QLQ C30 (for some PNH patients only), EQ-5D-5L and FACIT-F (both PNH & aHUS) questionnaires and Sponsor non validated questionnaire at each clinic visit. The data will be transcribed to the eCRF and subsequently analysed.

EORTC is a questionnaire designed to assess (some of) the different aspects that define the QoL of (a specific group of) patients

FACIT-F (functional assessment of chronic illness therapy - fatigue) is a 13-item fatigue scale, which uses a symptom specific measure.

The EQ-5D questionnaire is made up of two components; health state description and evaluation. In the description section, health status is measured in terms of five dimensions (5D); mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Mobility dimension asks about the person's walking ability. Self-care dimension asks about the ability to wash or dress by oneself, and usual activities dimension measures performance in "work, study, housework, family or leisure activities". In pain/discomfort dimension, it asks how much pain or discomfort they have, and in anxiety/depression dimension, it asks how anxious or depressed they are. The respondents self-rate their level of severity for each dimension using a five-level (EQ-5D-5L) scale. In the evaluation part section, the respondents evaluate their overall health status using the visual analogue scale (EQ-VAS).

The Questionnaire on self-injection will be completed by the patient (this is a non-validated questionnaire).

6 Stopping Rules and Discontinuation Procedures

6.1 Termination or suspension of the study

The Sponsor may prematurely terminate or suspend the study at any time for the following reasons:

- Safety concerns e.g. occurrence of many serious ADRs
- Achieving the purpose of the study is considered impossible (e.g. inadequate recruitment of subjects)

If the study is prematurely terminated or suspended, the Sponsor should promptly inform the Investigators. The Investigator or designee should promptly inform the

participating subjects and change the study medication to other appropriate therapy(ies).

The Investigator may prematurely terminate or suspend the study at their medical institution with the agreement of the Sponsor. This may be done at any time during the study if they consider that ensuring patient safety during the study is difficult due to safety concerns (e.g., occurrence of many SAEs).

The Sponsor may prematurely terminate or suspend the study at a particular medical institution at any time during the course of the study, if major violations/deviations of the protocol or other procedures has not been improved or ICH GCP has not been followed.

If the study is prematurely terminated or suspended, the Sponsor should promptly inform the Investigators. The Investigator or designee, should promptly inform the, participating subjects and change the study medication to another appropriate therap(ies) and inform the corresponding Ethics Committees. All supplies should be returned.

Whichever party terminates the study will provide a written statement as to the reason for the termination.

The Sponsor (or CRO) will notify Regulatory Authorities as appropriate of premature terminations. The Investigator or their designee should promptly inform the corresponding Ethics Committee (EC).

6.2 Withdrawal criteria

In accordance with applicable regulations, a patient has the right to withdraw from the study at any time and for any reason, without prejudice to their future medical care by the physician or at the Institution. Should a patient withdraw from the study, then the patient will not undergo any further study-specific procedures or receive any treatment mandated by the protocol.

If a subject fails to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

In the event of the premature withdrawal of a patient from the trial, the end of trial visit should be carried out as completely as possible. Minimally, a safety assessment should be performed.

In the case of withdrawal due to the occurrence of unacceptable toxicity, the patient will be requested to remain under the supervision of the Investigator until the toxicity has resolved or is no longer considered to be clinically significant by the Investigator.

If an Adverse Event classified as severe results in patient withdrawal from the study, the subject will be followed until the AE (or SAE) resolves or stabilises, and any interventions required to resolve or stabilise the event will be recorded in the eCRF.

All withdrawals must be documented in the eCRF. A patient may be withdrawn in any of the following circumstances.

- Withdrawal of consent (mandatory withdrawal)
- Intake of non-permitted concomitant medication (may be discussed with the Sponsor and dependent on the nature of the medication)
- Patient is non-compliant with more than three consecutive missed doses and two missed clinic visits, in the opinion of the Investigator (discretionary withdrawal)
- If discontinuation is considered necessary by the Investigator and/or Sponsor (mandatory withdrawal)
- Request of Regulatory Agency (mandatory withdrawal)
- Patient develops an illness that would compromise his participation in the study (may be discussed with sponsor)
- Patient is not achieving complete inhibition at the maximum assigned dose (inadequate response to rVA576 (Coversin) treatment)
- Pregnancy, unless the patient wishes to consent to a termination.

6.3 Accountability procedures

In accordance with GCP, the clinical unit will account for all study medication. The clinical unit are responsible for study medication accountability, reconciliation, and record maintenance.

Drug accountability records will be maintained during the study as follows:

- Amount of study medication received from the Sponsor
- Amount distributed to each patient and returned by them
- Amount of unused drug returned to the Sponsor or destroyed at Sponsor's request.

In addition, in the event of necessary disposal of opened but wasted medication, the disposal should be documented appropriately (i.e. witnessed) in accordance with applicable local regulations, and GCP procedures.

Patients are required to return used and expired vials to the clinical unit and report to the site the number of unused vials remaining in their fridge. Storage bags will be provided to each patient. For all unused study medication, the patient should adhere to the storage instructions until the study medication is returned to the clinical unit.

If for any reason a site cannot dispose of used vials at site due to local policy, then they need to inform the Sponsor immediately.

6.4 Compliance

Reasonable levels of compliance are assumed as a condition of entry (prior enrolment in and completion of a rVA576 (Coversin) clinical trial). As a measure of compliance, all empty rVA576 (Coversin) vials will be returned to the clinical unit and diary cards

will be reviewed by research staff. At the end of the study, all unused vials will be returned to the Sponsor or representative or destroyed at site.

In addition to the above measures, clinic staff may call the patient's home or set up an automated text message reminder according to the subjects dosing schedule.

Example text as follows: "A gentle reminder - please administer your medicine this morning/evening and record the time, dose and location of injection in the Patient Dosing Diary.

