CONSENT II: Coversin in Paroxysmal Nocturnal Hemoglobinuria (PNH) in patients with resistance to Eculizumab due to complement C5 Polymorphisms

US IND 131257

PROTOCOL NUMBER:	**AK585**
DATE:	**12 February 2018**
VERSION NUMBER:	**2.1**
SPONSOR:	**Akari Therapeutics Plc**

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SPONSOR SIGNATURE PAGE

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Protocol Number:	AK585
Version:	2.1

Authorized Sponsor Representative Signature:

Name: Date:

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Medical Director, Medical Monitor

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INVESTIGATOR'S AGREEMENT

Protocol Title:	CONSENT II: Coversin in Paroxysmal Nocturnal Hemoglobinuria (PNH) in patients with resistance to Eculizumab due to complement C5 Polymorphisms
Protocol Number:	AK585
Version:	2.1

I have received and read the Investigator's Brochure for Coversin. I have read the AK585 study Protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed relating to this Protocol. I agree to conduct the trial in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference of Harmonization (ICH) / Good Clinical Practice (GCP) and applicable regulatory requirements.

_____

Printed Name of Investigator:

_____

Signature of Investigator:

_____

Date:

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LIST OF ABBREVIATIONS

The following abbreviation and specialist terms are used in this trial Protocol.

Abbreviation	Definition / Term
AD	Ablating Dose
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
eCRF	Electronic Case Report Form
CH50 U Eq/mL	Classical hemolytic 50% lysis Units Equivalent/mL
CK	Creatinine Kinase
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECG	Electrocardiogram
ELISA	Enzyme-Linked Immunosorbent Assay
EQ-5D-5L	Euroqol's 5 dimensional 5 level
FACIT	Functional Assessment of Chronic Illness Therapy
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
Hb	Hemoglobin
HED	Human Equivalent Dose
Hrs	Hours
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
IMP	Investigational Medical Product
IRB	Institutional Review Board
ITT	Intention to Treat
i.v.	Intravenous
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Qualification
LTB4	Leukotriene B4
MAC	Membrane Attack Complex
$MgCl_2$	Magnesium chloride
MW	Molecular Weight
NHP	Non-Human Primate
NOAEL	No Observable Adverse Event Level
PBS	Phosphate Buffered Saline
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic(s)
PNH	Paroxysmal Nocturnal Hemoglobinuria
PP	Per Protocol

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Abbreviation	Definition / Term
PVP	Pharmacovigilance Provider
Q	Quaque (every)
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
RBC	Red Blood Cell
SAE	Serious Adverse Event
s.c.	Subcutaneous
SAD	Single Ascending Dose
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCC	Terminal Complement Complex
TMA	Thrombotic Microangiopathy
ULN	Upper Limit of Normal
WFI	Water for Injection

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SUBSTANTIAL AMENDMENT 2

2.5: Summary of Known and Potential Risks and Benefits to Human Subjects

Inclusion of definitions for Grading of injection site reactions.

5.2 Trial Procedure

The dosing times (0700 to 1100 and 1900 to 2300) in this section have been changed to 7am to 11am and 7pm to 11pm, to ensure they are consistent with the rest of the protocol.

The abbreviation for "Hours" has been changed to "Hrs" throughout the text to ensure it is consistent with the rest of the protocol.

Section 6.1 Definition of Inadequate Response

The following wording "An inadequate response to Coversin treatment is defined as **any** of the following events occurring during Part 2" has been updated to remove "occurring during Part 2". This was an administrative error which should not have been included in the previous amendment.

Table 11: Schedule of Events

The superscript lettering and numbering (pertaining to the table footnotes) have been changed for formatting purposes to ensure the superscripts within the table body are numbers and the superscripts within the table headers are letters.

"Including LDH" has been added to the "Chemistry" procedure row to ensure it is consistent with the rest of the table.

The dose volume has been added to each of the study day headers to provide clarification as to when each procedure and evaluation should be performed.

CH50 analyses have been added on Days 29, 36, 43, 60, 90, 120, 150, 180 and 120, as these were inadvertently not included in the previous amendment.

Hematology analyses have been added on Days 29, 36, 43, 60, 90, 120, 150 and 180, as these were inadvertently not included in the previous amendment.

Coversin level (PK), Total C5, ADA, LTB4, chemistry, hematology and a urine pregnancy test have been added to Day 210, to ensure the full safety profile of the patients can be obtained during this safety follow up visit.

The 'Patient Self-Administration Questionnaire' has been removed from Day 1 (baseline), Day 7 and Day 14 (pre-dose 22.5mg dose), to ensure it is consistent with the body of the protocol.

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'Initiation Phase' and 'Maintenance Phase' have been added to the headers of the Schedule of Events tables, to ensure that they reflect what is written within the Protocol body and aims to assist the Investigators in determining which phase the patients are in.

The abbreviation for "Hours" has been changed to "Hrs" throughout the table to ensure it is consistent with the rest of the protocol.

Appendix 1: Laboratory Assessments

"Local Laboratory Testing" has been added to the sub-headers in this section to clarify that the pertaining laboratory analyses should be performed at the local laboratory.

"LDH Isoenzymes" has been moved to the 'Central Laboratory' section, as this test will be performed at the central laboratory and not the local laboratory.

The days on which the patient's height and weight will be measured has been changed from "each clinic visit" to "Screening, baseline, Day 29 and Day 180" to reflect the Schedule of Events.

"Day 120 and 150" has been removed from the 'Clinical Efficacy Assessments' section to reflect the secondary endpoint information in the body of the protocol.

The days on which LDH measurements will be taken have been added, as these were inadvertently not included in the previous amendment.

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SUBSTANTIAL AMENDMENT 1

Amendment rationale:

The spelling throughout the protocol has been amended from English (United Kingdom) to English (United States).

The heading sections have been renumbered to include the protocol synopsis in the heading system.

Section 1: Protocol Synopsis Treatment Regimen and Section 5.1 Trial Design

The suggested times of the dosing for morning and evening doses have been amended from 8am to 10am and 8pm to 10pm to 7am to 11am and 7pm to 11pm but patients are still required to choose a set time for dosing in the morning and a set time for dosing in the evening (12 hours after the morning dose) administer the dose within 1 hour each side of the set time(s). The Sponsor believes that this gives the patients greater flexibility to select a dosing time that fits their lifestyle and potentially encourage patient compliance.

Section 1: Protocol Synopsis Efficacy Endpoints and Section 3.2 Endpoints

The primary endpoint has been updated to include Days 120 and 150 into the calculation for the mean so this endpoint now reads:

"Reduction in serum LDH from baseline to mean of Day 43, 60, 90, 120, 150 and 180".

The Sponsor believes that this is a more robust endpoint and will provide a more meaningful measure of the LDH level throughout the trial.

The secondary endpoint of "Change in proportion of Type III RBC clone from baseline to Day 180" has been deleted. Not all sites may be able to conduct flow-cytometry so the endpoint has been removed. The Sponsor does not believe that the removal of this endpoint will affect the scientific value of this trial.

Section 2.2 Summary of Non-Clinical and Clinical Studies Relevant to the Clinical Trial

This section has been updated to include the results of the recently completed Phase 1b study and include the terminal complement activity (measured by CH50 assay) time plot. The Sponsor believes that this information is important to provide the Investigators with the latest data available and understand the product.

Section 2.4 Previous Experience in Patients

Figure 6 in this section has been updated to reflect the latest LDH data on the eculizumab resistant patient currently being treated under study AK578. The Sponsor believes that this information will provide Investigators with further information to understand the latest data from the currently treated eculizumab resistant patient who will be similar to the proposed patient population treated in this study.

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Section 2.5 Summary of Known and Potential Risks and Benefits to Human Subjects

This section has been updated to include the current number of patients treated as of the 12 December which current stands at 42 (10 patients and 32 Healthy Volunteers) and also to include the latest safety information on the on-going studies AK578, AK579 and AK581. The Sponsor believes that since only ten patients have been treated and until now the safety data had been rather sparse this new information will help provide Investigators with the assurance that as a development compound Coversin is suitable for treatment of their patients.

Section 2.6 Description of/and Justification for Route of Administration, Dosage Regime and Treatment Period

No formal toxicokinetic studies have been conducted as part of the long-term toxicity studies but samples were obtained from the 1-month cynomolgus monkey study and have recently been analysed and included in a modelling simulation to calculate PK parameters. This data has now been included and exposure with respect to the safety factor calculations made in relation to the modelled PK data from the first 5 patients recruited to AK579. Together this data provides a justification for the dosing proposed to be used in this study and all the Sponsor's studies in PNH going forward.

Section 4.3 Meningitis Prophylaxis

The wording in this section has been amended to clarify for the Investigators when they might want to administer the Bexsero vaccine in relation to Coversin dosing. The Sponsor believes that this wording provides clearer guidance.

Section 4.5 Contraception

The wording in this section has been updated to reflect the data that has recently been obtained from the completed Segment 1 reproductive toxicity study. In addition, it provides clarification of the expectations of the Sponsor for participants of the trial in relation to the requirements for contraception. The sponsor believes that this information is important for the Investigator to be able to inform the patient appropriately and be able to make informed decisions.

Section 4.5.1 Exposure to Partners During the Study

The wording in this section has been updated to include the fact that barrier contraception should be used throughout the study and for 90 days after the last dose of Coversin. This section has been updated to make sure all the protocols are consistent with respect to 90 days of contraception after the last dose. As this was requested to be added during review of one of the Sponsor's protocols by the Polish Authority.

Section 5.2 Trial Procedure

The wording in this section has been updated to clarify the dosing times and when the patient should consider beginning self-injection. The Sponsor believes this information clarifies how and when the dose should be given to improve patient compliance and also provide better guidance on when the patient should try and self-inject from.

Section 5.3 Procedure for Increase in Frequency of Doses and Section 6.2 Events Triggering Consideration of Alteration of the Dose or Dose Interval

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This section has been updated to reflect the change in the lower limit of quantification from 8 to 10 U Eq/mL due to a change in the Central Laboratory conducting the assessment of samples and requalification of the assay by the new Central Laboratory.

Section 5.4 Missed Doses

The wording in this section has been updated to reflect the recommendations with respect to missed doses now that the dosing has been standardised for the PNH studies. The Sponsor believes this wording provides the Investigators with clarity and help them understand the process to follow when a patient misses a dose. It also confirms to the Investigator that patients should not inject more than 90 mg in a 24-hour period. This limit has been set to ensure exposure in humans is supported by data from long term toxicology studies.

Section 6.1 Definition of Inadequate Response

The wording in this section makes clearer what the Sponsor believes qualifies as an inadequate response and what steps the Investigator should follow in the event of an inadequate response. The Sponsor believes that the updated wording provides better guidance to the Investigator.

Section 6.3 Withdrawal Criteria

“Planned or actual pregnancy or breast-feeding (females) has been added to the withdrawal criteria which matches with the information included in Section 5.5 Contraception.

Section 11.2.1 General

The casual relationship definitions have been updated and tabulated. The Sponsor believes that these provide additional clarity for the Investigator.

Section 11.5 Data Safety Monitoring

The wording in this section has been updated to reflect the fact that the Sponsor has appointed PharmInvent as the Pharmacovigilance Provider and provide information on how the safety monitoring will be implemented with PharmInvent.

Section 12.1 Statistical Methods

This has been updated to reflect the change in primary endpoint.

Table 11: Schedule of Events

A separate line entry has been created for the monthly pregnancy test.

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1 PROTOCOL SYNOPSIS

Protocol Title:	**<u>CONSENT II:</u> Coversin in Paroxysmal <u>N</u>octurnal Hemoglobinuria (PNH) in patients with resistance to <u>E</u>culizumab due to complement C5 Polymorphisms**		
Protocol Number:	AK585		
Sponsor:	Akari Therapeutics Plc. 75-76 Wimpole Street London W1G 9RT UK		
Investigational Product(s):	Coversin (rVA576) powder for solution for subcutaneous injection 30 mg/mL		
Phase of Development:	II	**Indication:**	Paroxysmal nocturnal hemoglobinuria (PNH)
Study Centre(s):	Up to 6 centers		
Objectives:	**Primary Objective:** Safety of Coversin (rVA576) **Secondary Objective:** Efficacy of Coversin in the treatment of patients with PNH resistant to eculizumab *(Soliris®)*		
Study Design:	Phase II Open-label, single arm		
Planned Number of Subjects:	Up to 6		
Subject Population:	Patients with PNH, male or female, with proven resistance to eculizumab *(Soliris®)* due to complement C5 polymorphisms		
Criteria for Inclusion and Exclusion:	**Inclusion Criteria:** 1. Patients with known paroxysmal nocturnal hemoglobinuria (PNH). 2. Aged 18 and above. No upper age limit. 3. LDH ≥1.5 ULN.		

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	4. Patients must agree to avoid pregnancy and fathering children from the time of screening through the end of safety follow-up. Permitted contraceptive methods that are ≥99% effective in preventing pregnancy should be communicated to trial subjects and their understanding confirmed. 5. Resistance to eculizumab *(Soliris®)* proven by either a recognized C5 polymorphism on genetic screening or complement inhibition on CH50 ELISA of <100% at concentrations of eculizumab *(Soliris®)* in excess of 50µg/mL. Genetic conformation of the polymorphism should be obtained on all patients as soon as practicable but absence of such confirmation will not exclude a patient from starting treatment. 6. The patient has given voluntary written informed consent. 7. Willing to self-inject Coversin daily. 8. Willing to receive appropriate prophylaxis against Neisseria infection by both immunization and continuous or intermittent antibiotics. 9. Willing to avoid prohibited medications for duration of study tizanidine (if on ciprofloxacin) and eculizumab *(Soliris®)* should be discontinued before Coversin therapy is commenced. Ideally this should be 2 or more weeks before commencing Coversin unless, in the opinion of the Investigator, it would be in the best interests of the patient not to do so. 10. Coversin, in common with other complement inhibitors, has the potential to increase the risk of infection, particularly *Neisseria meningitides*. However, because these patients may have life threatening disease but currently have no other alternative treatment by virtue of their eculizumab *(Soliris®)* resistance, concurrent conditions such as recent infections requiring treatment with systemic antibiotics, immunodeficiency or recent immunizations with live attenuated vaccines are not absolute exclusions. Investigators should regard these as increased risk factors and act with caution and increased vigilance in such cases. Similarly, low platelet count and neutrophil count, both of which may be associated with their disease, are not absolute exclusions but should be cause for increased caution when instituting Coversin treatment.

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Exclusion Criteria:

1. Subjects with body weight <50 kg (110 lb) or >100 kg (220 lb) at screening visit.
2. Pregnancy or breast feeding (females).
3. Known allergy to ticks or severe reaction to arthropod venom (e.g. bee or wasp venom).
4. Unresolved *Neisseria meningitidis* infection. Patients who have positive nasal or throat swabs must be excluded until eradication of the organism by antibiotic treatment has been confirmed by repeat swabbing.
5. Patients who have not received adequate immunization against *Neisseria meningitides*, unless, in the opinion of the Investigator the risks of delaying therapy outweigh the risks of developing a meningococcal infection.
6. Impaired hepatic function (bilirubin > 1.5 x ULN and AST/ALT >2.5 x ULN) unless, in the opinion of the Investigator, the risks of delaying therapy outweigh the risks of treatment in the presence of impaired hepatic function.
7. Patients with a glomerular filtration rate (GFR) of <30 mL/min/1.73m^2 unless, in the opinion of the Investigator, the risks of delaying therapy outweigh the risks of treatment in the presence of impaired renal function.
8. Failure to satisfy the PI of fitness to participate for any other reason.

Concurrent Control

None

Treatment Regimen:

Treatment Dose / Phase	Day	Dose
Ablation	Day 1	60 mg (between 7am-11am)* 30 mg 12hrs later
Initiation	Day 2-Day 28	22.5 mg (between 7am-11am)* 22.5 mg (between 7pm-11pm)*
Maintenance	Day 29-Day 180	45 mg (between 7am-11am)*

* Patients to select a set time for dosing (e.g., 7am and 7pm) and administer dose within 1 hour either side of set time(s).

Ideally, all patients will be on a stable dose by Day 150 of the trial. This will allow adequate time to confirm that this dose is satisfactory for long-term treatment under the long-term safety trial or to ensure that

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<table>
<tr><td></td><td>arrangements can be put in place to allow the patient to be switched to alternative treatment with no interruption of treatment.
<table>
<tr><th colspan="4">Inadequate Response</th></tr>
<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>22.5 mg</td><td>12 hourly</td><td colspan="2">Withdraw patient</td></tr>
<tr><td>45 mg</td><td>24 hourly</td><td>22.5 mg</td><td>12 hourly</td></tr>
</table></td></tr>
<tr><td>Duration of Treatment:</td><td>180 days
Patients completing 180 days of treatment will have the option of entering an additional long-term safety trial at the discretion of their PI at Day 181. The long-term safety trial will continue until approval of Coversin.</td></tr>
<tr><td>Endpoints:</td><td>Efficacy Endpoints
Primary:
Reduction in serum LDH from baseline to mean of Day 43, 60, 90, 120, 150 and 180

Secondary:
• Change in LDH from baseline at monthly intervals after Day 28, 60, 90, 120, 150 and 180
• Change in mean Hb from baseline – Day 180
• Change in Functional Assessment of Chronic Illness Therapy (FACIT) score baseline – Day 28 - Day 180
• Change in EuroQol 5 dimensional 5 level (EQ-5D-5L) score from baseline – Day 28 - Day 180
• Number of transfusions from baseline to Day 180
Safety Endpoints:
• Frequency, type and relationship of AEs and SAEs to treatment
• Out of range laboratory parameters (hematology and chemistry)
• Vital signs (blood pressure, body temperature and pulse rate)
• Electrocardiogram (ECG) abnormalities baseline – Day 180 (A resting pre-dose ECG taken within 7 days of first dose will be compared with ECGs taken 1- 6 hours post-dose and at 180 days of treatment with Coversin)</td></tr>
</table>

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	• Change in weight will be noted baseline and at Day 180 • Injection site reaction and lymph node inspection • Anti-Coversin antibody production
Statistical Methods:	Descriptive statistics

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2 INTRODUCTION

Coversin is a small protein complement C5 inhibitor which prevents the cleavage of C5 by C5 convertase into C5a and C5b. It is effective in inhibiting terminal complement activity, irrespective of the activating pathway. In *in vitro* experiments, it has been found to be as effective as eculizumab *(Soliris®)* at a molar equivalent dose in preventing the hemolysis of affected clones of red blood cells (RBC) taken from patients with paroxysmal nocturnal hemoglobinuria (PNH). Following an initial successful Phase Ia clinical trial in healthy human volunteers, Coversin it is now being developed for the treatment of patients with PNH and other complement mediated diseases. Its high solubility, relative to the monoclonal antibody *Soliris®*, makes it suitable for small volume subcutaneous (s.c.) injection, with the advantage that patients can self-administer the drug and are not tied to bi-monthly intravenous (i.v.) infusions, which necessitate either attendance at a hospital clinic or a home visit by a suitably qualified nurse.