6.5 Interruption of Treatment

If treatment is interrupted, either for reasons outside the patient's or the investigator's control or because it is considered to be in the patient's best interest it may be resumed at the discretion of the investigator and Sponsor. Any interruption of >24 hours will require an ablating regimen of 60mg followed by 30mg 12 hours later before resuming normal dosing, this should be discussed with the Sponsor. In the event of an interruption of treatment of >28 days, the investigator should discuss with the Sponsor the advisability of resuming treatment.

7 Safety Reporting

All AEs occurring from the signing of the voluntary Informed Consent Form (ICF) to the end of the trial visit will be recorded. All adverse events, whether or not considered to be related to the study drug, will be monitored and reported at all stages of the study. Adverse events occurring between clinic visits will be reported by the patient or recorded at the next clinic visit and entered on the adverse event form of the case report forms. All adverse events must be fully recorded in the patient notes throughout the entire study period and will be transcribed into the subject's eCRF.

7.1 Safety Definitions

7.1.1 Adverse Event

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.
An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

7.1.2 Adverse Drug Reaction

All untoward and unintended responses to an investigational medicinal product (IMP) related to any dose administered.

All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse drug reactions.

7.1.3 Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

7.1.4 Serious Adverse Event (SAE) or Serious Adverse Reaction

Any untoward medical occurrence or effect that at any dose results in:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization, (Note: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE. [NB *This means that admission (i.e. inpatient, out patient, <24 hours, > 24hour) for blood transfusion does not constitute an SAE as it is for treatment of a pre-existing condition*].
- Results in persistent or significant disability/incapacity, (Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, or accidental trauma (e.g. sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption).
- Is a congenital anomaly/birth defect.

NOTE: *Other events that may not result in death, are not life threatening, or do not require hospitalization, may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include, but are not limited to, severe early onset reaction such as anaphylaxis, vasovagal episodes, episodes of hypotonia, hyperreactivity or hyperventilation, convulsions, etc.*

All SAEs will be reported to the Sponsor (or designee) within 24 hours of occurrence. The Sponsor (or their designee) will be responsible for reporting the AE to the appropriate regulatory authorities and the ECs within the legally specified period. It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. An AE of severe intensity need not necessarily be considered serious. For example, a migraine headache that incapacitates a patient for many hours may be considered a severe AE, whereas a stroke that results in a limited degree of disability may be considered mild, but should be reported as an SAE.

7.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or Summary of Product Characteristics for an approved product).

7.2 Procedures for Recording of Adverse Events

7.2.1 General

All adverse events occurring during the Study (from the timepoint of signing of the Informed Consent Form (ICF) until completion of patient`s study participation or premature withdrawal) observed by the Investigator or reported by the patient, whether or not attributed to the IMP, shall be recorded in patient`s medical records and on the eCRF.

The following information shall be recorded:

- description,
- date of onset and end date,
- severity,
- assessment of relatedness to the IMP,
- seriousness,
- measures taken for management of the AE,
- outcome of the event.

Follow-up information should be provided as necessary.

AEs considered as being related to the IMP as judged by a medically qualified Investigator, or the Sponsor, must be followed until their resolution or when patient`s status is considered as stable. All related AEs that result in a patient's withdrawal from the Study or are present at the end of the Study, should be re-evaluated and if needed followed until a satisfactory resolution occurs.

It will be left to the Investigator's clinical judgment whether or not an AE is of sufficient severity to require termination of IMP administration. A patient may also voluntarily withdraw from IMP administration due to AEs perceived as intolerable. If either of these occurs, the patient will be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The severity of reported events shall be assessed on the following scale:

- 1 = mild
- 2 = moderate
- 3 = severe
- 4 = life threatening
- 5 = death

The causal relationship of AEs to the IMP must be assessed by the Investigator, or by a medically qualified designee, in accordance with the following criteria:

Term	Definition
Unrelated	Clinical event with an incompatible time relationship to administration of the investigational medicinal product (IMP), and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the IMP
Possibly related	Clinical event with a reasonable time relationship to IMP administration, and that is unlikely to be attributed to concurrent disease or other drugs or chemicals
Related	Clinical event with plausible time relationship to IMP administration and that cannot be explained by concurrent disease or other drugs or chemicals

At the last scheduled visit, the Investigator shall instruct each patient to report any subsequent event(s) that the patient, or her personal physician, believes might reasonably be related to participation in this Study. The Investigator should notify the Sponsor (or designee) of any death or SAE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this Study.

7.2.2 Pre-existing Conditions

For purposes of this Study a pre-existing condition means a diagnosis, clinically significant finding, symptom, or laboratory abnormality present at baseline (Visit 1). Subsequently, during the course of the Study it shall be recorded as an AE/SAE if the frequency, intensity, or the character of the condition worsens during the study period.

7.2.3 Overdose

All overdoses with or without associated symptoms, should be reported as AEs on the appropriate eCRF page. An overdose is defined as a dose of 90mg or above in a 24 hour period. If sequelae meeting the criteria for a SAE have occurred in association with the overdose, the case must be reported immediately, within 24 hours. Action to be taken, if any, in event of an overdose should be discussed with the Sponsor's medical representative at the earliest opportunity. However, in animal toxicology, no adverse events have been observed following single intravenous doses of approximately 50 times the human therapeutic dose, so no specific toxicity is anticipated. There are no known antidotes to rVA576 (Coversin) and observation and supportive treatment are the only recommended measures. An assessment of whether the overdose was accidental or intentional should be recorded. If the overdose was a suicide attempt, this fact should be clearly stated. The AEs and SAEs that occur as a result of an overdose should be recorded on the eCRF.

7.2.4 Pregnancy

Coversin (rVA576) is contraindicated during pregnancy. If pregnancy is suspected, a blood sample for serum HCG examination must be sent to the sub-contracted laboratory within 48 hours. As during the first pregnancy weeks the test may be negative it may be confirmed by an ultrasound examination. If at least one of the above-mentioned examinations is positive, administration of the IMP should be stopped and the patient must be immediately withdrawn from the study **unless** the patient consents to a termination in which case treatment would continue. All pregnancies (even if only suspected) must be reported on the appropriate eCRF page (and Pregnancy form to the Pharmacovigilance provider (PVP) of the Sponsor) within 24 hours from the moment when the investigator became aware of the pregnancy (or suspected pregnancy). In any case each pregnancy must be followed till its termination (either by birth of a child or abortion) and the eCRF page (and Pregnancy form) has to be updated. In the event of live birth, the child will be followed for 6 months.

Reporting to PVP of Sponsor shall be done on the corresponding Pregnancy form provided to each centre during the initiation visit, and sent by fax or e-mail to:

[redacted]

[redacted]

[redacted] [redacted]*dverse Events*

Any signs or symptoms at an injection site following subcutaneous administration of the IMP are considered an Injection Site Reaction (ISR). An ISR is an AE and described in detail like an AE (e.g. onset date, relationship etc). The subcutaneous injection with the IMP is expected to produce localised events (e.g. mild pain/ mild erythema/ mild induration) over/around the injection site. These expected ISRs are listed in **Table 10**. The severity of an expected ISR is graded according to **Table 10**. The patient collects all ISRs in the diary card and only expected ISRs of grade 2 or higher are to be reported in the CRF by the investigator. Any other ISR (not listed in **Table 10**, i.e. blister/ulcer) of any grade will be reported in the CRF by the investigator.

Table 10: ISRs grading guidance

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with daily activity	Repeated use of non-narcotic pain reliever or interferes with daily activity	Any use of narcotic pain reliever or prevents daily activity	Accident & Emergency (A&E) visit or hospitalization
Tenderness	Mild discomfort to touch or does not interfere with daily activity	Discomfort with movement or limiting daily activity	Significant discomfort at rest or prevents daily activity	A&E visit or hospitalization
Itching	Does not interfere with activity	Limiting activities	Prevents daily activity	
Erythema/ Redness *	Erythema or redness ≤5 cm at the longest diameter	Erythema or redness: >5cm but ≤10cm at the longest diameter	Erythema or redness > 10cm at the longest diameter	A&E visit or hospitalization

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Induration/ Swelling	Soft swelling Induration ≤5 cm at the longest diameter	Soft swelling Induration: >5cm but ≤10 cm at the longest diameter	Soft swelling Or induration: > 10 cm at the longest diameter	Necrosis
Bruise/ hyperpigmentation	Bruise /hyperpigmentation ≤5 cm at the longest diameter	Bruise /hyperpigmentation: >5cm but ≤10cm at the longest diameter	Bruise /hyperpigmentation >10 cm at the longest diameter	Necrosis

AEs which appear to affect more than one patient, will be assessed for their severity, threat to the patient's health and drug relationship. Investigators may decide to withdraw their patients if continued study participation is not in the patient's best medical interest.

Only injection site reactions which are grade 2 or above will be reported.

All other adverse events, regardless of grade, will be reported.

7.3 Reporting Procedures for Serious Adverse Events

Any SAE occurring during the Study has to be managed by established Standards of Care to protect life and health of participating patients. If such treatment represents a significant deviation from the protocol, the Investigator shall immediately notify the study monitor and/or the Sponsor to determine whether the patient should be dropped out from the Study, or not.

All Serious Adverse Events, irrespective of their causality, must be notified to the Pharmacovigilance provider (PVP) of the Sponsor, **within 24 hours** of the Investigator becoming aware of the event. Reporting shall be done on the corresponding SAE form provided to each centre during the initiation visit, and sent by fax or e-mail to:

[redacted]

[redacted]

The information provided shall contain as much detail regarding the event as is actually available. Investigators should not wait to receive additional information to fully document the event, before notifying the SAE to Akari Therapeutics Plc. The SAE reporting form should detail all relevant aspects of the AEs listed in Section 7.2.1. Where applicable, information from relevant hospital records or autopsy reports should be obtained and provided to Akari Therapeutics Plc.

7.4 Expedited Safety Reporting

Any Serious Adverse Event, which is unexpected and at least possibly related to the IMP, requiring expedited reporting to the respective regulatory authority, EudraVigilance and ECs/ Institutional Review Boards (IRB) of the sites participating in this Study is subject to following timelines:

- 7 calendar days for SUSARs involving death and life-threatening events

- 15 calendar days for SUSARs involving hospitalization or prolongation of hospitalization or persistent or significant disability/incapacity or congenital anomaly/birth defect or any other significant clinical/laboratory event of major concern in the opinion of the Investigator.

Day zero (clock start) for expedited reporting purposes is the date of initial information or of the relevant follow-up information received in any form (in writing or verbally) by any personnel of the Sponsor or contracted parties including the CRO and the PVP.

All SUSARs will be reported to the respective competent authorities, ECs (IRBs) and Investigators within specified timelines in accordance with corresponding national legislation.

7.5 Development Safety Update Reports

Development Safety Update Reports will be prepared by Akari Therapeutics Plc (or designee), on an annual basis and distributed to all competent authorities and to relevant ECs in accordance with the corresponding national regulations.

8 Data Handling and Source Documents

Patient data will be collected on eCRFs and will be substantiated by source documents at the clinical site. The eCRFs will be completed according to guidelines provided by the CRO and their SOPs. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of all study procedures, AEs and patient status.

The Investigator must maintain source documents, such as laboratory reports, complete medical history, ECG read outs and physical examination reports. All source documents should be accessible for verification by the site monitor, auditor, the EC, or for inspections by the regulatory authorities. In addition, the site will allow the Sponsor and assigned CRO direct access to all source documents and will permit trial-related auditing of clinical, pharmacy and laboratory facilities.

Direct access to these documents must be guaranteed by the Investigator or their designee, or the study coordinator, who must provide support at all times for these activities.

The nature and location of all sources of original data required to complete the eCRF will be identified by the CRO and the site staff.