Nishimura et al, [2014] reported a polymorphism affecting the C5 gene which leads to an amino acid shift at a position within the eculizumab *(Soliris®)* binding epitope [Schatz-Jakobsen et al, 2016]. The polymorphism prevents binding of eculizumab *(Soliris®)* and leads to an inadequate therapeutic response. The amino acid polymorphism was found in 11 Japanese PNH patients (3.2%) who had an inadequate response to eculizumab *(Soliris®)* and was subsequently found to affect 3.5% of the general Japanese population and 1% of people of Han Chinese descent. It has now been identified in two Europeans with no known Japanese ancestry and one South American patient of Asian background. All of these patients had a poor clinical response to eculizumab *(Soliris®)* and when serum was tested *in vitro*, it was found that in each case, terminal complement activation could be completely blocked by Coversin at the predicted therapeutic concentration, but could not be fully inhibited by eculizumab *(Soliris®)* at any concentration tested.

Under this Protocol, patients with PNH and proven resistance to eculizumab *(Soliris®)* will be treated with Coversin for six months in order to determine the safety and efficacy of the drug in these circumstances. If such treatment is considered successful by the relevant Investigator and the patient has expressed a desire to continue on Coversin therapy, the patient will enter the long-term safety study, provided they have been on a stable dose of Coversin for at least two weeks prior to entry.

2.1 Investigational Product

Coversin powder for solution for s.c. injection 30 mg/ml.

Coversin is a compact small protein molecule with a lipocalin-like structure, consisting of alpha helices and a beta barrel. There is a surface active site which binds to the complement C5 molecule with a high affinity (K_D 1.0 x 10^{-9} M)) and an internalized active site capable of binding small eicosanoid molecules such as leukotriene B4 (LTB4) and ricinoleic acid [Roversi et al, 2007]. The relevance of the latter site in the pharmacological and presumed therapeutic activity of Coversin has not been fully determined.

The molecular mass of Coversin, as predicted by molecular modelling and confirmed by mass spectrometry, is 16.7855 kDa.

The amino acid sequence of Coversin showing disulphide bridges is shown below:

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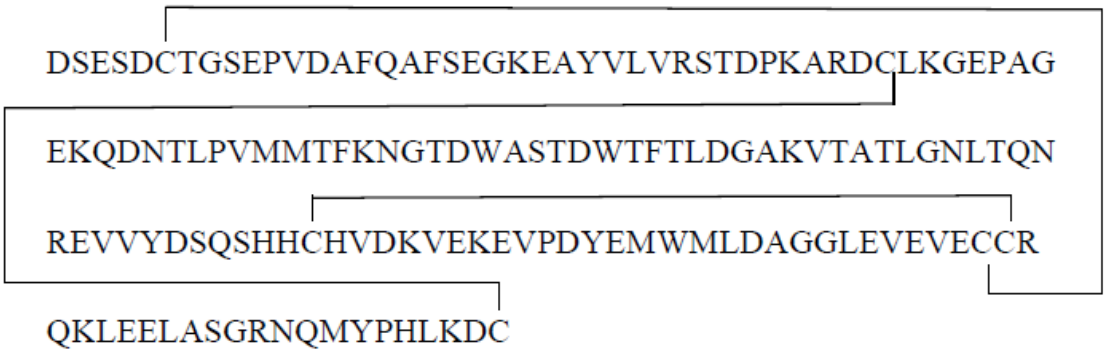

Coversin drug product is presented as 6 mL vials containing lyophilized powder, comprising sodium phosphate buffer and 18 mg Coversin per vial. The vials are stored at 2 – 8ºC. Prior to injection, the drug product will be reconstituted with 0.6 mL of sterile water for injection (WFI) to give a solution of 30 mg/mL Coversin in Phosphate buffered saline (PBS) pH 7.2. After reconstitution, the drug will normally be injected immediately, but if needed may be stored between 2 - 8ºC for not more than 24 hours. The extractable volume from each vial using a standard syringe is ≥0.5 ml, permitting administration of 15 mg Coversin per vial.

Table 1 Investigational Medicinal Product Preparation

Dose	Number of Vials	Volume to Inject (mL)	S.C. Injection
60 mg	4 vials	2.0 mL	Divide into 2 injections and two injection sites
30 mg	2 vials	1.0 mL	Single injection
22.5 mg	2 vials	0.75 mL	Single injection
45 mg	3 vials	1.5 mL	Divide into 2 injections and two injection sites*

*Unless single injection site preferred by patient

A change in dose frequency during the maintenance phase will be permitted at the discretion of the Investigator. If the change is because of lack of efficacy, as evidenced by a thrombotic or hemolytic event, rising serum LDH or creatinine, falling platelet count or any other sign of loss of disease control AND preferentially this is confirmed by measurement of rising complement activity by CH50 assay, the patient may receive an ablating dose (AD) consisting of a single dose (divided between two injection sites) of 60 mg, followed by one 30 mg dose 12 hours later following which the patient will revert back to 22.5 mg twice daily.

2.2 Summary of Non-clinical and Clinical Studies Relevant to the Clinical Trial

Coversin is a recombinant small protein (molecular weight (MW) 16.8 kDa), which is derived from a native protein discovered in the saliva of the *Ornithodoros moubata* tick [Nunn et al, 2005]. Its function in tick saliva is to assist the parasite in feeding, by suppressing the host immune reactions that would otherwise alert the host to the presence of the parasite which could then be removed by scratching or grooming. It has been known for some time that all species of ticks, which can feed undisturbed on their hosts including rodents, cattle, dogs and man, for periods of

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up to 14 days, secrete an array of immunomodulatory peptides and proteins in their saliva to take control of their hosts' local and systemic immune and inflammatory responses [Francischetti et al, 2009].

The complement system is an important part of the innate immune system in many animal species, including all mammals. There are three known pathways in the cascade: the classical, the alternative and the lectin, but all converge on a final common pathway. At this point, complement C5 (a product of the classical pathway) is acted upon by the enzyme C5 convertase, to form C5a and C5b. The latter then recruits a set of proteins (C5b, C6, C7, C8, and C9), which assemble to form the membrane attack complex (MAC). It is known that many human autoimmune diseases are associated with over activation of complement causing inflammation and tissue damage, most significantly via the products of the final common pathway C5a and the MAC. For example, in myasthenia gravis individuals form auto-antibodies to their own acetyl choline receptors (approximately 70% of all myasthenia gravis patients), which activate complement at the neuromuscular junction causing damage in particular via the MAC [Lang and Vincent, 2009].

Coversin binds to the C5 molecule, preventing any C5 convertase from activating and cleaving it to form C5a and the MAC. It appears to do this by interfering with a productive interaction between C5 and the C5 convertases, rather than by blocking the actual cleavage site on the C5 molecule [Fredslund et al, 2008]. The binding of Coversin to C5 is high affinity (K_D 1.0 x 10^{-9} M) and the rate of dissociation between C5 and Coversin is very low, but not irreversible [Roversi et al, 2013]. Other studies, including X-ray crystallography, have confirmed that Coversin complexes with human complement C5 [Fredslund et al, 2008].

Inhibition of the C5 complement system is a therapeutic target in a wide range of autoimmune and inflammatory diseases, including Crohn's disease, hypersensitivity pneumonitis, ischemia reperfusion injury, sepsis, myasthenia gravis, PNH, atypical hemolytic uremic syndrome and age related macular degeneration [Agostini et al, 2004; de Vries et al, 2003; Godau et al, 2004; Mollnes et al, 2006; Nozaki et al, 2006; Sarma et al, 2006; Tüzün et al, 2008; Ward et al, 2003].

The initial proposed clinical indication is PNH. The humanized monoclonal antibody eculizumab *(Soliris®)* was approved in Europe and the USA for the treatment of PNH in 2007 and is now the standard of care in this condition. Since Coversin has a similar mechanism of action to *Soliris®,* it is hypothesized that it will be effective as a therapeutic agent in the treatment of PNH, but may offer patient benefits in terms of convenience since it can be self-administered by s.c. injection, rather than having to be administered by a health-care professional by i.v. infusion every other week.

There are no satisfactory animal models of PNH and the presumed efficacy of Coversin in this condition relies on the fact that, since its mode of action is similar to that of *Soliris®*, with the exception that it binds to a different epitope on the C5 molecule, the clinical effects on patients with PNH are likely to be the same. In addition, Coversin has been tested in an *in vitro* flow cytometry model using blood from PNH patients with Type III RBC. In this model, the blood was either complement inactivated through heat treatment (negative control) or not, and complement activation was achieved by acidification and the addition of magnesium chloride ($MgCl_2$). Blood so treated was first spiked with either Coversin or *Soliris®* in ascending concentrations and the effect of complement activation on the relative populations of Type III and normal red blood cells

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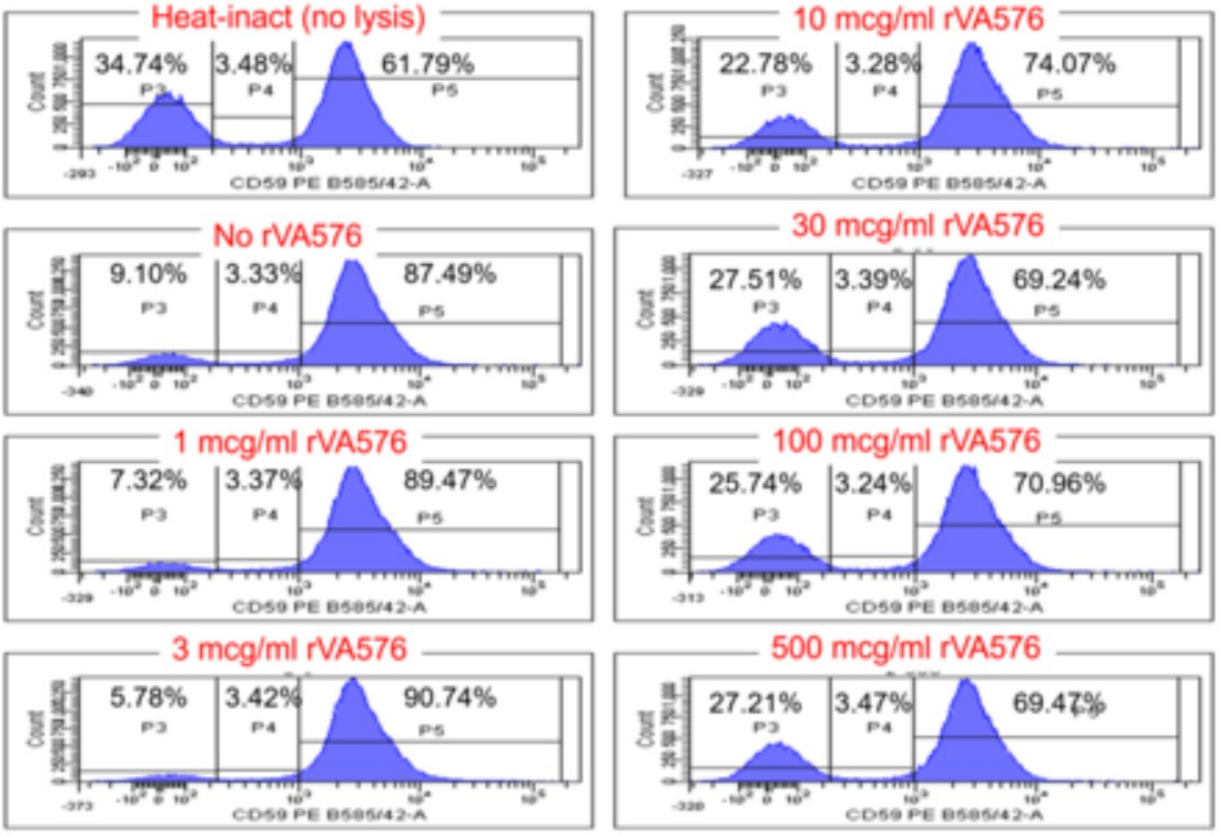
was observed. These results are shown in Figure 1 and Figure 2. They show that Coversin 10 µg/mL and *Soliris*® 50 µg/mL (molar equivalent concentrations) are equally effective in preventing hemolysis in blood from a PNH patient with Type III RBC.

Figure 1 Effect of ascending concentrations of Coversin on complement activation in blood from a PNH patient with Type III cells



Coversin shows a dose dependent effect in protection from complement mediated lysis of Type III RBCs

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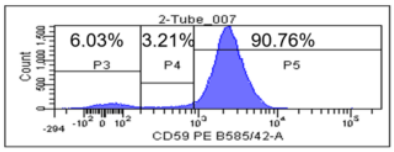
Figure 2 **Comparison of Coversin 10µg/mL and Soliris® 50µg/mL on blood from a patient with Type III cells**

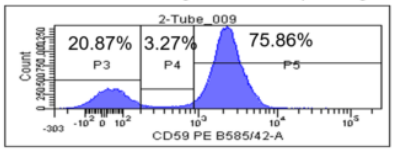
Effect of rVA576 on PNH Blood 2. Patient with Type III (complete deficiency) & normal red cells – Not on eculizumab

Acidified serum + MgCl



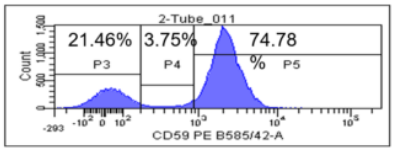
A) Whole human blood from patient with Type III deficiency showing effect of complement activation my MgCl in depletion of Close III red cells (left hand column) and increase in Close I cells (right hand column)

Acidified serum + MgCl + eculiz (50mcg/ml)



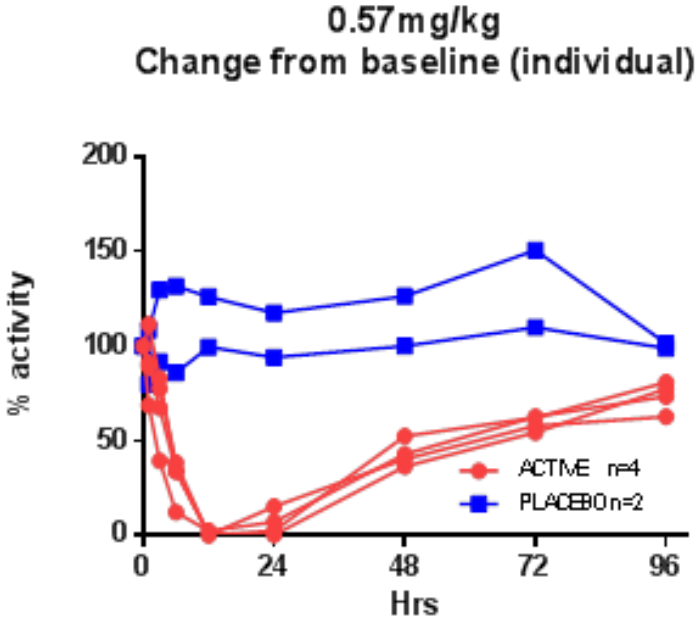
B) Same patient showing relative protection of Clone III cells by eculizumab 50µg / ml

Acidified serum + MgCl + Coversin (10mcg/ml)



C) Same patient showing relative protection of Clone III cells by Coversin 10 µg / ml (molar equivalent of eculizumab in B)

Figure 3 **CH50 activity in 6 normal subjects at the highest dose (0.57mg/kg) used in a Phase I single ascending dose (SAD) study following subcutaneous injection of Coversin**



A single ascending dose (SAD) Phase I clinical trial of Coversin, administered by s.c. injection, has been carried out to validate this route of administration and to confirm the dose needed to totally inhibit all C5 in the vascular compartment.

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Phase 1b Trial AK577

A Phase 1b dose range finding study (AK577) was conducted in which 4 cohorts of healthy volunteer subjects were studied. All subjects received an ablating dose of 4 x 30 mg doses 12 hourly (or the placebo equivalent), before going on to receive maintenance doses at 1 of 3 dose levels for a further 5-days, or in the case of Cohort 4 for a further 19 days.

There were 6 subjects in each of Cohort 1 (30 mg once a day maintenance dose), Cohort 2 (22.5 mg once a day maintenance dose) and Cohort 3 (15 mg once a day maintenance dose) with 4 active subjects receiving rVA576 and 2 subjects receiving placebo in each cohort. Cohorts 1, 2 and 3 subjects were followed during a 2-day recovery period from Day 7 to 9.

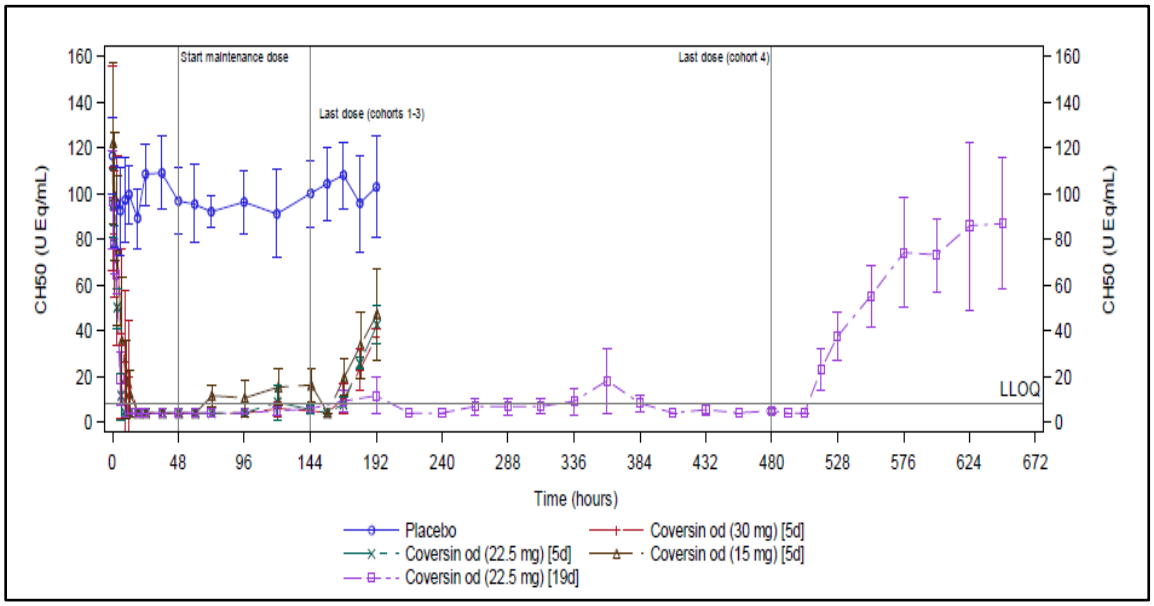
Cohort 4 (comprising 4 active subjects only) received the same ablating dose as Cohorts 1, 2 and 3 and a maintenance dose of 22.5 mg once a day for 19 days. Cohort 4 subjects were followed during a 7-day recovery period from Day 21 to 28.

As shown in Figure 4 the ablating dose rapidly reduced terminal complement activity (TCA) below the lower limit of quantification (LLOQ) for the ELISA CH50 assay and TCA was essentially completely inhibited at maintenance doses of 30 mg once daily for 5 days and 22.5 once daily for both 5 and 19 days.

One subject stopped treatment in Cohort 1. The subject, who had received 3 doses of rVA576 and 4 doses of ciprofloxacin, experienced significantly raised creatinine kinase (CK) and serum myoglobin level on Day 2. The Investigator considered that this adverse event (AE) was reported as rhabdomyolysis. The Investigator considered it to be related to the administration of ciprofloxacin, as it is a known but rare side effect of the drug.

In general, all adverse events were mild to moderate in intensity and all resolved. For further details, please refer to the IB and Table 3.

Figure 4 AK 577 Mean (+/-SD) CH50-Time Plot



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2.3 Dose and Dose Interval Considerations

The pharmacokinetics (PK) and pharmacodynamics (PD) of Coversin in humans and laboratory animals is different in a number of ways. In part, this is due to humans having a greater percentage of subcutaneous fat compared to laboratory animals including NHP, which leads to both slower absorption, as drug remains in the injection site for longer.

It has also been found, that the replenishment of complement C5 by the liver and other tissues is slower in humans than in laboratory animals, including rodents and NHP. On absorption into the bloodstream, Coversin rapidly binds to circulating complement C5 forming stable inactive conjugates with an expected half-life of 63 hours, the same as that of un-complexed C5. Any excess Coversin remaining, once all C5 has been bound, is rapidly excreted via the kidneys. In planning a dosage regimen, it is important to find doses and dose intervals that will allow all C5 to be neutralized without too great a loss of unbound Coversin. The results shown in Figure 3 suggest that for most subjects/patients, following the initial AD, a single daily injection of between 25 and 50% of the AD should be sufficient to keep complement activity (CH50) below 10% of baseline, which is considered important to achieve the optimal therapeutic effect. In the dose range finding study (AK577) there were six subjects in each of Cohort 1 (30 mg once a day maintenance dose), Cohort 2 (22.5 mg once a day maintenance dose) and Cohort 3 (15 mg once a day maintenance dose), with four active subjects receiving Coversin and two subjects receiving placebo in each cohort. All subjects received an AD of four x 30 mg doses 12 hourly (or the placebo equivalent) before going on to one of three maintenance doses for a further 5-days. Cohort 4 consisted of four subjects receiving the AD of four x 30 mg doses 12 hourly followed by 19 days maintenance dose and then 7 days follow-up. In all placebo-treated subjects, CH50 results remained at around baseline levels throughout the dosing period. In contrast, the Coversin AD fully inhibited complement activity. CH50 results were inhibited by >90% from 24 h after the start of the AD period until the end of the AD period (i.e. the morning of Day 3). During maintenance dosing with 15 mg Coversin, once daily, for 5 days, complement activity remained low, but not fully inhibited (Table 2). During maintenance dosing with 22.5 and 30 mg Coversin, once daily, for 5 days, complement activity remained almost completely inhibited. For the maintenance dose of 22.5 mg Coversin, all 4 subjects had CH50 values up to about 10% of baseline at 24 h after the final maintenance dose of Coversin (Table 2). Thus, 22.5 mg Coversin, once daily, was selected as an effective dose that could minimize Coversin exposure. To further explore this effective dose, a longer dosing period was tested in Cohort 4, in which all subjects received a maintenance dose of 22.5 mg Coversin for 19 days. In all 4 subjects, complement activity was almost completely inhibited throughout the maintenance dosing period and for the 24 h after the final maintenance dose (Table 2). Recovery to baseline complement activity took approximately 5 days.

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Table 2 Summary of CH50 results at 24 h after the final maintenance dose

Assessment (units)		Placebo*[1] (N=6)	Coversin Maintenance Dose* 15 mg[1] (N=4)	22.5 mg[1] (N=4)	30 mg[1] (N=3)[3]	22.5 mg[2] (N=4)
CH50 result (U Eq/mL)	Mean (SD) [range]	107.89 (14.614) [91.9–130.5]	19.64 (8.262) [13.4–31.1]	7.74 (3.249) [4.0–11.9]	10.20 (6.251) [4.0–16.5]	4.00 (0) [4.0–4.0]
Inhibition (%)	Mean (SD) [range]	6.1 (15.79) [-22–23]	83.8 (4.95) [78–88]	92.1 (2.36) [89–95]	91.4 (6.25) [84–96]	95.7 (0.94) (95–97)
Subjects with CH50 ≤10% of baseline	n (%)	0	0	3 (75.0)	2 (66.7)	4 (100.0)

***** 30 mg Coversin twice daily (AD) or placebo on Days 1 and 2, followed by maintenance dose or placebo from Day 3 onwards.
1: once daily on Days 3–7; 2: once daily on Days 3–21; 3: N=3 because Subject 105 was discontinued from treatment on the morning of Day 2.

During the AD period, most subjects had detectable serum concentrations of unbound Coversin within about 6–12 h after the first dose of Coversin on Day 1, with all remaining subjects having detectable concentrations by 18 h after the first dose. The results are consistent with the observation that complement is almost completely inhibited within 24 h after the start of the AD. During maintenance dosing, unbound Coversin concentrations initially decreased; thereafter pre-dose concentration remained at a constant level over the dosing period. After the final maintenance dose, serum concentrations of unbound Coversin increased at 12 h after dosing, and returned to pre-dose concentrations at 24 h after dosing. Taken together, the results show that Coversin is absorbed, and unbound Coversin is quickly cleared, over the 24 h after subcutaneous administration.

Steady state concentrations were maintained over the maintenance dosing period (Days 3–7 in Cohorts 1–3; Days 3–21 in Cohort 4), as shown by consistent pre-dose (trough) concentrations of unbound Coversin. The maintenance dose of 30 mg Coversin resulted in the highest pre-dose concentrations, whereas 22.5 mg and 15 mg Coversin resulted in lower pre-dose concentrations, which were around the Lower Limit of Qualification (LLOQ). Despite the lower exposure, 22.5 mg appeared to be as effective as 30 mg, as shown by the CH50 results. Extending the maintenance dose of 22.5 mg Coversin from 5 days to 19 days did not affect steady-state concentrations of unbound Coversin: the concentration at 12 h after final dosing was similar in both treatment groups.

In the currently on-going open label Phase II trial (AK579) in patients with PNH, five patients received an AD of 60 mg followed by 3 x 30 mg every 12 hours. They were then treated with 15 mg twice daily from Day 3 to Day 28 and it was then planned that they would move to 30 mg once daily for the remainder of the study (up to Day 90). Data obtained from the study so far has shown that all five patients achieved full ablation as measured by CH50 after the second dose and so further doses of 30 mg are now considered superfluous. Therefore, to ensure patients are not administering unnecessary large volumes the two extra doses have been dropped. In addition, for

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two of the five patients a dose of 15 mg 12-hourly was insufficient to control the LDH levels during the initiation phase and it was necessary to increase the dose to 22.5 mg 12-hourly. The earliest that the dose was changed was after 14 days of treatment. One patient received 22.5 mg twice daily Coversin for 41 days and two other patients received Coversin for 6 and 14 days respectively. The maintenance dose was planned to be 30 mg once daily, but in three out of five patients their dose was increased to 45 mg once daily. Only one patient completed the trial on 30 mg once daily. One patient with a suspected comorbidity left the trial before moving onto a once daily dose.

Based on this data, the proposed dosing for this study is an AD of 60 mg followed 12 hours later by a 30 mg dose and then 22.5 mg twice daily up to Day 28 (± 3 days) and then 45 mg once daily up to Day 180. If the once daily dosing is deemed inadequate, then the patient may revert back to 22.5 mg twice daily dosing.

2.4 Previous Experience in Patients

To date (12 December 2017), ten patients have received Coversin. One under a compassionate program, one resistant patient under study AK578 and eight as part of the Phase II (AK579) study in patients with PNH.

A 4-year-old male with a thrombotic microangiopathy (TMA) associated with bone marrow transplant related graft versus host disease, was treated with Coversin on a named patient basis for 58 days. The patient had previously been treated with eculizumab (*Soliris®*) for 3 months with no apparent clinical benefit and was then found to have a polymorphism of C5, which prevented proper binding of the antibody to C5. This polymorphism had previously only been reported in patients of Japanese origin [Nishimura et al, 2014], although this patient was Caucasian. It has been demonstrated *in vitro* that when complement is activated in serum from this patient and from another non-Japanese PNH patient with resistance to eculizumab (*Soliris®*), complement activity can be completely blocked with Coversin but not eculizumab (*Soliris®*) and it was decided on that basis to attempt to treat the patient with Coversin.

As there was limited available drug supply following the Phase 1a SAD trial, the patient was only able to receive treatment for a limited period. The critically ill patient responded well to Coversin for the 58 days that he was treated. After treatment ended (no further supply available), the patient's condition deteriorated and he died 24 days later. During treatment, there were no AEs attributable to Coversin, no injection site reactions and no evidence of drug neutralization.

The 4-year-old European boy's serum was used to examine inhibition of complement activity by eculizumab *(Soliris®)* and Coversin using a Quidel MicroVue ELISA kit that detects formation of the MAC. MAC formation is dependent on activation of C5. Coversin was found to inhibit Terminal Complement Complex (TCC) formation equally well (<5% of the CH50 value without drug at $\geq$ 10µg/ml) in normal human serum and serum from the European boy with the p.Arg885His *C5* polymorphism (Eculizumab *(Soliris®)* completely inhibited MAC in normal human serum at the expected dose (35µg/ml approximately $\leq$10% of CH50 value for serum without drug), but did not completely inhibit TCC formation in the patient's serum (Figure 5). Approximately 20% of the CH50 value without drug remained at even the highest concentration (60µg/ml) of eculizumab *(Soliris®)* (Figure 5).

The results showed that complete inhibition of both the patient serum (two replicates) and normal control occurred at a Coversin concentration of about 15 µg/mL. Eculizumab *(Soliris®)* fully

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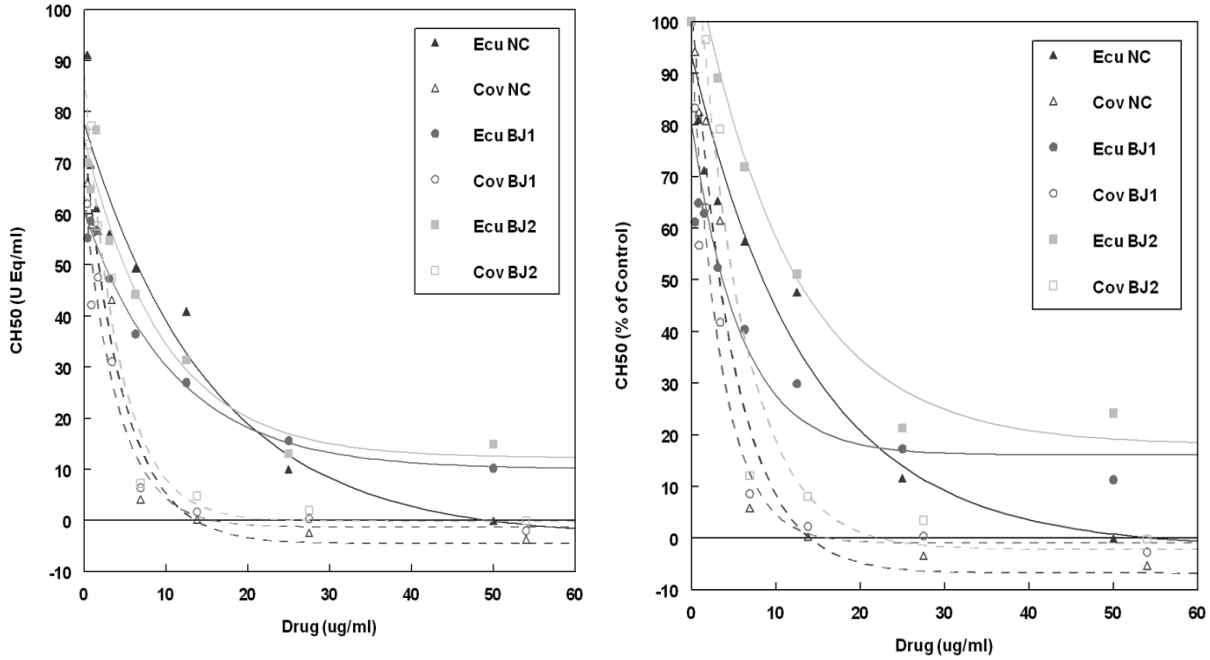
inhibits normal human serum at a concentration of 50 µg/mL, the predicted therapeutic concentration, whereas inhibition of the patient samples with eculizumab *(Soliris®)* was incomplete at all concentrations.

Figure 5 Comparison of CH50 values (terminal complement activity) compared to dose (concentration) of Coversin (Cov) and eculizumab (Ecu) in a patient affected by eculizumab resistance (BJ) and in normal controls (NC)



Shown on the left as absolute values and on the right as percentage of CH50 value in absence of drug.

Partial inhibition of the serum by eculizumab *(Soliris®)* is understandable since this child and all other individuals with the p. Arg885His *C5* polymorphism identified to date are heterozygotes with a normal copy of C5 and a copy of p.Arg885His *C5*. Therefore, assuming equal expression levels of each copy of C5 (since the gene is not on the X chromosome) eculizumab *(Soliris®)* will fully inhibit 50% of the C5 protein present in these individuals. Therefore, in patients treated with eculizumab *(Soliris®)* one would expect the rate of TCC formation in p. Arg885His heterozygotes to be roughly 50% of the rate of TCC formation in normal human serum. The 20% residual CH50 activity, rather than expected 50% residual activity may also reflect the fact that the patient was receiving fresh blood products every day, which likely increased the ratio of normal C5 to p.Arg885His C5, thus reducing the relative concentration of C5 (p.Arg885His) not inhibited by eculizumab *(Soliris®)*.

Complete inhibition of the 4-year-old patient's serum by Coversin is also understandable since Coversin has been shown to be an equally effective inhibitor of C5 activation in all mammalian species in which it has been tested including man and pig (Barratt-Due et al, 2011), rat, mouse, guinea pig, rabbit and cynomolgus monkey. This indicates that binding of Coversin C5 is far more tolerant of differences in the amino acid sequence of C5 than eculizumab *(Soliris®)* which only inhibits human C5 [Rother et al, 2007].

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A single PNH eculizumab *(Soliris®)* resistant patient has received daily doses of Coversin since the 8 Feb 2016 under protocol AK578. At enrollment, the patient was a 30-year-old male with PNH, (granulocyte clone size: 90%) and severe hemolysis (LDH 3 to 17 x upper limit of normal prior to treatment with Coversin), transient renal failure, extreme fatigue, symptoms of muscle dystonia and no history of thrombosis. He remained severely hemolytic during 6 months of eculizumab *(Soliris®)* treatment despite adequate drug levels and no human anti-drug antibodies (ADA). Other causes of hemolysis were excluded. The patient was shown to have a p.Arg885Ser polymorphism in C5 which rendered him non-responsive to eculizumab *(Soliris®)* therapy.

Coversin was initially administered by s.c. injection at an AD of 0.57 mg/kg on Day 1, followed by a maintenance dose of 0.14 mg/kg per day thereafter. Peripheral blood samples were drawn for PK/PD. Since this was the first occasion that Coversin had been administered to a PNH patient, it was important to tailor the dose for best therapeutic effect. The protocol therefore allowed doubling of the dose and/or shortening of the dose interval on the basis of clinical symptoms and CH50 levels to achieve adequate and sustained complement inhibition.

There was a good initial response to the AD of 0.57mg/kg Coversin, with CH50 levels decreasing from baseline 96 U Eq/mL to <8 U Eq/mL the limit of quantification in the CH50 ELISA. Clinical symptoms and laboratory markers of hemolysis improved during the first few days dosing at 0.14mg/kg every 24 hours. However, as shown in Figure 6, 6 days into the treatment, pre-dose CH50 had increased to 20.9 U Eq/ml and the patient experienced hemolysis-associated symptoms with dark urine and no further decrease of his LDH. The same occurred after doubling of the dose to 0.29 mg/kg once per day so the dose and dose interval were changed to 0.14mg/kg administered every 12 hours. This resulted in stable complement inhibition with CH50 levels <8 U Eq/mL (the limit of quantification) and no breakthrough symptoms. The LDH rapidly decreased to around 500 IU/L and thereafter to approximately 1.5xULN, indicated by the horizontal broken red line at 273 LDH IU/L in Figure 6.