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.

The Study Monitor will perform 100% source data verification to ensure adequate quality control and assurance of patient data. An explanation of missing data must be given.

All data entered into the eCRF will be saved directly into the study database. This data will be validated both manually and programmatically. Clarification of data will be requested from the study site as requested. The database will be quality assured and will be available for statistical analysis according to the SAP.

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.

9 Statistics

9.1 Statistical methods

A Statistical Analysis Plan (SAP) is in place. There will be no formal statistical inferences. All the study data will be analysed descriptively. Standard summary statistics will be produced for observed values, and changes from entry (where applicable) at the relevant post-entry timepoint.

For continuous variables, these statistics will include the number of patients with available data, mean, standard deviation, median, minimum, maximum. For categorical variables, these statistics will consist of patient counts and associated percentages. Unless otherwise specified, missing data will not be included in the denominator for percentage calculation. Time to event data will be summarised using graphs and summary statistics from the Kaplan-Meier method.

Listings will also be used to display data at the individual patient's level.

Data will be reported at each 3-month time point since the start of the study (where applicable) and over the entire period of the study (where applicable).

Results will be reported for all patients and then separately for PNH and aHUS patients.

- The incidence of AEs, and serious adverse events (SAEs) will be summarised over time for all patients.

- Vital signs, results of standard laboratory tests (clinical chemistry, haematology and urinalysis), and results of limb lead or 12 lead electrocardiograms (ECGs) will be summarised over time for all patients.

- The proportion of subjects with no adverse change in overall scores of Quality of Life using the EORTC QLQ-C30 (some PNH patients only), the EQ-5D-5L and FACIT-F instruments will be summarised over-time.

For PNH patients, additional summaries will include :

- The proportion of subjects with thrombotic and haemolytic event-free status

- The time to thrombotic or haemolytic event since entry.

- The time to first transfusion since entry.

- The 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).

- The 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).

- The proportion of subjects who require PRBC transfusion.

- The proportion of transfusion independent subjects, with haemoglobin (g/L) above the baseline haemoglobin value they had at the start of the parent trial.

- The 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 parent trial.

- The incidence, number and time to first Major Adverse Vascular Event (MAVE) for each PNH subject will be summarised.

Results may also be reported separately for i) subjects who were transfusion-dependent when they started receiving rVA576 (Coversin), and ii) subjects who were transfusion-independent when they started receiving rVA576 (Coversin), 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) and where applicable i) transfusion-independent prior to receiving rVA576 (Coversin) and remain transfusion-independent and ii) transfusion-dependent prior to receiving rVA576.

For aHUS patients, additional summaries will include:

- The proportion of subjects with Normal Platelet count [defined as Platelet count ≥ 150 x1 09/L]

- The proportion of subjects entering the study with complete TMA response who continue to exhibit complete TMA response with preserved renal function, defined as haematologic normalization (platelet count ≥150 X 109/L and LDH ≤ ULN) and preservation of kidney function (<25% increase in SCr from baseline of the parent trial).

- The proportion of subjects with complete TMA response with improved renal function defined as normalization of haematological parameters (normalisation of platelet count and LDH≤ULN) and ≥ 25% decrease in SCr from baseline of the parent trial.

- The proportion of subjects who exhibit haematological normalisation (platelet count ≥150 X 10^9/L and LDH ≤ ULN).

The proportion of subjects with improvement in renal function defined as a decrease in SCr over three consecutive measurements from baseline of the parent trial without the need for dialysis even if not within the normal range.

- The proportion of subjects who are TMA event-free.

- Platelet mean count change over-time.

Other endpoints will be described as indicated above depending on whether its outcome measure is a continuous or categorical variable.

9.2 Number of patients

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

9.3 Interim analyses

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.

9.4 Assessment of pharmacokinetics and complement activity

Blood (5mL) samples for CH50 assays and rVA576 (Coversin) levels will be collected according to the schedule presented in **Table *8*** & **Table *9***. Serum samples will be taken to measure complement activity, rVA576 (Coversin) levels and anti-drug antibodies. Blood-EDTA and blood-citrate will be used for other measures. Safety blood samples will take precedence over all other procedures.

PK parameters will be described over-time using summary statistics and lines and mean plots as appropriate.

PD parameters will be described over-time using summary statistics and graphical displays such as waterfall plots and lines plots as appropriate.

9.5 Significance level

All analyses will be descriptive.

9.6 Missing, unused or spurious data

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).

9.7 Deviation from the statistical analysis plan

It is not envisaged that there should be any deviations from the SAP. Any unexpected deviations will be included in any interim reports and the Final Study Report.

9.8 Patients to be included in the statistical analysis

The primary analysis will be intention to treat (ITT) and all patients entered and who sign informed consent will be included.

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.

'End of study' will be defined as the point at which the last patient has exited the study and has been seen at the 3 month end of study follow-up visit.

The final analysis will be performed using data collected up to the end of the study. This data will be presented in a Final Study Report.

The Database will be locked when the last patient last follow-up visit occurs.

10 Quality Control and Assurance

The hospitals / departments taking part in the trial are responsible for maintaining their own SOPs and QA / QC procedures. The Sponsor or their delegate will also implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the study is conducted and data are generated, documented and reported in compliance with the Protocol, ICH GCP and all applicable regulatory requirements. The Sponsor or delegate will be responsible for monitoring the trial and carrying out 100% source data verification. The Sponsor will be responsible for overseeing clinical trial activities.

The study will be in accordance with the provisions of the Declaration of Helsinki and all revisions thereof, in accordance with ICH GCP and as required by applicable regulatory requirements.

Any necessary training for the study will be provided to Investigators and study personnel by the Sponsor or their designee prior to study initiation.

11 Ethical Conduct of the Study

11.1 Ethical considerations and EC approval

The study will be conducted in accordance with all appropriate regulatory requirements and under an approved protocol. The study will be conducted in accordance with current ICH GCP, all applicable patient privacy requirements and the ethical principles outlined in the Declaration of Helsinki.