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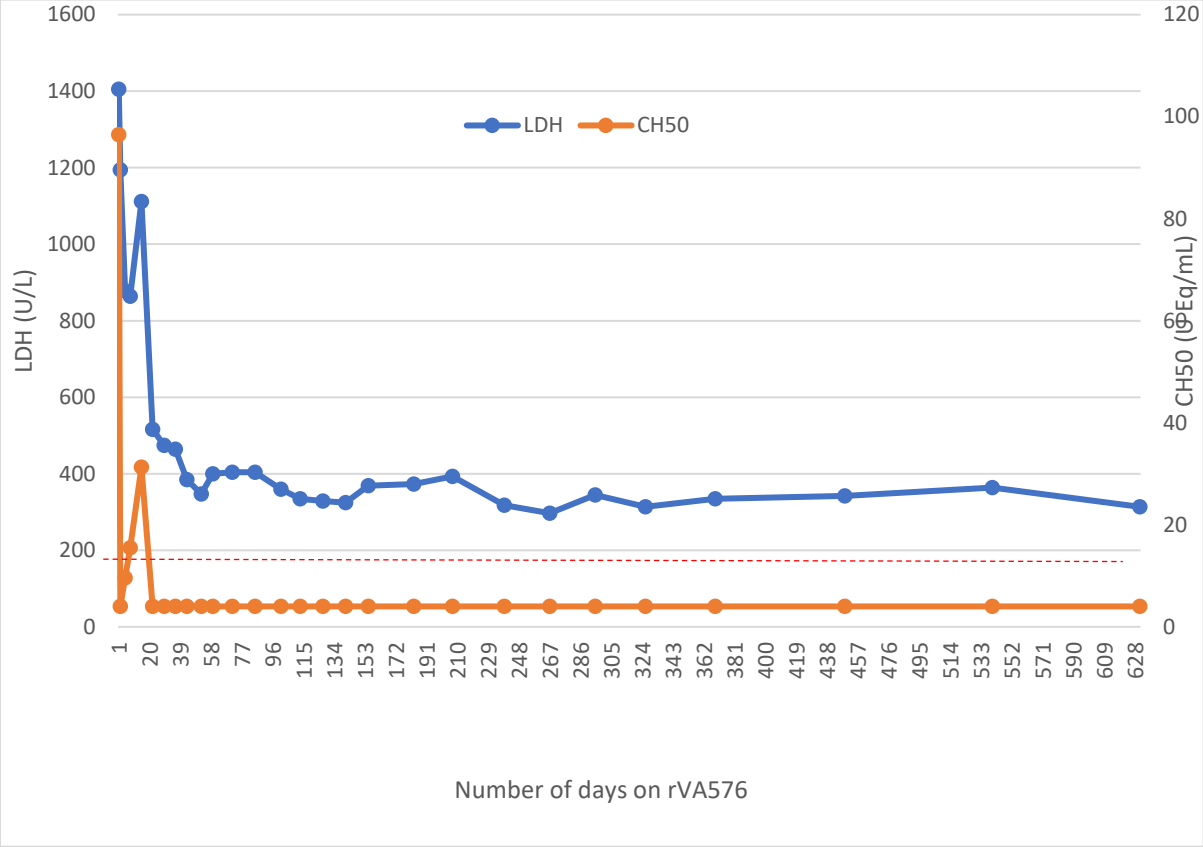
Figure 6 Lactate dehydrogenase (LDH) level and complement activity (CH50 U Eq/mL) during treatment with Coversin for AK578



2.5 Summary of Known and Potential Risks and Benefits to Human Subjects

Although there has been limited clinical experience with Coversin to date, the clinical implications of complement C5 blockade can be deduced from a combination of genetic and epidemiological studies, animal studies and experience with eculizumab *(Soliris®)*. Complement C5 deficiency in humans is a rare, familial condition caused by a variety of genetic defects including mutations in the C5 exons. Those affected have a predisposition to gram negative infections, particularly meningococcal meningitis [Densen, 1989], herpetic infections and seborrheic dermatitis [Bartholomew & Shanahan 1990].

To date (12 December 2017) Coversin has been administered to approximately 42 subjects, 32 healthy volunteers and 10 patients. In these patients Coversin has generally been found to be well tolerated. In the single ascending dose trial (VA576) the drug was well tolerated, there were no serious or severe adverse reactions and only mild injection site reactions. A total of three adverse reactions were reported in 2 of 16 subjects who received the active drug and in 1 of 8 subjects who received placebo. There was no dose relationship, three of the four AEs occurring at the lowest dose and one in the third of four ascending doses. The AEs were mild and self-limiting and consisted of light headedness (1), symptoms of a cold (1), pain in the arm related to the injection site (1) and intolerance to bright light (1).

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In the multi-dose Phase I b study (AK577) there was a subject in Cohort 1 who received 3 doses of Coversin and 4 doses of ciprofloxacin and experienced a significantly raised CK and serum myoglobin level on Day 2. The subject was clinically stable and troponin was negative. The PI decided to stop Coversin and ciprofloxacin and withdraw the subject. The subject did not experience any symptoms relating to the raised CK and myoglobin levels. The CK level dropped significantly by Day 6 and had returned to normal by Day 28. The Investigator considered that this AE was related to the administration of ciprofloxacin, as it is a known but rare side effect of the drug. He did not consider that it was related to Coversin. Cohort 4 (comprising 4 active subjects only) received the same AD as Cohorts 1, 2 and 3 and a maintenance dose of 22.5 mg once a day for 19 days. Cohort 4 were followed during a 7-day recovery period from Day 21 to 28.

Table 3 shows the treatment-emergent adverse events observed in study AK577. In general, all adverse events were mild to moderate in intensity and all resolved. As described above, there was one patient who withdrew from treatment.

Table 3 Summary of Treatment-Emergent Adverse Events from AK577

		Doses					
System Organ Class	**Preferred term**	**Placebo N= 6 N (%)**	**Coversin 30 mg od 5d N= 4 N (%)**	**Coversin 22.5 mg od 5d N= 4 N (%)**	**Coversin 15 mg od 5d N= 4 N (%)**	**Coversin 22.5 mg od 19d N = 4 N (%)**	**Total Coversin N = 16 N (%)**
Number of subjects with AEs		1 (16.7)	2 (50.0)	1 (25.0)	1 (25.0)	3 (75)	7 (43.8)
General disorders and administration site conditions	Total number of subjects	1 (16.7)	0	1 (25.0)	1 (25.0)	2 (50.0)	4 (25)
	Injection site pain	1 (16.7)	0	0	1 (25.0)	2 (50.0)	3 (18.8)
	Injection site reaction	0	0	0	0	2 (50.0)	1(6.3)
	Influenza like illness	0	0	1 (25.0)	0	0	1 (6.3)
	Injection site bruising	0	0	0	0	1 (25.0)	1 (6.3)
	Injection site erythema	0	0	0	0	1 (25.0)	1 (6.3)
	Injection site swelling	0	0	0	0	1 (25.0)	1 (6.3)
Musculoskeletal and connective tissue disorders	Total number of subjects	1 (16.7)	1 (25.0)	1 (25.0)	1 (25.0)	0	3 (18.8)
	Back pain	0	0	0	1 (25.0)	0	1 (6.3)
	Musculoskeletal pain	1 (16.7)	0	0	0	0	0
	Pain in extremity	0	0	1 (25.0)	0	0	1 (6.3)

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System Organ Class	Preferred term	Doses					
		Placebo N= 6 N (%)	Coversin 30 mg od 5d N= 4 N (%)	Coversin 22.5 mg od 5d N= 4 N (%)	Coversin 15 mg od 5d N= 4 N (%)	Coversin 22.5 mg od 19d N = 4 N (%)	Total Coversin N = 16 N (%)
	Rhabdomyolysis	0	1 (25.0)	0	0	0	1 (6.3)
Nervous system disorders	Total number of patients	0	1 (25.0)	1 (25.0)	0	1 (25.0)	3 (18.8)
	Headache	0	1 (25.0)	1 (25.0)	0	1 (25.0)	3 (18.8)
	Presyncope	0	0	1 (25.0)	0	0	1 (6.3)
Eye Disorders	Total number of subjects	0	2 (50.0)	0	0	0	2 (12.5)
	Lacrimation increased	0	1 (25.0)	0	0	0	1 (6.3)
	Photophobia	0	1 (25.0)	0	0	0	1 (6.3)
Respiratory, thoracic and mediastinal disorders	Total number of subjects	0	1 (25.0)	0	0	0	1 (6.3)
	Cough	0	1 (25.0)	0	0	0	1 (6.3)
	Rhinorrhea	0	1 (25.0)	0	0	0	1 (6.3)
Injury, poisoning, and procedural complications	Total number of subjects	0	0	0	0	1 (25.0)	1 (6.3)
	Contusion	0	0	0	0	1 (25.0)	1 (6.3)
Skin and subcutaneous tissue disorders	Total number of subjects	0	0	1 (25.0)	0	0	1 (6.3)
	Rash pruritic	0	0	1 (25.0)	0	0	1 (6.3)

There has been a single patient enrolled in the PNH eculizumab resistant protocol (AK578) to date and one SAE was reported during the first week of treatment. This 30-year-old male patient experienced a PNH-related complaint (fatigue, dark urine) on Day 6 of daily maintenance dosing. He was admitted into the hospital for additional laboratory examinations and discharged on Day 7 and fully recovered. The investigators considered that this SAE was unrelated to Coversin but the dose was increased and hemolysis was brought under control. This patient also reported 28 AEs during the 22-month study period (Table 4). All AEs were mild or moderate, resolved spontaneously and no treatments were given.

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Table 4 Summary of Adverse events observed in AK578

System Organ Class	Preferred Term	Related	Possibly Related	Not related
No of subjects with AEs			1 (100%)	
Total number of AEs	28	8 (29%)	16 (57%)	4 (14%)
General disorders and administration site reactions	Total no of AE's	8	5	0
	Injection site reaction	8	0	0
	Flu-like symptoms	0	3	0
	Malaise	0	1	0
	Fatigue	0	1	0
Nervous system disorders	Total no of AE's	0	7	0
	Headache	0	6	0
	Insomnia	0	1	0
Respiratory and thoracic and mediastinal disorders	Total no of AE's	0	3	0
	Cough	0	1	0
	Dyspnea	0	1	0
	Sore throat	0	1	0
Gastrointestinal disorders	Total no of AE's	0	1	1
	Stomach pain	0	0	1
	Abdominal pain	0	1	0
Skin and subcutaneous tissue disorders	Total no. of AE's	0	0	1
	Papulopustular rash	0	0	1
Blood and lymphatic systems	Total no. of AE's	0	0	1
	Breakthrough hemolysis	0	0	1
Musculoskeletal and connective tissue disorders	Total no. of AE's	0	0	1
	Non-cardiac chest pain	0	0	1

In the AK579 study seven out of the eight patients who participated in the study experienced treatment-emergent adverse events. The most common TEAE was injection site reactions which accounted for the majority of the adverse events which were all mild to moderate in intensity and declined towards the end of the 90-day trial. These reactions were to be expected with a subcutaneous formulation. It should be noted that the clinical trial is on-going and so the adverse events are not yet finalized and may change once the data is fully cleaned and verified.

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Table 5 Adverse Events from AK579 (COBALT)

System Organ Class	No. of patients	Related			Possibly Related			TOTAL
	N (%)	Grade 1	Grade 2	Total	Grade 1	Grade 2	Total	
General disorders and administration site conditions	**7 (87.5)**	**46**	**1**	**47**	**65**	**3**	**68**	**115**
Injection site erythema	5 (62.5)	31	0	31	11	0	11	43
Injection site pruritus	4 (50.0)	7	0	7	6	3	9	16
Injection site bruising	3 (37.5)	6	0	6	3	0	3	9
Injection site pain	3 (37.5)	0	0	0	24	0	24	24
Injection site swelling	2 (25.0)	2	1	3	11	0	11	14
Injection site discharge	1(12.5)	0	0	0	8	0	8	8
Injection site hypersensitivity	1 (12.5)	0	0	0	1	0	1	1
Injection site induration	1 (12.5)	0	0	0	1	0	1	1
Gastrointestinal Disorders	**2 (25.0)**	**1**	**0**	**1**	**2**	**0**	**2**	**3**
Abdominal discomfort	1 (12.5)	1	0	1	0	0	0	1
Diarrhea	1 (12.5)	0	0	0	1	0	1	1
Paresthesia	1 (12.5)	0	0	0	1*	0	1	1
Investigations	**1 (12.5)**	**0**	**0**	**0**	**2**	**0**	**2**	**2**
Neutrophil count decreased	1 (12.5)	0	0	0	1	0	1	1
White blood cell count decreased	1 (12.5)	0	0	0	1*	0	1	1
Metabolism and nutrition disorders	**1 (12.5)**	**0**	**0**	**0**	**4**	**0**	**4**	**4**
Hypophosphatemia	1 (12.5)	0	0	0	2	0	2	2
Hypoproteinemia	1 (12.5)	0	0	0	2	0	2	2
Musculoskeletal and connective tissue disorders	**1 (12.5)**	**0**	**0**	**0**	**0**	**1**	**1**	**1**
Osteoarthritis	1 (12.5)	0	0	0	0	1*	1	1
Nervous System disorders	**1 (12.5)**	**0**	**0**	**0**	**1**	**0**	**1**	**1**

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System Organ Class	No. of patients	Related			Possibly Related			TOTAL
	N (%)	Grade 1	Grade 2	Total	Grade 1	Grade 2	Total	
Headache	1 (12.5)	0	0	0	1	0	1	1
Skin and subcutaneous tissue disorders	**1 (12.5)**	**0**	**0**	**0**	**0**	**3**	**3**	**3**
Pruritus	1 (12.5)	0	0	0	0	1	1	1
Rash	1 (12.5)	0	0	0	0	2	2	2
Vascular disorders	**1 (12.5)**	**0**	**0**	**0**	**1**	**0**	**1**	**1**
Hematoma	1 (12.5)	0	0	0	1*	0	1	1

* AEs on-going not resolved and not recovered

In AK579 there have been four SAEs to date, none of which were treatment related. These SAEs have occurred in two patients. In one patient (826-001-102) there was a staphylococci infection which was considered grade 3 and was determined to be a staphylococcus epidermidis infection which resolved with concomitant medication. One patient (826-102-001) has experienced angina pectoris (grade 3), dyspnea (grade 2) and lethargy (grade 2). The angina pectoris resolved, dyspnea was resolving and lethargy was on-going at the time of this report. None of the patients needed to have their treatment disrupted or changed.

In the long-term safety study only 2 patients have experienced treatment-related adverse events to date. As seen in AK579 these are mostly injection site reactions and they have all resolved.

Table 6 Adverse Events for AK581

System Organ Class	No. of patients	Related			Possibly Related			TOTAL
	N (%)	Grade 1	Grade 2	Total	Grade 1	Grade 2	Total	
General disorders and administration site conditions	**2**	**4**	**0**	**4**	**0**	**0**	**0**	**4**
Injection site pruritus	1	1	0	1	0	0	0	1
Injection site pain	1	2	0	2	0	0	0	2
Injection site swelling	1	1	0	1	0	0	0	1
Gastrointestinal Disorders	**1**	**0**	**2**	**2**	**0**	**0**	**0**	**2**
Nausea	1	0	1	1	0	0	0	1
Vomiting	1	0	1	1	0	0	0	1

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Overall, the adverse event profile shows few adverse events other than injection site reactions which are to be expected with daily subcutaneous injections. Going forward, AKARI proposes not to report injection site reactions which are classified as Grade 1 but only injection site reactions which are Grade 2 or above will be reported. All other adverse events regardless of grade will be reported.

A Grade 1 injection site reaction can be classified as pain, swelling or tenderness, associated with an injection when one or more of the following is also present:

- Redness surrounding the injection site and appearing within 72 hours of the injection
- Localised increase in skin temperature surrounding the injection site
- Whealing (blistering) in the vicinity of the injection site
- Itching at or around the injection site starting between 30 minutes and 72 hours of the injection [NB the injection itself may cause itching in under 30 minutes]
- Positive results of a skin biopsy (presence of increased numbers of eosinophils and/or lymphocytes)

The Common Terminology Criteria for Adverse Events (CTCAE Version 5.0) definitions should be used to classify injection site reactions of Grade 2 and above:

Grade	**2**	**3**	**4**	**5**
Description	Pain; lipodystrophy; edema; phlebitis	Ulcerations or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences, urgent intervention indicated	Death

In a retrospective review of PNH patients on long term treatment with eculizumab *(Soliris®)*, two of ninety-six patients developed meningococcal meningitis [Hillmen et al, 2013]. Currently subjects taking eculizumab *(Soliris®)* are advised to maintain prophylaxis against *Neisseria meningitidis* either by active immunization or by taking long term antibiotics or both [Dmytrijuk et al, 2008]. 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 *(Soliris®)* and Coversin, no AEs 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 immunization.

GLP-compliant daily s.c. repeat dose studies in mice (1, 3 and 6 months) and cynomolgus monkeys (6 months) have been completed. In the 3-month mouse study (high dose group 5 mg/kg) no drug related affects were detected other than an increase in the incidence and severity of microscopic signs of inflammation detected by histopathology at the site of injection (scapular region only in mice) that were considered related to Coversin. In the 6-month mouse study high dose 6.5 mg/kg was determined to be the No Observable Adverse Event Level (NOAEL) but histopathological

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inflammatory changes were observed at the site of administration. Minor immunostimulation in local lymph nodes in both sexes were observed at 6.5 mg/kg and in the spleen in males treated.

Because Coversin is a xenologous protein (derived from a tick salivary protein), there is a possibility that its chronic use may be associated with the formation of antibodies which could neutralize the effect of the drug or cause untoward adverse reactions. The immunogenicity study in mice and 58-day dosing of the 4-year-old child described above and the ongoing treatment of the Dutch PNH patient resistant to eculizumab *(Soliris®)* has gone some way to mitigating this possibility, as well as experience with other parasite derived therapeutic molecules, such as the leech-derived anticoagulant lepirudin [Greinacher and Warkentin, 2008].

The potential of Coversin to induce phototoxicity is at present unknown. For this reason, patients taking Coversin should be advised to avoid excessive exposure to sunlight or UV light (e.g. sunbeds) for the duration of the study and for five half-lives after the last administration of Coversin (5 hours).

2.6 Description of/and Justification for the Route of Administration, Dosage regime and Treatment period

The human complement C5 standing pool is about 200 mg in a 70-kg individual (amount of C5 protein that is maintained at a steady state by the liver and macrophages in a healthy person), assuming 2.8L serum and a C5 concentration of 70 µg/ml serum. Given the (MW) of C5 (196kDa), the MW of Coversin (16.8kDa) and the fact that one molecule of Coversin binds one molecule of C5, it would be expected that 1mg of Coversin would bind 11.7 mg of C5. However, in the Phase Ia single ascending dose (SAD) study, which measured the concentration of C5 in the serum of individual healthy volunteers of known weight, it was shown that approximately a 1.8:1 molar excess of Coversin was necessary to completely inhibit C5 activation [Barratt-Due et al, 2011]. This means that it would take approximately 31.0 mg of Coversin to completely neutralise the standing pool of C5 in a 70-kg human. In the Phase Ia study, Cohort 4 subjects showed complete complement inhibition when administered 0.57 mg/kg Coversin. The heaviest patient in Cohort 4 that received Coversin weighed 93.6 kg and therefore was given a single total dose of 53.4 mg Coversin.