12 Financing, Indemnity and Insurance

The Sponsor will have a commercial contract in place with the CRO and the hospitals/universities will be responsible for any payments to patients for payment of travel and other expenses reimbursable by the Sponsor on delivery of receipts.

The Sponsor has a clinical trials insurance policy in place. A copy of the policy/certificate of insurance will be supplied separately. Provision is made for (1) The indemnity or compensation in the event of injury or death attributable to the clinical trial and (2) Insurance or indemnity to cover the liability of the Investigator or Sponsor.

Akari Therapeutics Plc will indemnify the Investigators from all or any claims arising out of this study except for their negligence or malpractice and providing that the study is conducted according to the standards established by the protocol.

In the event that it can be demonstrated that a patient suffers any significant deterioration in health or well-being or any harmful susceptibility or toxicity, as a direct result of their participation in this study, then Akari Therapeutics Plc will agree to abide by the current Association of the British Pharmaceutical Industry (ABPI) Guidelines with regard to compensation payable to the patient residing in the UK. The amount of compensation will be calculated by reference to the level of damages commonly awarded according to local law for similar injuries occurring in patients residing outside the UK.

13 Publication Policy

The key design elements of this protocol will be posted in a publicly accessible database.

The CRO has no independent publication rights.

Akari Therapeutics Plc actively encourages publication of clinical trial data in reputable peer reviewed journals. Authorship will be discussed and agreed in advance. If the Investigator drafts a publication, he/she agrees to send it to Akari Therapeutics for review and comment before its submission to the journal. In cases where Akari Therapeutics Plc considers that the proposed publication contains information which should be protected as valuable confidential information or is out of compliance with applicable laws and regulations, Akari Therapeutics Plc reserves the right to delay submission to the journal, until the required deletion or amendment of the confidential information from the proposed publication has been performed.

14 Study Record Retention

The Investigators shall ensure that the documents contained in the Investigator Site File are retained for 15 years after the conclusion of the trial. The Sponsor shall ensure that the documents contained in the Trial Master File are retained for 25 years after the conclusion of the trial. The Sponsor and Investigators will ensure that during this period the files are complete, legible and readily available to the licensing authority on request.

All data derived from the study will remain the property of Akari Therapeutics Plc.

All correspondence (e.g. with the Sponsor, or designee, Ethics Committee) relating to this study should be kept in the appropriate files. Records of patient's source documents, eCRF's, IMP inventory pertaining to the study must be kept on file.

If the Investigator moves, withdraws from the study or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

14.1 Clinical study report (CSR)

The results of this clinical study must be summarised by the Sponsor (or designee) and a final audited report must be retained on file. This report will include discussions on the study objectives, methodology, findings and conclusions. The Principal Investigator(s) will be asked to review and comment on the draft report and the Chief Investigator will be required to sign the final version. All Investigators will be provided with a final copy of the Clinical study report. The report must be archived with all other study documents. An interim CSR may also be required to support authorisation applications.

14.2 Handling and retention of blood and pathological samples

Samples should be handled according to the instructions provided in the Laboratory Manual. The duration of retention of blood and pathological samples will be in accordance with details provided in the patient information leaflet and agreed to by signing the ICF.

15 References

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16 Appendices

Appendix 1:

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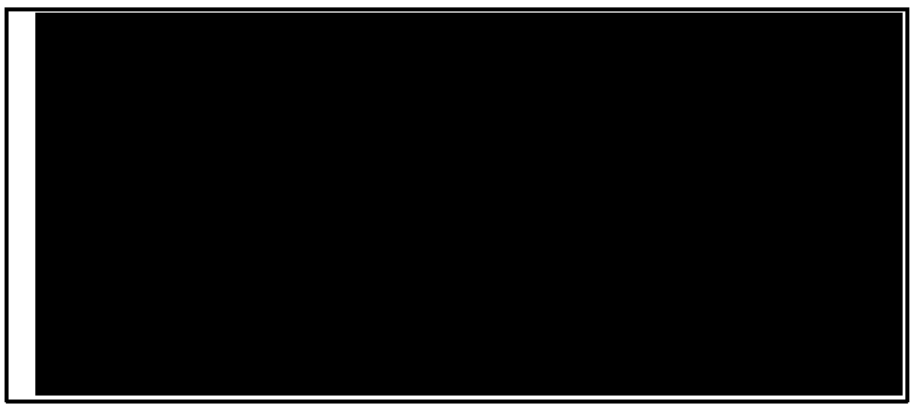