Pharmacokinetic studies in rats have shown that unbound Coversin is rapidly excreted by the renal route and that the serum half-life is ~30 minutes, whereas Coversin complexed with C5 has a circulating half-life of ~30 hours in rats [Hepburn et al, 2007]. The rate of production of C5 by humans is not known precisely. Sissons *et al*. using the Fick Principle and intravenously injected ^{125}I labelled C5, calculated a daily turnover in normal humans of between 71 and 134 µg/kg/hr (mean 90 µg/kg/hr) [Sissons et al, 1977]. It is considered that turnover in autoimmune disease is not substantially different to that in normal patients. On this basis, the mean amount of C5 produced daily is roughly 151.2 mg and, using the calculation above it would take roughly 23.0 mg of Coversin to completely ablate it.

These figures indicate that a minimal loading ablation dose for a human is approximately 0.44 mg/kg (calculation 31 mg/70 kg) and minimal maintenance dose is approximately 0.018 mg/kg/hr (calculation 23.0 mg/24h).

Single i.v and 5-day s.c. dose toxicology studies in rats and cynomolgus monkeys were undertaken at doses up to 28.5 mg/kg. On a weight basis, this is 16 times more than the highest dose

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administered to humans in a single day, which is 90 mg during the ablating phase equating to 1.8mg/kg in the lightest 50kg subjects.

Once daily repeat dose toxicology studies in mice (1-, 3- and 6-months) and cynomolgus monkey (1-month) have been performed using doses of up to 6.5 mg/kg (mouse, 6 months) and 4.8mg/kg (monkey, 1 month). On a weight basis, this is 7.2 times (mice) and 5 times (monkeys) more Coversin than the human maintenance dose of 45 mg QD administered to the lightest (50kg) patients which equates to 0.9mg/kg. To determine actual exposure to Coversin, empirical data on free drug levels and terminal complement activity in the cynomolgus monkeys dosed at 4.8mg/kg QD for 28 days was used re-parameterise the human PK/PD model for Coversin permitting an estimate of free Coversin C_{max}, T_{max}, C_{min} and AUC. Comparison of these values with the same values derived from humans under the dosing regimen proposed for AK580 CAPSTONE and this study showed that C_{max} and AUC of free Coversin are similar, and thus the 1-month toxicology findings in NHP provide a valid reference for anticipated safety in humans (Table 7). It was not possible to derive exposure data from the long-term mouse toxicology studies because blood samples were not taken at sufficiently short intervals after dosing.

Table 7 Safety Factor Calculation

PK Parameter	NHP[a]	Human[b]	Safety factor[c]
$C_{max,ss}$	267.4 (236.0 to 302.5)	317.1 (265.8 to 370.1)	0.843 (0.685 to 1.03)
$C_{trough,ss}$	49.56 (38.30 to 61.47)	30.06 (24.65 to 36.92)	1.649 (1.13 to 2.21)
$AUC_{ss(0-24)}$	3185 (2743 to 3656)	3332 (2949 to 3721)	0.956 (0.793 to 1.16)
$T_{max,ss}$	0.326 (0.310 to 0.344)	0.918 (0.831 to 1.011)	0.355 (0.317 to 0.396)

However, Akari recognise that this exposure data is important and Akari are currently undertaking a study in same strain of mice as used for the long-term mouse toxicology studies to evaluate PK/PD. The expectation from these studies is that mice dosed s.c. at 6.6 mg/kg will have a very high C_{max} due to rapid absorption and relatively small AUC due to rapid elimination of unbound Coversin by mice. When available, these data will be presented in the Investigator Brochure.

In rat, mouse and cynomolgus monkey studies no drug related affects were detected other than for the 3- and 6-month mouse studies where there was an increase in the incidence and severity of microscopic signs of inflammation detected by histopathology at the site of injection (scapular region only in mice) which were considered related to Coversin. In the 6-month mouse study minor immunostimulation in local lymph nodes in both sexes was observed in the highest dose group (6.5 mg/kg) and in the spleen of treated males. In the 6-month mouse and 1-month NHP study the NOAEL was determined to be 6.5 mg/kg and 4.8 mg/kg respectively.

The Phase I SAD study (VA576) maximum activity was seen between 6 and 12 hours after injection. Recovery due to gradual replenishment of C5 by the liver and other tissues was such that at 96 hr post-dose, CH50 had only returned to approximately 75% of baseline. At the time this result was obtained, it was unexpected since onset of action was faster and duration of action shorter in animals, including cynomolgus monkeys, than in humans. Subsequent empirical data

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and PK/PD modelling of the dynamics of Coversin in cynomolgus monkey and man, indicate that the absorption rate from the s.c. site of administration in monkeys and man is equivalent but that the smaller intravascular volume and higher relative clearance rate of Coversin result in more rapid onset and offset of action in monkeys than in man.

In the Phase Ib study (AK577) in all placebo-treated subjects, CH50 results remained at around baseline levels throughout the dosing period. In contrast, the Coversin AD fully inhibited complement activity. CH50 results were inhibited by >90% from 24 h after the start of the AD period until the end of the AD period (i.e. the morning of Day 3). During maintenance dosing with 15 mg Coversin, once daily, for 5 days, complement activity remained low, but not fully inhibited (Figure 4). During maintenance dosing with 22.5 and 30 mg Coversin, once daily, for 5 days, complement activity remained almost completely inhibited. For the maintenance dose of 22.5 mg Coversin, all 4 subjects had CH50 values up to about 10% of baseline at 24 h after the final maintenance dose of Coversin (Figure 4). Thus, 22.5 mg Coversin, once daily, was selected as an effective dose that could minimise Coversin exposure. To further explore this effective dose, a longer dosing period was tested in Cohort 4, in which all patients received a maintenance dose of 22.5 mg Coversin for 19 days. In all 4 patients, complement activity was almost completely inhibited throughout the maintenance dosing period and for the 24 h after the final maintenance dose (Figure 4). Recovery to baseline complement activity took approximately 5 days.

Pharmacokinetic/pharmacodynamics (PK/PD) data obtained from healthy volunteers and patients in the Phase II study (AK579) has been used to develop a kinetic model to more fully understand the dynamics of the Coversin-complement C5 system in relation to dosing and individual variation between subjects. As briefly described below (and more fully in the IB) the PK/PD modelling analysis supports increasing the fixed initiation and maintenance doses of Coversin to 22.5 mg and 45 mg for treatment of PNH.

At steady state Coversin administered subcutaneously enters the circulation relatively rapidly with free Coversin levels peaking between 1 to 3 hours after administration depending on the dose. The level of free Coversin then declines over 24 hours to C_{min} immediately prior to the next dose. The C_{min} value determines the degree of residual complement inhibition 24 hours after the last dose by determining the proportion of C5 that is bound by Coversin which therefore cannot be activated by the alternative and classical/lectin C5 convertases. For the first 5 PNH patients admitted to AK579 by PK/PD modelling the mean values ± SD for C_{max}, T_{max} and C_{min} were estimated. During the ablating phase C_{max} was 164.5 ± 46.8 µg/L, T_{max}= 0.93 ±0.43h and C_{min}= 87.5 ± 25.3 µg/L. During the initiation phase with a dose of 22.5 mg bid, C_{max} was 138.8 ± 69.2 µg/L, T_{max} = 1.03 ± 0.28h and C_{min}= 87.1 ± 66.0 µg/L. During the maintenance phase at a dose of 45 mg once daily the C_{max} was 160.7 ± 75.6 µg/L, T_{max} = 1.24 ± 0.34h and C_{min} = 65.5 ± 58.4 µg/L.

Coversin has a short half-life when it is not bound to C5, estimated at approximately 1h in man, whereas the half-life of Coversin bound to C5 is estimated to be equivalent to the half-life of unbound C5 which has a reported average of 63 hours in man [Sissons et al, 1977]. When considering the Coversin dosing regimen a critical value is the lowest concentration of free rVA576 that inhibits terminal complement activation by 95%. Both simulation PK/PD modelling and theoretical estimates put this value at 20 µg/L. To maintain control of complement this value must be exceeded at C_{min} i.e. immediately before receiving the next dose. As illustrated in the

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preceding paragraph the dosing regimen proposed for initiation and maintenance dosing exceed 20 µg/L.

A second consideration in selection of dose is to ensure that the concentration of Coversin stays above 20 µg/L even when the drug is not administered at exactly the same time each day. This is more likely to fall below 20 µg/L on maintenance dosing than on initiation dosing. The PK/PD model was used to undertake a simulation to determine the elapsed time from the last QD dose until free C5 exceeds 5% (this is equivalent to terminal complement activity of 5%). For 45 mg QD maintenance dosing the median time is 26.5 hours, with interquartile ranges of 25.5 and 31. The median is preferred to the arithmetic mean because the time from dose until free C5>5%, like many PK-related parameters, is log normally distributed. This on 45 mg QD the majority of patients have a window of a few hours each day in which to dose themselves to maintain complement activity below the limit of quantification (i.e. <8 CH50 U Eq/mL).

A third consideration which has informed our proposed fixed dosing regimen for Phase III is inter-individual variation in subjects' initial C5 concentrations and CH50 values. The PK/PD model was used to simulate 1000 patients. Covariate values for initial C5 concentrations and CH50 values were sampled from log-normal distributions with parameters set to sample estimates calculated from the data observed in patients and healthy volunteers to date. The analyses showed that terminal complement activation is more completely controlled in a higher proportion of patients on 22.5 mg q.12h than15 mg q.12h dosing, and on 45 mg QD than 30 mg QD dosing. For example, the percentage of the simulated patient population with free C5 < 5% of baseline at Coversin trough is 80.7% on 45 mg QD and 58.1% on 30 mg QD.

In the AK579 Phase II trial rVA576 has proven safe and well tolerated at 22.5 mg q.12h and 45 mg QD, and these doses will provide near complete control of terminal complement activation in most patients therefore our proposed fixed dosing regimen for AK585 is 60 mg start dose followed by 30 mg 12h later to ablate complement, then 22.5 mg q.12h for 27 days initiating dose, and 45 mg QD maintenance dosing for the rest of the trial.

Coversin is administered by patients subcutaneously and the proposed dosing regimen as stated above is an initially 60 mg dose followed by 30 mg 12 hours later, then 22.5 mg q.12 hourly up to Day 28 and then 45 mg once daily for the remainder of the study or patients may be switched back to 22.5 mg q.12 hourly if not fully responding. This dosing schedule has been based on the initial data from the Phase Ib (AK577) and Phase II AK579 study and the data from the first five patients and also on the PK modelling data provided above. This dosing schedule has been successfully trialled in 3 patients so far and has been followed by all three patients with no deviations. It was found that the expected doses that had shown an effect in health volunteers did not quite provide the same effect in patients with patients needing slightly higher doses.

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3 TRIAL OBJECTIVES AND ENDPOINTS

3.1 Trial Objectives

The trial objectives of this study are to demonstrate the safety and efficacy of Coversin when given to patients with PNH and known resistance to eculizumab *(Soliris®)*.

1) To assess the safety and tolerability of Coversin for patients between 50 and 100kg (110lb -220lb) body weight when given as a fixed maintenance dose following an initial AD and Initiation Phase.
2) To assess whether this dosage regimen is sufficient to control the signs and symptoms of PNH (see Endpoints).

3.2 Endpoints

Primary Efficacy Endpoint:

- Reduction in serum LDH from baseline to mean of Day 43, 60, 90, 120, 150 and 180

Secondary Efficacy Endpoints:

- Change in LDH from baseline at monthly intervals after Day 28, 60, 90, 120, 150 and 180
- Change in mean Hb: baseline – Day 180
- Change in FACIT score: baseline – Day 28 - Day 180
- Change in EQ-5D-5L QLQ C30 score: baseline – Day 28 - Day 180
- Number of transfusions: baseline to Day 180

Safety Endpoints:

- Frequency, type and relationship of AEs and SAEs to treatment
- Out of range laboratory parameters (hematology and chemistry)
- Vital signs (blood pressure, body temperature and pulse rate)
- ECG abnormalities baseline – Day 180 (A resting pre-dose ECG taken within 7 days of first dose will be compared with ECGs taken 1- 6 hours post-dose and at 180 days of treatment with Coversin)
- Change in weight will be noted baseline and at Day 180
- Injection site reaction and lymph node inspection
- Anti-Coversin antibody production

4 TRIAL POPULATION

The study population will be up to 6 patients above the age of 18 with PNH and known resistance to eculizumab *(Soliris®)*. Patients may be male or non-pregnant females using adequate methods of contraception, if of childbearing potential, who meet the inclusion and exclusion criteria.

4.1 Inclusion criteria

1. Patients with known paroxysmal nocturnal hemoglobinuria (PNH).
2. Aged 18 and above. No upper age limit.
3. LDH ≥1.5 ULN.

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4. Patients must agree to avoid pregnancy and fathering children from the time of screening through the end of safety follow-up. Permitted contraceptive methods that are ≥99% effective in preventing pregnancy should be communicated to trial subjects and their understanding confirmed.
5. Resistance to eculizumab *(Soliris®)* proven by either a recognized C5 polymorphism on genetic screening or complement inhibition on CH50 ELISA of <100% at concentrations of eculizumab *(Soliris®)* in excess of 50µg/mL. Genetic conformation of the polymorphism should be obtained on all patients as soon as practicable but absence of such confirmation will not exclude a patient from starting treatment.
6. The patient has given voluntary written informed consent.
7. Willing to self-inject Coversin daily.
8. Willing to receive appropriate prophylaxis against Neisseria infection by both immunization and continuous or intermittent antibiotics.
9. Willing to avoid prohibited medications for duration of study (see Section 6.4). Tizanidine (if on ciprofloxacin) and eculizumab *(Soliris®)* should be discontinued before Coversin therapy is commenced. Ideally this should be 2 or more weeks before commencing Coversin unless, in the opinion of the Investigator, it would be in the best interests of the patient not to do so.
10. Coversin, in common with other complement inhibitors, has the potential to increase the risk of infection, particularly *Neisseria meningitidis*. However, because these patients may have life threatening disease but currently have no other alternative treatment by virtue of their eculizumab *(Soliris®)* resistance, concurrent conditions such as recent infections requiring treatment with systemic antibiotics, immunodeficiency or recent immunizations with live attenuated vaccines are not absolute exclusions. Investigators should regard these as increased risk factors and act with caution and increased vigilance in such cases. Similarly, low platelet count and neutrophil count, both of which may be associated with their disease, are not absolute exclusions but should be cause for increased caution when instituting Coversin treatment.

4.2 Exclusion Criteria

1. Subjects with body weight <50 kg (110 lb) or >100 kg (220 lb) at screening visit.
2. Pregnancy or breast feeding (females).
3. Known allergy to ticks or severe reaction to arthropod venom (e.g. bee or wasp venom).
4. Unresolved *Neisseria meningitidis* infection. Patients who have positive nasal or throat swabs must be excluded until eradication of the organism by antibiotic treatment has been confirmed by repeat swabbing.
5. Patients who have not received adequate immunization against *Neisseria meningitides*, unless, in the opinion of the Investigator the risks of delaying therapy outweigh the risks of developing a meningococcal infection.
6. Impaired hepatic function (bilirubin > 1.5 x ULN and AST/ALT >2.5 x ULN) unless, in the opinion of the Investigator, the risks of delaying therapy outweigh the risks of treatment in the presence of impaired hepatic function.
7. Patients with a glomerular filtration rate (GFR) of <30 mL/min/1.73m^2 unless, in the opinion of the Investigator, the risks of delaying therapy outweigh the risks of treatment in the presence of impaired renal function.
8. Failure to satisfy the PI of fitness to participate for any other reason.

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4.3 Meningitis Prophylaxis

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

Prophylaxis against *Neisseria sp.* will be at the discretion of the Investigator and according to local practice. Immunizations of any sort are designed to induce an antibody response and this is accompanied by complement activation. Some Investigators have raised concerns that, in the context of PNH, this could lead to a thrombotic event or breakthrough hemolysis particularly with the Bexsero® meningitis B vaccine. For this reason, they prefer to either vaccinate prior to beginning Coversin treatment or delay immunization, until after complement inhibition has been established and to rely on antibiotic prophylaxis instead. In addition, immunization by the Bexsero® meningitis B vaccine may cause side effects in some patients which may be difficult to distinguish from possible Coversin-related AEs.

A suggested regimen is to commence prophylaxis with a 14-day course of oral antibiotics to be followed by indefinite oral Penicillin V (for penicillin allergy an alternative antibiotic prophylaxis may be used consistent with local antimicrobial policy). It is expected that the patient will receive at least 14 days of a suitable antibiotic post first dose of Coversin. Doses will be according to the manufacturers' recommendations.

A dose of the conjugated quadrivalent vaccine against meningitis A, C, W-135 and Y may be given within a week either side of the start of Coversin treatment and, if desired, an initial dose of Bexsero® meningitis B vaccine may be given once the patient is fully stabilized on Coversin therapy or prior to beginning treatment with Coversin. It should not coincide with the switch to once a day dosing at Day 29. A second dose of Bexsero® meningitis B vaccine should then be given between 1 and 2 months later. In countries in which Bexsero® meningitis B vaccine is not yet approved, it may be omitted. This is a suggested regimen.

4.4 Throat and Nasal Swabs

All patients selected for entry into this trial will have throat and nasal swabs taken once they have consented. Any positive *Neisseria sp.* results will be grounds for excluding that patient from the trial and will mandate special vigilance on the part of the Investigator and all medical and nursing staff. Repeat throat and nasal swabs should then be taken at weekly intervals until the organism has been eradicated and prophylactic antibiotic cover should be maintained until at least 14 days after the last dose of Coversin.

4.5 Contraception

There are no specific, identified risks to mother or fetus from 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 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 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 Coversin on body weight, food intake, mating activity,

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fertility and mating, pregnancy or uterine implantation. There were no findings at necropsy considered to be related to 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 reproductive toxicology studies are completed, patients being treated with 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, two approved methods of highly effective contraception from the time of signing the Informed Consent Form (ICF) until 90 days after the last dose of Coversin. Women of child bearing potential are considered those women who have menarche and until becoming post-menopausal unless permanently sterilized. Permanent sterilization 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 at least one barrier method:

- Surgical sterilization (i.e. bilateral tubal removal, bilateral ovary 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 the study, they and their partner should use two of the contraceptive methods listed above. Based on the current available knowledge the effects of Coversin on a fetus are unknown therefore the company recommendation is for any female patient who becomes pregnant patient to be withdrawn from the study or terminate pregnancy, unless in the opinion of the PI, the patient has no other treatment options and is at risk of life-threatening hemolysis if Coversin is discontinued.

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

4.5.1 Exposure to Partners During the Study

There is a risk of drug exposure through ejaculate (which also applies to vasectomized 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 Coversin administration.

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4.5.2 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 Coversin administration.

4.5.3 Egg Donation

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

4.5.4 Breast Feeding

Female patients should not breast feed infants for the duration of the study and for at least 90 days after the last day of Coversin administration.

5 TRIAL DESIGN AND PROCEDURES

5.1 Trial Design

The trial is a 180-day open-label, non-comparative study in up to 6 patients with PNH who have received eculizumab *(Soliris®)* without apparent benefit and in whom it has been demonstrated that their serum is resistant to eculizumab *(Soliris®)* at any concentration but sensitive to Coversin using a CH50 assay. They should also have the presence of a C5 polymorphism confirmed by genetic testing, but treatment need not be delayed until these results are available, since the results of the CH50 spiking assay are sufficiently sensitive to identify patients who are resistant to eculizumab *(Soliris®)*, but sensitive to Coversin and genetic testing may take up to 8 weeks. Patients must also meet the inclusion and exclusion criteria.

Table 8 Treatment Regime

Treatment Dose/Phase	Day	Dose
Ablation	Day 1	60 mg (between 7am -11am)* 30 mg (between 7pm -11pm)*
Initiation	Day 2 – Day 28	22.5 mg (between 7am-11am)* 22.5 mg (between 7pm-11pm)*
Maintenance	Day 29 – Day 180	45 mg (between 7am-11am)*

*Patients to select a set time for dosing (eg., 7am and 7pm) and administer dose within 1 hour either dose of set time(s).

The trial will last 180 days in total for all patients, although the exact length of each phase will be adjusted to ensure that optimal laboratory and clinical support is available during the change from q. 12 hourly to q. 24 hourly dosing.

The dosing regimen is designed to be flat (fixed dose) for all patients between 50 and 100kg (110 lb -220 lb) in weight. The obvious advantage of this is that, since it is intended that patients will self-inject Coversin, it simplifies the drawing up and administration of the drug and reduces the possibility of error. All patients treated under this protocol will be given adequate support to ensure that they are able to draw up and self-administer Coversin accurately and safely.

The alternative, that of individualizing doses to the patient's weight, makes calculating and drawing up doses complicated and subject to error if the patient's weight varies during the course

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of the study, or thereafter for patients who go on to the long-term safety study. On the basis of both human clinical experience in 10 patients and 32 normal volunteer subjects and extensive animal toxicology, Coversin appears to be of low toxicity and therefore it is considered that the risk of administering a relatively higher dose to lower weight patients, that is inherent in a flat dose system, is more than offset by the benefit of a simple, easy to understand, dosing regimen.

At the conclusion of 180 days, patients who have responded well to Coversin and who wish to do so, may enter the long-term safety study. The Sponsor will then continue to supply them with Coversin until such time as it is approved and available in their territory.

The AD and the initiation phase across 28 days cumulatively assists to totally inhibit all circulating complement C5. Once the circulating pool of C5 has been neutralized, subsequent doses are designed to counteract the continued diurnal production of C5 by the liver, macrophages and other sources. It is anticipated that this can be achieved in most patients by a single fixed daily s.c. dose following the first 28 days initiation of therapy. However, in some patients, particularly those with low body fat, absorption from the s.c. space may be unduly rapid resulting in loss by the renal route of excess unbound drug and it may be necessary for this reason to divide the dose into two injections every 12 hours. In some other patients, the rate of production of C5 ('C5 turnover') may be unusually rapid requiring more frequent maintenance dosing (every 12 hours). However, it is predicted that the majority of patients will respond well to once daily maintenance dosing once the initiation phase is complete.

In this trial, all patients between 50 and 100 kg (110 lb -220 lb) will start with a 60 mg AD followed by one dose of 30 mg Coversin 12 hours later (the AD) and then 22.5 mg 12 hourly for 27 days (± 3 days). Response will be gauged by a combination of CH50 assays, serum LDH and clinical assessment (absence of breakthrough events). At Day 29 (the exact day of switching will be adjusted to ensure that laboratory results will be available with minimal delay caused by weekends or holidays) patients will switch to 45 mg 24 hourly. If there is laboratory or clinical evidence of any loss of control, the patient will revert to 22.5 mg 12 hourly. An AD prior to reversion to 22.5 mg 12 hourly will be given.

The fixed dose regimen employed is calculated to suit patients at the heavier end of the admissible weight range (100 kg or 220 lb), so all patients of lower body weight will in fact receive a dose in excess of that which is estimated as sufficient for their weight. To date, Coversin appears to be of low toxicity in non-clinical toxicology studies and in humans, so it is considered that this dose regimen is safe and to have a lower risk of loss of disease control.

In order to mitigate the risk of infection by *Neisseria meningitidis* all subjects or patients taking part in the trial will be carefully instructed about precautions to be taken in case of actual or suspected infection. All patients entering the study must have received or have commenced active immunization against *N. meningitidis* and, in the event that this has been initiated less than 2 weeks from entry into the study, receive suitable bridging antibiotic prophylaxis. For further details of immunization and antibiotic prophylaxis (see Section 4.3).

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5.2 Trial Procedure

The trial consists of an AD, to rapidly inhibit all terminal complement activity (the dosage will always be 60 mg followed by 30 mg 12 hours later), followed by 2 treatment phases:

Table 9 Treatment Phases

Phase	Duration	Purpose	Comments
Initiation Phase (22.5 mg 12 hourly)	Day 2-28 (±3 days)	To establish a s.c. reservoir of Coversin prior to switching to once daily dosing	A 3-day window is permitted after Day 28 in order to avoid switching dose over a weekend
Maintenance Phase (45 mg 24 hourly)	Up to Day 180	To demonstrate full and continuing disease control on the effective dose	Should be 45 mg every 24 hrs for most patients. In the event of an inadequate response patients will revert to 22.5 mg 12 hourly.

Prior to the 60 mg ablation dose in the morning, the site staff should discuss with the patient the most convenient time for them to dose in the morning and evening to suit their lifestyle. Once the time has been confirmed (we propose somewhere between 7am and 11am and 12 hours later between 7pm and 11pm), that timing should be maintained and only a **1 hour window either side will be permitted.** For example, if the patient leaves home in the morning at 8:30am the best time to dose might be 8am in the morning and in the evening again at 8pm, should the dose be missed by an hour or taken an hour earlier that would be acceptable provided the patient fell into their normal routine once again following their next dose.

Patients should self-inject their evening dose on Day 2 and morning dose on Day 3 to allow the clinic staff to correct any errors and guide the patient on technique. Patients may return home after the morning dose on Day 3 or, if preferred, may continue to attend the Investigator's clinic for as long as is considered necessary until they are comfortable with the self-administration technique.

In this trial, the 60 mg dose will be contained in a volume of 2 mL and the 45 mg dose in a volume of 1.5 mL, both of which may be divided between two injection sites for comfort. The 45mg dose can be given as one injection if the patient prefers, provided suitable training has been given. The 22.5 mg dose (0.75 mL) dose can be given as a single s.c. injection.

Ablating Dose Day 1

Initiation of Coversin treatment will be in the Investigator's clinic and will commence with an initial dose of 60 mg followed by a 30 mg dose 12 hours later. During that time, it is suggested that patients remain overnight as either resident in the hospital, a hospital hotel or in suitable accommodation (e.g. a hotel) nearby. Patients may return home after the morning dose on Day 3 or, if preferred, may continue to attend the Investigator's clinic for as long as is considered necessary.

Clinic Blood Draw – Day 1-2

Blood and urine samples will be taken from all patients according to the schedule of events in Table 11. Following baseline sampling, central lab blood draws will be taken post dose at 3hrs, 6hrs, 9hrs, 12hrs and then 18hrs pre-dose. A 30-minute window to draw blood is permitted. A urinalysis test will also be performed at 12hrs.

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What to do if complete inhibition is not achieved?

The AD is calculated to be sufficient to completely inhibit terminal complement activity in all patients. In the unlikely event that this does not occur, genetic testing will be carried out to investigate if this is due to a previously unknown C5 polymorphism that impairs Coversin binding. If the patient turns out to be resistant to Coversin the patient will be withdrawn from the trial and offered alternative treatment by the Investigator.

Initiation Phase Day 2-28 (±3 window except Day 1 – Day 3)

All patients will start on a twice daily dose of 22.5 mg at Day 2.

On Day 2, a pre-dose central lab blood draw will be taken at 24hrs and 36hrs (this timing is relative to the first AD of Coversin received). A 30-minute window to draw blood is permitted. A urinalysis test will also be performed at 24hrs.

On Day 3, a pre-dose central and local lab draw at 48hrs will be taken (this timing is relative to the first AD of Coversin received). A 30-minute window to draw blood is permitted. A urinalysis test will also be performed at 48hrs.

On Day 7 (±3 days), Day 21 (±3 days), Day 29 (±3 days) pre-dose blood samples will be drawn according to the schedule of events, Table 11. A 30-minute window to draw blood is permitted.

Intensive Monitoring clinic Day 14-15 (±3 day window)

An overnight stay is required at Day 14 to perform Intensive PK sampling at timepoints 3hrs, 6hrs, 9hrs, 12hrs, 18hrs pre-dose and 24hrs pre-dose. A 30-minute window to draw blood is permitted.

The clinic visit at Day 29 will ensure pre-dose blood samples are collected for Day 28, completing the blood draw sampling for the initiation phase.

Home Care Nursing – Initiation Phase

Trained home care nurses, supplied by the Sponsor or site, will supervise administration of the dose by the patient to ensure compliance and that the correct self-injection technique is being used (apart from doses given during clinic visits). It is essential that such visits are scheduled to ensure Coversin is administered within the specified time window (i.e. 12 hours ± 1 hour after the previous dose during the Initiation Phase).

Day 3 Evening: Trained nurses supplied by the Sponsor/site will supervise administration of the Day 3 evening dose by the patient to ensure compliance and that the correct self-injection technique is being used.

Day 4-6: The home care nurse will visit the patient's home in the morning and evening.

Day 8-13: Home care nursing will recommence on Day 8 until Day 13. The home care nurse will visit the patient's home in the morning. If evening supervision is required, this can be arranged by the site.

Day 15-20: No home care visits are required unless requested by the patient or Investigator.

Day 22-28: No home care visits are required unless requested by the patient or Investigator.

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Home visits may stop at Day 7 or Day 14 if the Investigator is satisfied that the patient is capable of self-administration following a demonstration by the patient at clinic. If further supervision is required, the home nurses will continue home visits until the time the patient is comfortable with self-administration without supervision and the Investigator has approved no further supervision is required.

The home care nurses will ensure that the injections are being given correctly and sign and date the appropriate patient diary card. Doses of Coversin will be given at the same time each day ±1 hour, preferably between 7am and 11pm in the morning and 12 hours later in the evening (±1 hour), preferably between 7pm and 11pm.

At the appropriate time (Day 8 or Day 15 onwards), daily visits will be replaced by twice a day phone call, text message or a calendar reminder on the patient's phone to remind the patient to take their dose and record the administration time, site of administration and their temperature in the patient diary card.

Patients self-administering Coversin will use suitable sites on the anterior femoral and anterior abdominal regions.

What to do if complete inhibition is not achieved during the Initiation Phase?

Failure to respond adequately during this phase may prompt the Investigator to consider withdrawing the patient from the study (clinical symptoms will be taken into account) and switching him/her to alternative complement inhibitory therapy if available.

Maintenance Phase Day 29-180 (±3 day window)

At Day 29 the patient will attend clinic. All procedures and blood draws will be performed pre-dose as per the schedule of events (Table 11). The patient will then administer their 45 mg once a day dose in clinic.

Intensive Monitoring Clinic Day 36-37 (±3 day window)

If the patient is responding well to once daily dosing, an overnight stay is required at Day 36 to perform Intensive PK sampling at timepoints 3hrs, 6hrs, 9hrs, 12hrs, 18hrs & 24hrs. A 30-minute window to draw blood is permitted.

On Day 43 a clinic visit will take place and a local and central blood draw will be taken.

Central and local Blood draws will be taken at the clinic during the clinic visits on **Day 60, 90, 120, 150 and 180 (±3 day window).**

What to do if complete inhibition is not achieved during the Maintenance Phase

In the event that there is an inadequate response on 45 mg once daily, a further AD should be given and the dose reverted to 22.5 mg 12 hourly. If the response remains or becomes inadequate on that dose, the Investigator may need to consider withdrawing the patient from the study and switching him/her to alternative complement inhibitory therapy if available.

Doses of Coversin will continue to be given at the same time each day, preferably between 7am and 11am and 7pm and 11pm. Patients self-administering Coversin will use suitable sites on the anterior femoral and anterior abdominal regions and the site, date and time of injection, as well as

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body temperature will be entered in the patient diary card as usual and be reviewed and initialed by the supervising nurse at the next clinic visit.

At Day 150, if the patient wishes to continue Coversin treatment and if the Investigator is satisfied as to the suitabilitIt's the y of Coversin treatment, the patient may be transferred to the long-term safety protocol at the end of the study (Day 180).

How to Manage a Hemolytic Episode?

If there is any indication that the patient is experiencing a hemolytic episode, the patient is instructed to contact the site using the emergency numbers provided.

Unscheduled Visits

All patients will return to the hospital clinic to meet with the Investigator at intervals shown on the schedule of events (Table 11). More frequent visits may be necessary at the discretion of the Investigator.

Additional Blood Draws

If the patient experiences an AE, the Investigator will determine whether a safety blood draw is required. If the safety blood draw includes a CH50 analysis that sample will be sent to the central laboratory.

Follow Up Visit – Day 210 (+5 days)

At Day 210 (+5 days), a follow up visit will occur to ensure all outstanding or new AEs are addressed. Patients entering the long-term safety trial are excluded from the follow up visit.

Entering the Long-Term Safety Trial

After 180 days, the patient may enter the long-term safety trial or begin an alternative treatment.

The decision to continue on Coversin after the 180 day treatment period should be made by the patient in consultation with the Investigator at or about the 150 day time point. This allows alternative treatment logistics to be arranged if the patient prefers alternative therapy after study completion.

If the patient and Investigator are satisfied with Coversin treatment the patient may enroll onto the long-term safety trial at Day 181. Coversin will be provided through this mechanism until it is approved and locally reimbursed.

5.3 Procedure for Increase in Frequency of Doses

Evidence from animal PK/PD studies, single and multiple dose studies in normal volunteers and experience in 10 patients suggest that an inadequate response or breakthrough hemolysis is highly unlikely to occur during the AD or Initiation Phase.

On completion of the Initiation Phase, a single 45 mg daily maintenance dose will be given for the remainder of the trial unless, it becomes apparent that full complement inhibition is not being maintained, in which case appropriate dose interval adjustments will be made and the patient will revert back to 22.5 mg twice daily after receiving another AD.

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The maintenance dose can be changed after Day 36 if there is evidence of CH50 > 10 CH50 U Eq/mL, a rise in serum LDH for two consecutive readings of over 0.4 x ULN or a single rise over 0.8 x ULN above the lowest level previously achieved or clinical symptoms. In this case the dose should revert back to 12-hourly dosing (assuming compliance is satisfactory and that the patient has not missed any doses) or consideration should be given to the patient withdrawing from the study.

The schedule for dosing during the Initiation and Maintenance Phases, is as follows:

Table 10 Schedule of Dosing for Initiation & Maintenance Phase

Inadequate Response			
Existing		**Switch to**	
Dose	*Interval*	*Dose*	*Interval*
22.5 mg	12 hourly	Withdraw patient	
45 mg	24 hourly	22.5 mg	12 hourly

In patients with exceptionally low body fat (<16%) it may be difficult for a reservoir effect to be set up, resulting in over-rapid absorption of the dose into the blood stream and loss of any excess Coversin via the kidneys. These patients may benefit from divided dosing (12 hourly) and it is suggested that consideration should be given to dividing the dose into two 12 hourly increments in patients with low body fat who are not responding optimally to 45 mg/day given as a single dose.

Samples for CH50, antibodies and drug level should be processed as shown in the Laboratory Manual and sent to a central laboratory. All other laboratory tests should be done locally in the PI's hospital laboratory. Extra samples for PK/PD may be taken at the discretion of the Investigators during illness or infection.

The patient will continue treatment for 6 months or until it has been decided by the Investigator in consultation with the Sponsor that further Coversin treatment is futile or not in the patient's best interests.

If Coversin therapy is discontinued for any reason, all patients will be followed for a minimum of 30 days. Any patient with an unresolved adverse event at that time will be followed until resolution or until stabilization and when no further improvement is anticipated.

5.4 Missed Doses

A missed dose is defined as a dose not taken within greater than a two-hour time window after the earliest time the patient would normally dose. For example, a patient may normally dose with drug at 8am, but the patient is permitted to dose between 7am and 9am (i.e. +/- 1 hour of usual 8am dosing time) without this being considered a missed dose.

Patient on a twice daily dose of 22.5 mg

a) The patient becomes aware of a missed dose more than 2 hours but less than 6 hours after the earliest time they would normally administer a 22.5 mg dose. The patient should

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immediately contact a research nurse for advice then shortly afterwards take their current 22.5 mg dose and then resume their usual 22.5 mg twice daily dosing schedule. For example, a patient who normally takes their evening 22.5 mg dose at 8pm realizes at 10pm that they forgot to take their dose at the usual time. The patient should dose themselves with 22.5 mg of drug then resume 22.5 mg twice daily dosing at the usual time of their morning dose the next day.

b) The patient becomes aware of a missed dose 6 -12 hours after the earliest time they would normally administer a 22.5 mg dose. The patient should immediately contact a research nurse for advice then shortly afterwards take a 45 mg dose and then resume their usual 22.5 mg twice daily dosing schedule. For example, a patient who normally takes their evening 22.5 mg dose at 8pm each evening realizes at 7am the next day that they forgot to take their dose the night before. The patient should dose themselves with 45 mg of drug then resume 22.5 mg dosing at the usual time that evening.

c) The patient becomes aware that they have missed two or more doses. The patient should immediately contact a research nurse for advice and then shortly afterwards administer an ablating dose of 60 mg followed by a 30 mg dose 12 hours later and then resume their usual 22.5 mg twice daily dosing schedule. If the research nurse cannot be contacted within 60 minutes the patient should not delay further but go ahead and administer the ablating dose of 60 mg followed by a 30 mg dose 12 hours. The patient should then resume their usual dosing schedule of 22.5 mg each morning and evening. For example, a patient realizes at 8am that they have forgotten to take a 22.5 mg dose in both the morning and in the evening the previous day. The patient should dose themselves with 60 mg followed by 30 mg 12h later then resume their 22.5 mg twice daily dosing the next day. In another example, if the patient realized at 9pm that they have forgotten to take their previous two 22.5 mg doses they should dose themselves with 60 mg followed by 30 mg 12h later then resume their 22.5 mg twice daily dosing at their usual time on the evening of the next day. The patient should arrange to see the investigator within the next few days.