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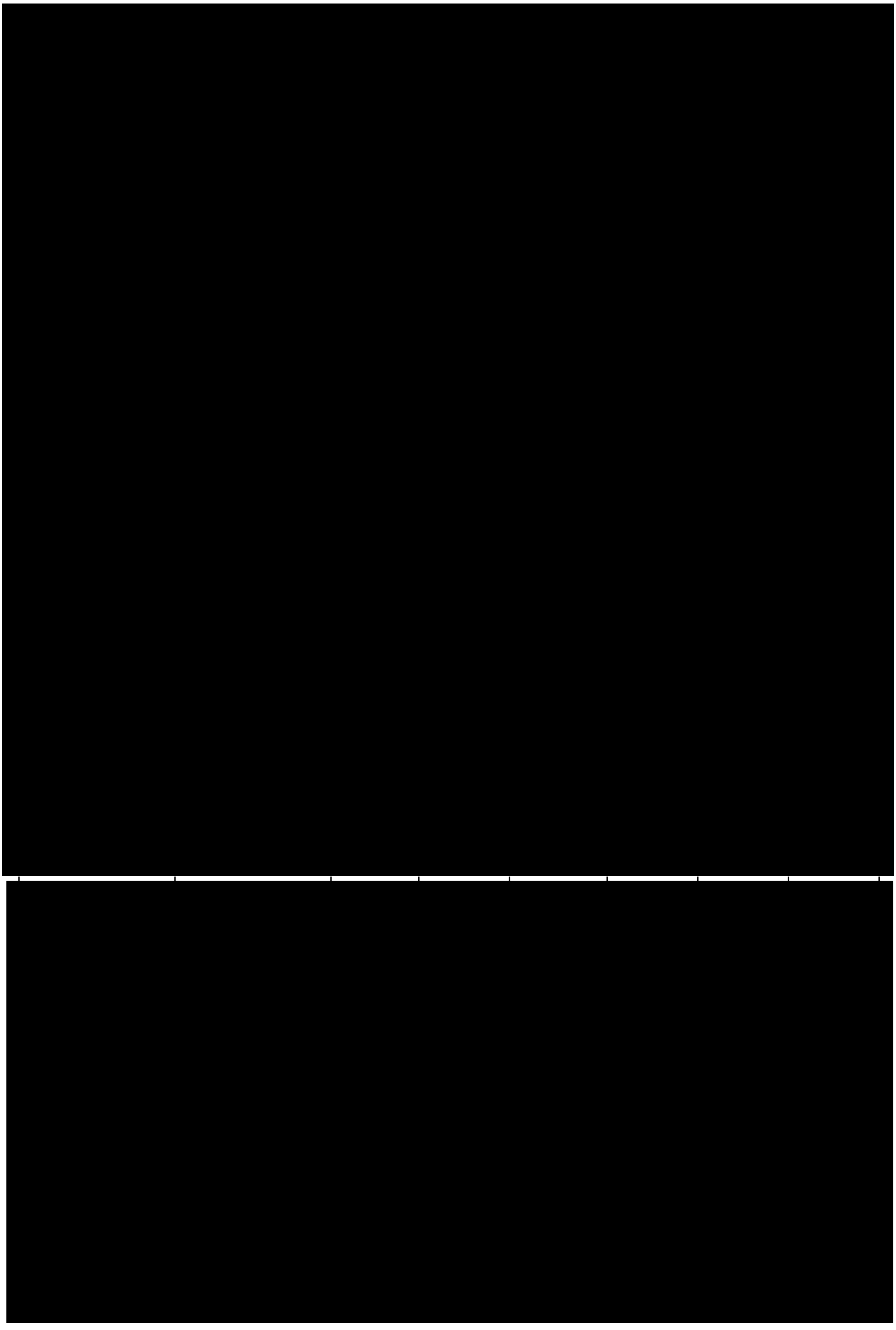

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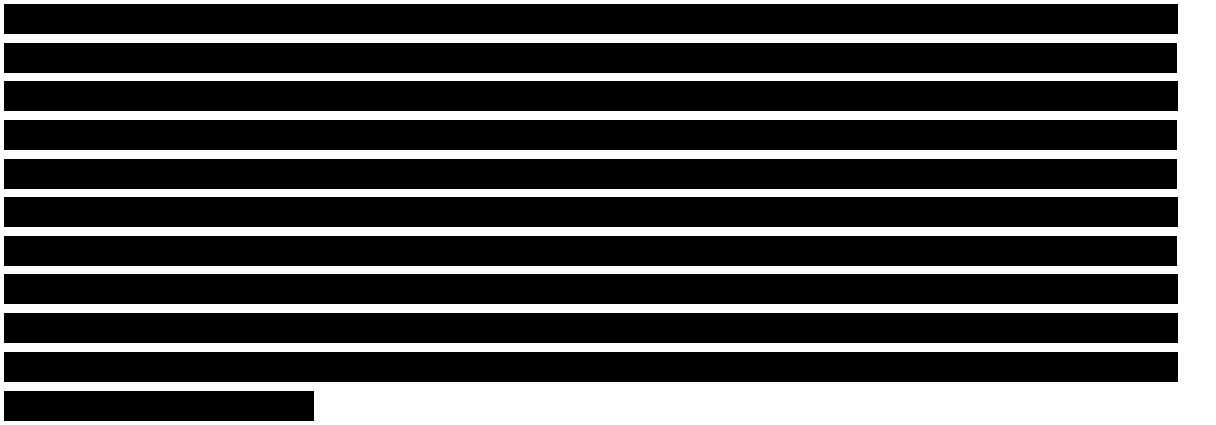