Patient on a single daily dose of 45 mg

a) Patient becomes aware of a missed dose more than 2 hours but less than 16 hours after the earliest time they would normally administer a 45 mg dose. The patient should immediately contact a research nurse for advice and then shortly afterwards take a dose of their current dosing schedule (45 mg) and then resume the usual dosing schedule at the specified time. For example, a patient who normally doses themselves at 8am each morning realizes at 10am that they forgot to take their dose at the usual time. The patient should speak to a research nurse for advice and then dose themselves with 45 mg of drug then resume 45 mg dosing at 8am the next day.

b) Patient becomes aware of a missed dose 16 to 24 hours after the earliest time they would normally administer a 45 mg dose. The patient should immediately contact a research nurse for advice and then shortly afterwards administer an ablating dose of 60 mg followed by a 30 mg dose 12 hours later and then resume their usual 45 mg dosing schedule the next day. If the research nurse cannot be contacted within 60 minutes the patient should not delay further but go ahead and administer the ablating dose of 60 mg followed by a 30 mg dose 12 hours later. For example, a patient who normally doses themselves at 8am each morning, realizes at 7am the next day that they forgot to take their once daily 45 mg dose the previous

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day. The patient should dose themselves with 60 mg followed by 30 mg 12h later then resume their 45 mg once daily dose at 8am the next day.

c) Patient becomes aware that they have missed two or more doses. The patient should immediately contact a research nurse for advice and then shortly afterwards administer an ablating dose of 60 mg followed by a 30 mg dose 12 hours later and then resume their usual 45 mg dosing schedule the next day. If the research nurse cannot be contacted within 60 minutes the patient should not delay further but go ahead and administer the ablating dose of 60 mg followed by a 30 mg dose 12 hours. The patient should then resume their usual dosing schedule of 45 mg each morning. For example, a patient realizes they have forgotten to take their once daily 45 mg dose for two days. The patient should dose themselves with 60 mg followed by 30 mg 12h later then resume their 45 mg once daily dose at 8am the next day. The patient should arrange to see their clinician within the next few days.

d) Patient misses two or more doses. The patient should take an immediate ablating dose of 60 mg followed by a 30 mg dose 12 hours later and then resume the usual dosing schedule at their specified times. The patient should inform the research nurse as soon as possible.

The missed dose guidelines are intended to ensure that patients do not inject more than 90 mg in a 24-hour period.

The clinic staff should support the patient to prepare the 60 mg and 30 mg dose over the phone or via a clinic visit.

In all cases the clinic staff may arrange for a blood draw to be taken at 24 hourly intervals after first becoming aware of missed doses to ensure the situation is under control. The sample for PD (CH50) analysis should be taken just prior to the next morning dose of Coversin. As the CH50 results are unlikely to be available for some days the Investigator should be guided by the disease history, clinical signs and measures, including platelet count and LDH to determine next steps.

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 patient should continue in the study.

6 STOPPING RULES AND DISCONTINUATION CRITERIA

6.1 Definition of Inadequate Response

An inadequate response to Coversin treatment is defined as **any** of the following events:

- A persistent rise in CH50 to >10 U Eq/mL at any time after Day 2
- A rise in serum LDH for two consecutive readings of over 0.4 x ULN or a single rise over 0.8 x ULN above the lowest previously achieved. A LDH measurement (unscheduled visit) should be made a couple of days after the first LDH reading of 0.8 x ULN to confirm the result before deciding whether or not to switch the patient to 22.5 mg q.12h.
- Persistent clinical symptoms considered by the clinical investigator to indicate that control of the disease is worsening

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The decision to revert a patient from 45 mg QD dosing back to 22.5 mg q.12 h dosing should be made on the following basis by means of consultation between site clinical investigator and the Sponsor's Medical Director:

- In consultation with the patient, consideration should be given as to whether patient compliance with drug administration (dose, dose technique, dose frequency and dose interval) is satisfactory. Particular consideration should be given as to whether or not a patient has missed one or more recent doses.
- If compliance is considered satisfactory the patient may benefit from a switch to 22.5 mg q.12h dosing and consideration of other factors (described below) should be used to determine whether the patient should switch to 22.5 mg q.12h dosing.
- If compliance is not considered satisfactory the patient should be retrained and re-ablated (60 mg followed by 30 mg 12 hours later) then continue on 45 mg QD dosing. 1-2 weeks after retraining the patient should be brought into the clinic for assessment of CH50, LDH and symptoms. If no improvement is seen the patient should be switched to 22.5 mg q.12h.
- Consideration should be given as to whether or not the rise in CH50, LDH or worsening symptoms may be explained by an ongoing infection or newly arisen comorbidity or a worsening comorbidity.
- If the infection or comorbidity is likely to be acute consider maintaining the 45 mg QD dose until the infection or comorbidity has resolved. Patient should be monitored via unscheduled visits if need be. If CH50, LDH or worsening symptoms do not improve after the infection or comorbidity has resolved patient should be switched to 22.5 mg q.12 h.
- If the infection or comorbidity is likely to be chronic plan a second clinical visit a few days later to assess whether CH50, LDH and symptoms are still elevated before then switching to 22.5 mg q.12h.

All patients reverting to q.12 h. dosing will receive another AD first (60 mg followed by 30 mg 12 hours later). An overnight stay is not required but patients should be trained by hospital staff on how to prepare the 60 mg and 30 mg dose. The patients will also have the instructions in the dosing instructions manual.

Patients who are considered to still have an inadequate clinical response 3 weeks after dividing the 45 mg QD dose to 22.5 mg q.12 h. will be deemed treatment failures and withdrawn from the study. Any patient being withdrawn will have all last visit assessments performed at that time.

Patients who are moved to q.12 h. dosing as a result of a rise in LDH associated with a possible stress event such as long-term infection or comorbidity that eventually resolves may, at the discretion of the PI, and in consultation with the Sponsor's Medical Director, go back onto once a day 45 mg dosing. This change back to 45 mg QD should not take place less than 30 days from the start of the q.12 h. dosing and should only occur if CH50, LDH and symptoms have fallen back to acceptable levels.

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6.2 Events Triggering Consideration of Alteration of the Dose or Dose Interval

In order that patients receive optimal complement inhibition and disease control, it is important that patients who may benefit from a change to 12 hourly dosing, rather than once daily, are identified as early as possible. In all cases a careful assessment of compliance and injection technique should be made with the patient. Assuming adequate drug administration is confirmed, the following event mandates administering an AD and reverting to 12 hourly dosing immediately:

- Clinical evidence of a thrombotic event after Day 29

One or more of the events listed below should prompt suspicion of inadequate control and consideration of reverting to 12 hourly dosing (if in the MP) or withdrawing the patient. In all cases the clinician should take into account the overall clinical status of the patient, whether there is a continuing trend towards improving disease control and whether extrinsic factors (e.g. intercurrent infection) may have precipitated the event. Before deciding to revert to 12 hourly dosing or withdraw the patient, the Investigator should discuss the case with the Clinical Research Organization's (CRO) and the Sponsor's Medical Director. These events are:

- Clinical evidence of intravascular hemolysis (macroscopic hemoglobinuria)
- Whilst no absolute value can be set for this, successful control of PNH should result in a rapid and sustained fall in LDH between Day 1 and Day 28 of treatment. Typically, the fall will be to 50% or less of pre-treatment levels by Day 7 and a maximal reduction is normally seen by Day 28. However, Investigators should be guided by whether the LDH is continuing to fall between Day 1 and Day 28, rather than by absolute values. A rise in LDH of 0.8xULN above the lowest level previously achieved, or two consecutive rises of ≥ 0.4x ULN should be taken as mandating a reversion back to twice a day dosing, assuming that compliance is satisfactory and that the patient has not missed any doses.
- Unexplained rise in LDH for two or more consecutive readings at any time by >40% above the lowest value recorded after commencement of Coversin treatment
- CH50 >10 CH50 U Eq/mL on or after Day 14 providing that the assay has been performed by the Central laboratory

If after changing dosing regimen the patient is still inadequately controlled on the basis of the CH50 result (i.e. CH50 >10 U Eq/mL), the Investigator should discuss with the Sponsor's Medical Director the possible withdrawal of the patient.

6.3 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. All patients will be followed up for 30 days for safety.

If a patient 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.

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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 AE, classified as severe, results in patient withdrawal from the study, the patient will be followed until the AE (or SAE) resolves or stabilizes, and any interventions required to resolve or stabilize the event will be recorded in the electronic case report form (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 study procedures in the opinion of the Investigator (mandatory 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
- Planned or actual pregnancy or breast feeding (females).

If a patient is withdrawn, a decision to recruit an additional patient will be made by the Investigator and Sponsor. Screen failures can be considered for re-screening at the discretion of the Medical Director.

6.4 Termination or Suspension of the Study

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

- Difficulty ensuring the safety of the patients' due to safety concerns (e.g. occurrence of many serious ADRs)
- Achieving the purpose of the study is considered impossible (e.g. inadequate recruitment of patients)

If the study is prematurely terminated or suspended, the Sponsor should promptly inform the Investigators. The Investigator or designee should promptly inform the participating patients 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 have not been improved or International Committee on Harmonisation Good Clinical Practice (ICH GCP) have not been followed.

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If the study is prematurely terminated or suspended, the Investigator or their designee should promptly inform the corresponding Ethics Committee (EC) or IRB, any participating patients, and change the study medication to another appropriate therapy. 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.

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7 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, including the amount of study medication received from the Sponsor, the amount distributed to each patient, and the amount of unused drug returned to the Sponsor or destroyed at Sponsors 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 unused vials and syringes to the clinical unit. 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.

8 COMPLIANCE

Whilst patients are in a hospital setting, medical, pharmacy and nursing/technical staff will be responsible for administering the trial medication. On Days 2 - 3, the patient will be trained on how to self-administer. When patients return home, for the first two weeks compliance will be assured by home care nurses. Nurses will visit twice daily in the morning and evening to supervise the administration of the dose which should be taken every 12 hours. Thereafter, compliance will be the responsibility of the patient who will sign the appropriate entry on the patient diary card to record the location of administration, time and date of each dose. Support via the home care nurses will be provided to the patient following the initial 2 weeks, if requested. All empty Coversin vials should be returned to the clinical unit as an additional compliance check. The site staff are required to review the patient diary card during the clinic visits for any missing data to ensure the diary card is complete, and count the number of vials for administration compliance.

9 INTERIM ANALYSES

A formal interim analysis will not be performed. 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.

10 ASSESSMENT OF PHARMACOKINETICS AND COMPLEMENT ACTIVITY

Blood (5 ml) samples for CH50 assays and Coversin levels will be collected according to the schedule of events. Serum samples will be taken to measure complement activity 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. Samples will be processed in accordance with the Laboratory Manual. All samples will be taken shortly before the next dose (termed pre-dose). In some cases, samples may be taken and retained for later evaluation.

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11 SAFETY REPORTING

11.1 Definitions

11.1.1 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.

11.1.2 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.

11.1.3 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).

11.1.4 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,
- Results in persistent or significant disability/incapacity, or
- 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.

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11.1.5 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).

11.2 Procedures for Recording of Adverse Events

11.2.1 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

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:

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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
Possible 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.

11.2.2 Pre-existing Conditions

For purposes of this Study a pre-existing condition means a diagnose, 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.

11.2.3 Overdose

All overdoses with or without associated symptoms, should be reported as AEs on the appropriate eCRF page. An overdose is defined as dose exceeding the specified dose for each week. If sequelae meeting the criteria for a SAE have occurred in association with the overdose, the case must be reported immediately, within 24 hours. An assessment 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.

11.2.4 Pregnancy

Coversin 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. Based on the current available knowledge the effects of Coversin on a fetus are unknown therefore the company recommendation is for the patient to be withdrawn from the study or terminate pregnancy, unless in the opinion of the PI, the patient has no other treatment options and is at risk of life-threatening hemolysis if Coversin is discontinued. All pregnancies (even if suspected) must be reported on the appropriate eCRF page (Pregnancy form) 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 Pregnancy form has to be updated.

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11.3 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 Investigator's knowledge of the event. Reporting shall be done on the corresponding SAE form, provided to each center during the initiation visit, and sent by fax or e-mail to:

PVP SAE hotline:
Fax: +420 227 204 958
E-mail: safety@akaritx.com

The provided information shall contain as much details regarding the event as actually available. Investigators shall 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 11.2.1. Where applicable, information from relevant hospital records or autopsy reports should be obtained and provided to Akari Therapeutics Plc.

11.4 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 verbal) by any personnel of 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.

11.5 Development Safety Update Reports

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

11.6 Data Safety Monitoring

A Monitor will be assigned by the Sponsor to ensure the data is source data verified. Additionally, the Sponsor's designated Pharmacovigilance Provider (PharmInvent) will hold the safety database, their primary role will be to notify the Sponsor of any safety issues related to Coversin and perform reconciliation between the clinical and safety database. There will be a monthly review by the

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Sponsor's Medical Director(s) to review all clinical data as it becomes available with a view to picking up any possible safety signals including laboratory trends that occur within the range of normal. Based on the available data thus far, there are no obvious safety signals or trends, however close monitoring and evaluation will be carried out.

12 STATISTICS

12.1 Statistical Methods

The statistical approach taken will depend on the number of patients recruited.

If less than 4 patients are recruited, each patient will be analyzed separately and no formal statistical analysis plan will be written. Changes in the primary efficacy outcome during the period baseline to mean of Day 43, 60, 90, 120, 150 and 180 will be analyzed using linear regression using all measurements in the analysis. Secondary efficacy outcomes measured multiple times will be analyzed in an equivalent manner.

If 4 or more patients are recruited, the patients will be analyzed as a single group. Differences between specific time points (e.g. baseline and mean of Day 43, 60, 90, 120, 150 and 180) for the primary and secondary efficacy endpoints will be performed using the paired t-test.

Additionally, the change in the primary efficacy outcome over time will also be examined using all measurements. Mixed model will be used to allow for repeat measurements from the same patients, with the patient considered as a random effect.

12.2 Number of Patients

A total of up to 6 patients may be enrolled under this Protocol.

12.3 Significance Level

All significance tests will be purely descriptive.

12.4 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 site or the laboratory and, if all parties agree, it will be corrected and endorsed by both the Investigator and the Sponsor.

Unused data (e.g. superfluous blood pressure recordings or hematological 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).

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12.5 Deviations from the Statistical Analysis Plan

It is not envisaged that there should be any deviations from the SAP. Any unexpected deviations (e.g. a requirement for a trend analysis not foreseen in planning the trial) will be discussed with regulatory agencies and the rationale for such an analysis will be included in the SAP and Final Study Report.

12.6 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. If there is a difference between this population and all dosed patients (e.g. because a patient decides to withdraw after selection but before the first dose has been administered or because of major Protocol violations such as missed doses) a per Protocol (PP) analysis will also be performed.

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 will be made for all patients reaching that point.

'End of study' will be defined as last patient, last visit (Day 180).

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.

All patients in the study will be included in the safety analysis whether completing the trial according to the Protocol or not. The efficacy analysis will include all measurements made whilst the patient(s) correctly followed the trial protocol.

13 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 Sponsor. 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 IRB, or for inspections by the regulatory authorities. In addition, the site will allow the Sponsor 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 monitor and the site staff.

The Study Monitor will perform 100% source data verification to ensure adequate Quality Control (QC) 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

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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 Monitor during site visits and the entire team will review the database at timed intervals prior to the database lock.

All correspondence (e.g. with the Sponsor, or designee, IRB) 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.

Biological samples may only be stored indefinitely for the purpose of additional research related to this protocol if the patient has given informed consent for additional scientific research (directly related to this protocol). If no informed consent was obtained, samples must be destroyed after the patient has completed all protocol treatment and procedures.

If the patient withdraws consent to participate in this study they may require all previously retained identifiable samples to be destroyed to prevent further analysis.

The patient will be informed about any unforeseen new analyses on retained identifiable material that were not foreseen when the patient consented to participate in the study and a new consent will be requested of the patient. The patient can refuse any new analyses and it will not influence their participation in the study.

Storage of biological samples on site is subject to the site's guidelines. When samples are shipped to another facility (e.g. a central laboratory), they should be stripped from any identifying information and labeled with a code (trial name, patient study number, date and time of collection).

14 QUALITY CONTROL AND QUALITY ASSURANCE

The hospitals/departments taking part in the trial are responsible for maintaining their own SOPs and Quality Assurance (QA) / QC procedures. The Sponsor or their delegate will also implement and maintain QC and QA 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 and 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 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.

14.1 Ethical Conduct of the Study

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

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appropriate patient privacy requirements and the ethical principles outlined in the Declaration of Helsinki.

14.2 Ethical Considerations and EC or IRB Approval

The EC or IRB will safeguard the rights, safety and well-being of patients in the study by reviewing the following documentation; Protocol, ICF, any other written information given to patients, Investigator Brochure, safety updates, annual progress reports (if applicable) and patient recruitment procedures (if applicable) and any significant revisions to these documents.

The EC or IRB will be appropriately constituted in accordance with ICH GCP and local requirements as applicable. The study will commence only after the EC or IRB has given full approval and the Investigator has written approval. Additionally, the clinical trial may not commence until appropriate regulatory agreement has been obtained.

Amendments to the Protocol will be subject to the same requirements as the initial review. The Investigator will submit periodic reports and updates to the EC, as required and will inform the EC or IRB of any reportable AEs.

15 FINANCING, INDEMNITY AND INSURANCE

The Sponsor will have a contract in place with the hospitals/universities and 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, underwritten by AON Limited. A copy of the policy/certificate of insurance will be supplied separately.

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.

16 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 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 reserves the right to delay submission to the journal, until the required deletion of the confidential information from the proposed publication has been removed.