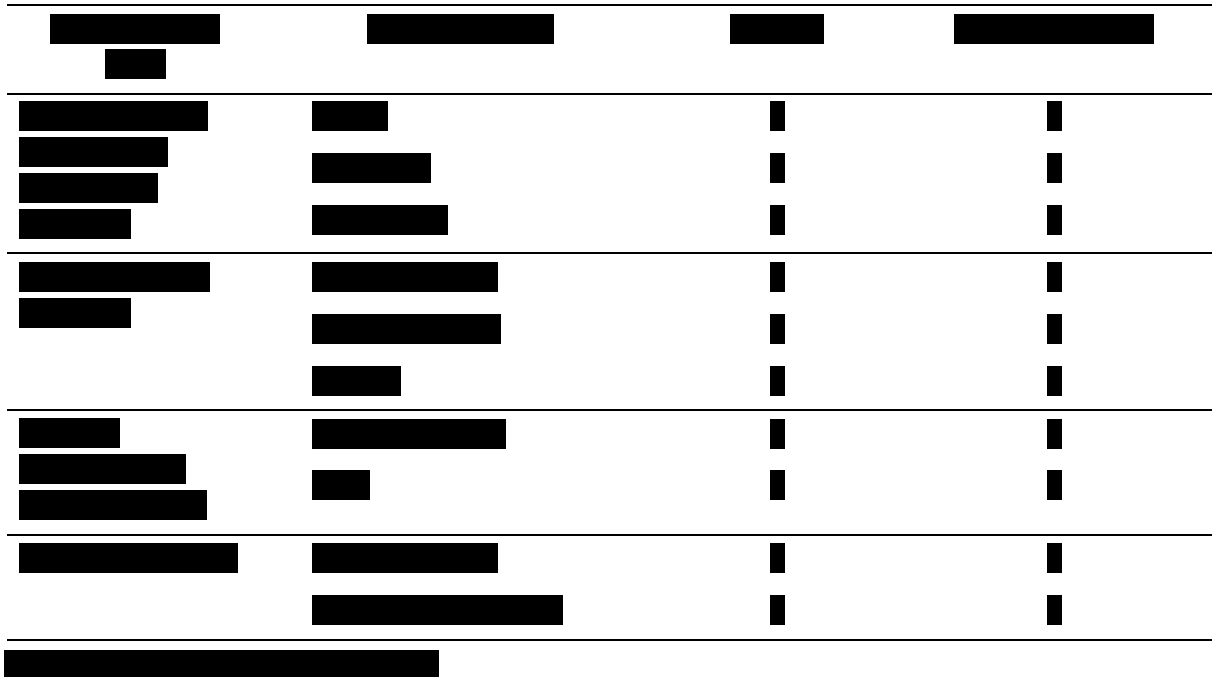

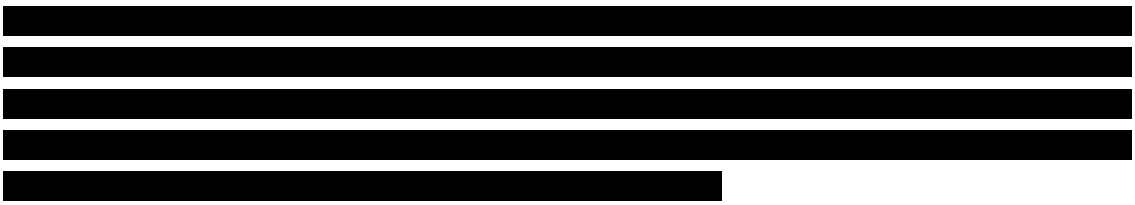

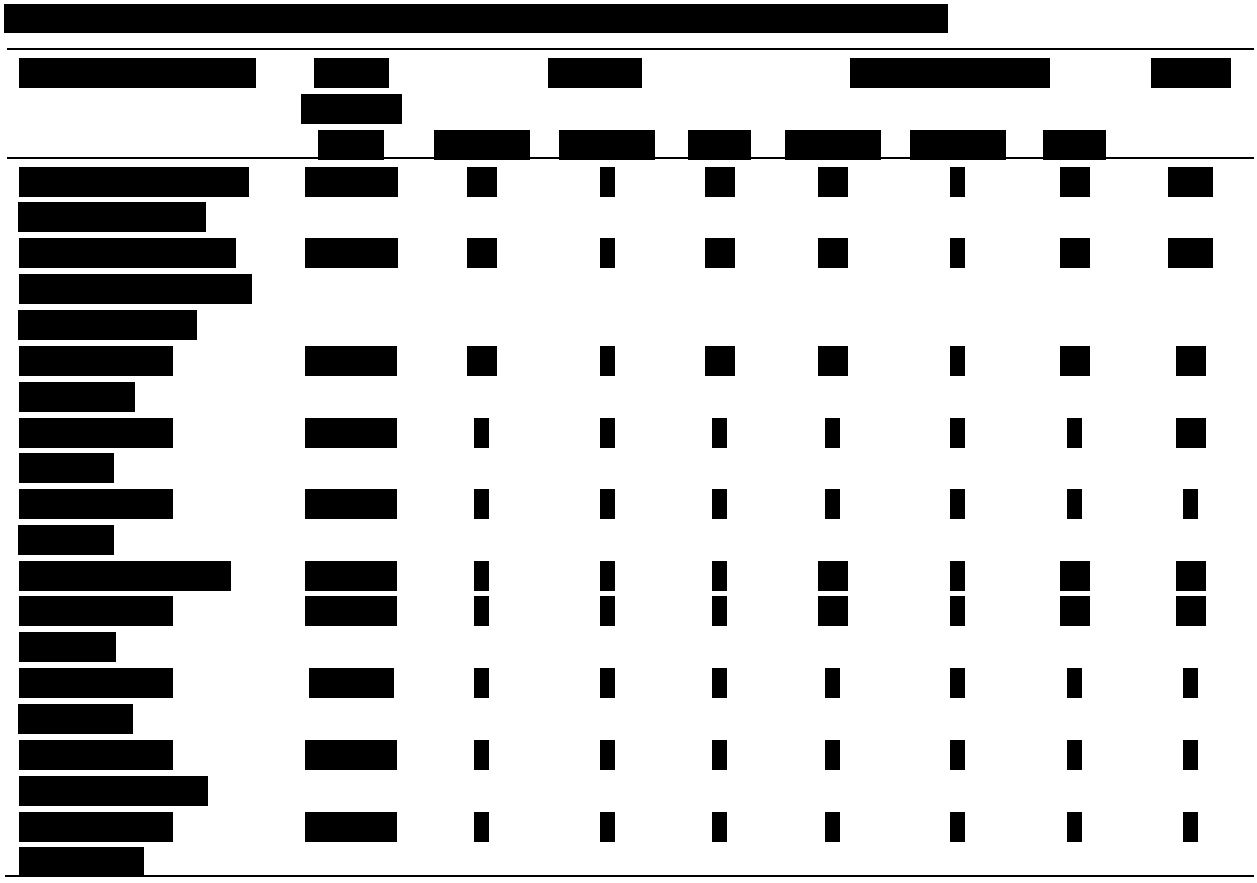

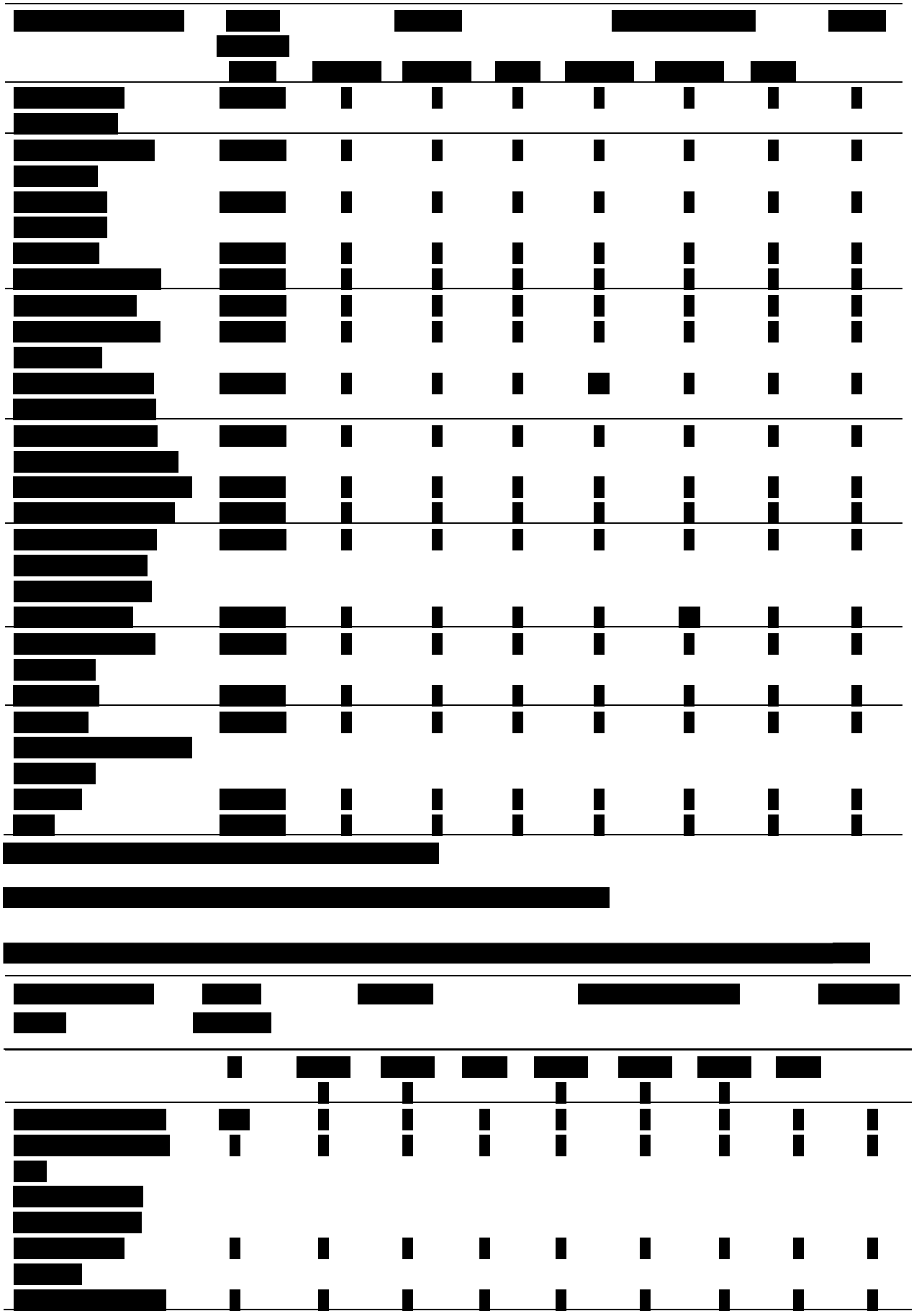

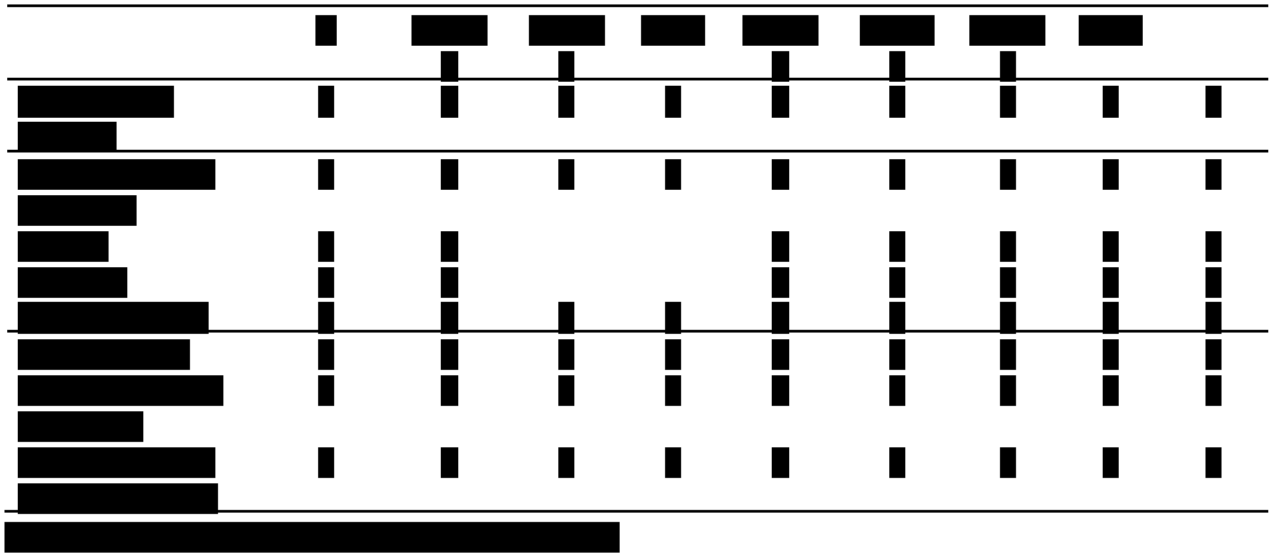

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