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17 STUDY RECORD RETENTION

The Investigators shall ensure that the documents contained in the Investigator Site File are retained for 25 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, EC or IRB 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.

18 CLINICAL STUDY REPORT

The results of this clinical study must be summarized 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 PI(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.

19 HANDLING OF BLOOD COLLECTION SAMPLES

Samples should be handled according to the instructions provided in the Laboratory Manual.

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21 APPENDIX

21.1 Appendix 1 Laboratory Assessments

Clinical Efficacy Assessments

The primary efficacy endpoint will be obtained from the clinical laboratory test panel for LDH values prior to Coversin administration on Study Days 1 (baseline), 43, 60, 90, 120, 150 and 180.

Secondary endpoints will be evaluated at these time points (above), as well as Day 28 , to support development of the Coversin efficacy profile.

In addition, LDH will also be measured at Days 3, 7, 14, 21 and 36.

Clinical Safety Assessments

This is a mandatory minimum number of visits and procedures. Investigators may choose to see patients more frequently if appropriate and extra samples may be taken if needed.

Quality of Life Questionnaires

The patient will complete the EQ-5D-5L and FACIT at Day 1 (pre-dose, baseline), 7, 14, 21, 29, 36, 43, 60, 90, 120, 150 and 180. The data will be transcribed to the eCRF and subsequently analysed as a secondary efficacy endpoint.

The patient will complete a non-validated questionnaire at Day 29, 90 and 180 to determine whether self-injection by patients with PNH is well-accepted and the support provided sufficient.

Medical History and Present Conditions

A complete medical history will include evaluation (past and present) of the following:

- General
- Heart/cardiovascular
- Chest/respiratory
- Dermatological/skin
- Psychiatric assessment
- Past surgeries
- Substance abuse
- Hematologic/lymphatic
- Urogenital
- Endocrine/metabolic
- Allergies/drug sensitivities

Physical Examination

- General appearance
- Dermatological/skin
- Hematologic/lymphatic
- Heart/cardiovascular
- Respiratory

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- Vein and injection site inspection

Weight & Height

Patients' weights will be recorded at screening, baseline, Day 29 and Day 180. Height will be collected at baseline.

Vital Signs

Blood pressure and pulse rate will be measured in the supine position after the patient has rested comfortably. Body temperature will be recorded using whatever device is routinely used in the Investigator's clinic (e.g. oral, ear etc.). Measurements will be recorded in the patient's eCRF.

Cardiac Safety

Routine ECG should be performed at any time pre-dose within 7 days of the first dose, 1 hour after the first dose and at the conclusion of the study (Day 180). The ECG traces will be reviewed, signed, and dated by a physician and he/she will record on the trace whether the ECG is normal or abnormal and if deemed abnormal, whether the abnormality is clinically significant (CS) or not clinically significant (NCS).

Clinical Laboratory Safety Tests

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.

Hematology Parameters (Local Laboratory Testing)

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

Chemistry Parameters (Local Laboratory Testing)

LDH	Glucose (Random)
Sodium	Alkaline phosphatase
Potassium	Alanine Aminotransferase (ALT)
Bicarbonate	Aspartate 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)	

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Urinalysis Parameters (Local Laboratory Testing)

Leukocytes	Ketones
Protein	Nitrates
Bilirubin	Blood (absolute)
Glucose	hCG (female patients)
pH	Specific gravity

At Discretion of PI Based on Urinalysis Results

Microbiology
Urine Microscopy
Pregnancy testing
Urobilinogen

Fluorescent Aerolysin (FLAER)

Taken at baseline and Day 180.

Pregnancy Test

Pregnancy testing will be conducted at screening for female patients and monthly thereafter. Baseline and Day 180 will be serum samples. The monthly tests will be performed as a urine pregnancy test.

Central Laboratory Testing

LTB4	Anti-Drug Antibody (ADA)
CH50 (PD)	Unbound Coversin level (PK)
Total C5 Levels	LDH Isoenzymes

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Table 11: AK585 Schedule of Events	**60 mg followed by 30 mg 12hrs later**						**22.5 mg twice daily Initiation Phase**											
Evaluation & Procedures	**Screening**	**Day 1 Intense Monitoring (Ablation)** *overnight stay*						**Day 2**		**Day 3**	**Day 7** (±3 days)	**Day 14-15** (±3days) **Intense Monitoring** *overnight stay*							**Day 21** (±3 days)
	Up to -14 days	**Baseline Pre-60mg dose**	**3hrs Post 60mg dose**	**6hrs Post 60mg dose**	**9hrs Post 60mg dose**	**12hrs Pre 30mg dose[a]**	**18hrs Post 30mg dose[b]**	**24hrs Pre-22.5mg dose**	**36hrs Pre-22.5mg dose**	**48hrs Pre-22.5mg dose**	**Pre-22.5mg dose**	**Pre-22.5mg dose**	**3hrs Post-22.5mg dose**	**6hrs Post-22.5mg dose**	**9hrs Post-22.5mg dose**	**12hrs Pre-22.5mg dose[a]**	**18hrs Post-22.5mg dose[b]**	**24hrs Pre-22.5mg dose**	**Pre-22.5mg dose**
Eligibility, ICF & Medical History and demographics	x																		
Physical Examination [1]	x										x	x							x
Nasal & Throat Swabs [2]	x																		
Vital Signs [3] (including height & weight)	x	x						x		x	x	x						x	x
ECG [4]		x	x																
CH50 (PD)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Coversin Drug Level (PK)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Total C5		x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x
Antibodies (ADA)		x									x	x							x
LTB4		x		x		x		x	x		x	x							x
LDH Isoenzymes		x																	
FLAER		x																	
Meningitis prophylaxis [5]	As per site schedule																		
Chemistry including LDH	x	x								x	x	x							x
Hematology	x	x								x	x	x							x
Urinalysis		x				x		x		x	x	x							x
Pregnancy Test Monthly[6]	x	Serum																	
Questionnaire on Self Injection																			
EQ-5D-5L & FACIT		x									x	x							x
Drug Accountability											x	x							x
IMP administration (±1hr)		x				x		x	x	x	x	x				x		x	x
AEs & Concomitant Medications	x	x	x	x		x	x	x	x	x	x	x	x	x		x	x	x	x

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Table 11: AK585 Schedule of Events	**45 mg once daily Maintenance Phase**														
Evaluation & Procedures	**Day 29** (±3 days)	**Day 36-37** (± 3 days) **Intense Monitoring** *overnight stay*							**Day 43** (±3 days)	**Day 60** (±3 days)	**Day 90** (±3 days)	**Day 120** (±3 days)	**Day 150**[d] (±3 days)	**Day 180** (±3 days) **Early Termination**	**Follow up Visit Day 210 (+5 days)**[e]
	Pre-45mg dose	**Pre-45mg dose**	**3hrs Post-45mg dose**	**6hrs Post-45mg dose**	**9hrs Post-45mg dose**	**12hrs Post-45mg dose**	**18hrs Post-45mg dose**	**24hrs Pre-45mg dose**[c]	**Pre-45mg dose**	**Pre-45mg dose**	**Pre-45mg dose**	**Pre-45mg dose**	**Pre-45mg dose**	**Pre-45mg dose**	
Eligibility, ICF & Medical History										X [7]					
Physical Examination [1]	x	x								x	x	x	x	x	x
Nasal & Throat Swabs [2]															
Vital Signs [3] (including height & weight)	x	x						x		x	x	x	x	x	x
ECG [4]											x	x	x	x	
CH50	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Coversin Drug Level (PK)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Total C5	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Antibodies (ADA)	x	x								x		x		x	x
LTB4	x	x							x	x		x		x	x
LDH Isoenzymes											x			x	
FLAER														x	
Meningitis prophylaxis [5]	As per site schedule														
Chemistry	x	x							x	x	x	x	x	x	x
Hematology	x	x							x	x	x	x	x	x	x
Urinalysis	x	x								x	x	x	x	x	x
Pregnancy Test Monthly [6]	x									x	x	x	x	Serum	x
Questionnaire on Self Injection	x										x			x	
EQ-5D-5L & FACIT	x	x							x	x	x	x	x	x	
Drug Accountability	x	x							x	x	x	x	x	x	
IMP administration (±1hr)	x	x				x		x	x	x	x	x	x	x	
AEs & Concomitant Medications	x	x	x	x		x	x	x	x	x	x	x	x	x	x

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[a] These samples are to be taken 12hrs after the first dose in the morning and pre-second dose of Coversin

[b] These samples are to be taken 18hrs post dose referring to the first Coversin dose given the morning before

[c] This sample is to be taken 24hrs after the last Coversin dose and prior to the next 24-hourly dose

[d] Day 150 – Investigator and patient to confirm if patient will continue onto the long-term safety trial or begin alternative treatment. At Day 181, the patient will enter the long-term safety trial on Coversin or begin alternative treatment and not enter the long-term safety trial.

[e] Safety follow up visit is not required if the patient is entering the long-term safety and efficacy trial

(1) Physical Examination – Inclusive of vein assessment and injection site inspection.

(2) Nasal & Throat swabs - Any positive Neisseria sp. results will be grounds for excluding the patient from the trial, and will mandate special vigilance on the part the Investigator and all medical and nursing staff. Repeat throat and nasal swabs should then be taken at weekly intervals until the organism has been eradicated and prophylactic antibiotic cover should be maintained as per standard of care. The patient can then begin the trial.

(3) Vitals – Diastolic and Systolic blood pressure, pulse rate and oral temperature (weight only required at Screening, Baseline (pre-dose Day 1), Day 29 and Day 180 and height is only required at Baseline).

(4) Routine ECG at any time pre-dose within 7 days of the first dose, 1 hour after the first dose and at the conclusion of the study at Day 180. ECG – A pre-dose standard ECG can be done at any time within 7 days of the first dose and between 1 and 6 hours post-dose and at the end of the study.

(5) This Protocol is flexible and permits each site to follow their own standard of care procedures for Meningitis prophylaxis. It is expected that the patient will receive at least 14 days of an appropriate antibiotic post first dose of Coversin and no vaccines are to be given during the change from 12 hourly dosing to 24 hourly dosing.

(6) Serum Pregnancy test will be performed at Baseline and end of treatment Day 180 or early termination. Throughout treatment, monthly urine pregnancy tests will be performed.

(7)

Shipment of samples on a Friday are not permitted therefore a 3-day window is permitted for every visit

All blood draws should be performed immediately prior to the next dose of Coversin, except as noted for the additional PK sampling

21.2 Appendix 2 Memorial Sloan Kettering Cancer Center (MSKCC) Treatment Plan - Single Patient Use

Date: February 12, 2018

To: Roger S. Wilson, MD

IRB/PB

From: Hugo Castro-Malaspina, MD

Adult Bone Marrow Transplant Service - Department of Medicine

Re: Single Patient Use Request- Treatment Plan

The purpose of this memo is to provide a summary of the treatment plan in support of my application to treat a single patient diagnosed with PNH with Coversin.

Coversin will be administered subcutaneously as per the treatment regimen below:

Treatment Phase	Day	Dose
Ablation	Day 1	60 mg (between 7am-11am)* 30 mg (between 7am-11am)*
Initiation	Day 2-Day 28	22.5 mg (between 7am-11am)* 22.5 mg (between 7pm-11pm)*
Maintenance	Day 29-Day 180	45mg (between 7am-11am)*

* Patients to select a set time for dosing (e.g. 7am and 7pm) and administer dose within 1 hour either side of set time(s).

The treatment plan will last 180 days in total, although the exact length of each phase will be adjusted to ensure that optimal laboratory and clinical support is available during the change from q. 12 hourly to q. 24 hourly dosing. At the conclusion of 180 days, if the patient has responded well to Coversin and wishes to do so, they may enter the long-term safety study. The Sponsor will then continue to supply them with Coversin until such time as it is approved and available in their territory.

In this treatment plan, if the patient is between 50 and 100 kg (110 lb - 220 lb), they will start with a 60 mg Coversin dose, followed by one dose of 30 mg 12 hours later (the ablating dose (AD)) and then 22.5 mg 12 hourly for 27 days (± 3 days). Response will be gauged by a combination of CH50 assays, serum LDH and clinical assessments (absence of breakthrough events). At Day 29 (the exact day of switching will be adjusted to ensure that laboratory results will be available with minimal delay caused by weekends or holidays), the patient will switch to 45 mg 24 hourly. If there is laboratory or clinical evidence of any loss of control, the patient may revert to 22.5 mg 12 hourly. An AD (60 mg followed by 30 mg 12 hours later) will be give prior to reversion to 22.5 mg 12 hourly.

The patient on this treatment plan will be admitted to the hospital for a minimum of 4 nights (Day 1 – 3, 14, and 36) for initiation of Coversin treatment, for clinical observation and for blood sampling (PK/PD). Treatment will continue on an out-patient basis and overnight visits will be required at certain time points as per the schedule of events table (Table 1).

At the completion of the Day 60 visit, the patient will be allowed to return home and only return to the treatment center for the subsequent Day 90, 120, 150, 180 and follow-up visits as indicated. As the patient resides in Argentina, drug would be shipped once Compassionate Use approval/ Import License has been obtained in Argentina. The plan is to ship Coversin and all supplemental supplies of Coversin from MSKCC to Cordoba Pharmacy using a courier appointed by Akari Therapeutics. The patient will then receive the drug either via bi-weekly shipments from Cordoba Pharmacy or by collecting their supply from Cordoba Pharmacy. The patient's treating Physician will be responsible to the Argentina FDA equivalent in overseeing the Compassionate Use named patient approval. The patient is scheduled to return home to Argentina from Day 60 onwards, therefore, drug shipment will only be required from Day 60 onwards.

For Coversin doses not administered in clinic, the patient will self-administer Coversin and will be taught how to draw up the appropriate volume of solution for injection and how to inject subcutaneously. They will also be taught how to store Coversin correctly in their fridge.

In order to mitigate the risk of infection by *Neisseria meningitidis*, the subject will be carefully instructed about the necessary precautions which they should take in case of actual or suspected infection. The patient will have received or have commenced active immunisation against *N. meningitidis* and, in the event that this has been initiated less than 2 weeks from entry into the study, receive suitable bridging antibiotic prophylaxis.

STOPPING RULES AND DISCONTINUATION CRITERIA

Definition of Inadequate Response

An inadequate response to Coversin treatment is defined as any of the following events:

- A persistent rise in CH50 to >10 U Eq/mL at any time after Day 2
- A rise in serum LDH for two consecutive readings of over 0.4 x ULN or a single rise over 0.8 x ULN above the lowest previously achieved. A LDH measurement (unscheduled visit) should be made a couple of days after the first LDH reading of 0.8 x ULN to confirm the result before deciding whether or not to switch the patient to 22.5 mg q.12h.

- Persistent clinical symptoms considered by the clinical investigator to indicate that control of the disease is worsening

The decision to revert the patient from 45 mg QD dosing back to 22.5 mg q.12 h dosing should be made on the following basis by means of consultation between site clinical investigator and the Sponsor's Medical Director:

- In consultation with the patient, consideration should be given as to whether patient compliance with drug administration (dose, dose technique, dose frequency and dose interval) is satisfactory. Particular consideration should be given as to whether or not a patient has missed one or more recent doses.
- If compliance is considered satisfactory the patient may benefit from a switch to 22.5 mg q.12h dosing and consideration of other factors (described below) should be used to determine whether the patient should switch to 22.5 mg q.12h dosing.
- If compliance is not considered satisfactory the patient should be retrained and re-ablated (60 mg followed by 30 mg 12 hours later) then continue on 45 mg QD dosing. 1-2 weeks after retraining the patient should be brought into the clinic for assessment of CH50, LDH and symptoms. If no improvement is seen the patient should be switched to 22.5 mg q.12h.
- Consideration should be given as to whether or not the rise in CH50, LDH or worsening symptoms may be explained by an ongoing infection or newly arisen comorbidity or a worsening comorbidity.
- If the infection or comorbidity is likely to be acute consider maintaining the 45 mg QD dose until the infection or comorbidity has resolved. Patient should be monitored via unscheduled visits if need be. If CH50, LDH or worsening symptoms do not improve after the infection or comorbidity has resolved patient should be switched to 22.5 mg q.12 h.
- If the infection or comorbidity is likely to be chronic plan a second clinical visit a few days later to assess whether CH50, LDH and symptoms are still elevated before then switching to 22.5 mg q.12h.

If the patient is to revert to q.12 h. dosing they will receive another AD first (60 mg followed by 30 mg 12 hours later). If the patient still has an inadequate clinical response 3 weeks after dividing the 45 mg QD dose to 22.5 mg q.12 h. they will be deemed a treatment failure and withdrawn from the study.

If the patient is moved to q.12 h. dosing as a result of a rise in LDH associated with a possible stress event such as long-term infection or comorbidity that eventually resolves may, at the discretion of the PI, and in consultation with the Sponsor's Medical Director, go back onto once a day 45 mg dosing. This change back to 45 mg QD should not take place less than 30 days from the start of the q.12 h. dosing and should only occur if CH50, LDH and symptoms have fallen back to acceptable levels.

Events Triggering Consideration of Alteration of the Dose or Dose Interval

The following event mandates administering an AD and reverting to 12 hourly dosing immediately:

- Clinical evidence of a thrombotic event after Day 29

One or more of the events listed below should prompt suspicion of inadequate control and consideration of reverting to 12 hourly dosing or withdrawing the patient. In all cases the clinician should take into account the overall clinical status of the patient, whether there is a continuing trend towards improving disease control and whether extrinsic factors (e.g. intercurrent infection) may have precipitated the event. Before deciding to revert to 12 hourly dosing or withdraw the patient, the Investigator should discuss the case with the Sponsor's Medical Director. These events are:

- Clinical evidence of intravascular hemolysis (macroscopic hemoglobinuria)
- Whilst no absolute value can be set for this, successful control of PNH should result in a rapid and sustained fall in LDH between Day 1 and Day 28 of treatment. Typically, the fall will be to 50% or less of pre-treatment levels by Day 7 and a maximal reduction is normally seen by Day 28. However, Investigators should be guided by whether the LDH is continuing to fall between Day 1 and Day 28, rather than by absolute values. A rise in LDH of 0.8xULN above the lowest level previously achieved, or two consecutive rises of $\geq$ 0.4x ULN should be taken as mandating a reversion back to twice a day dosing, assuming that compliance is satisfactory and that the patient has not missed any doses.
- Unexplained rise in LDH for two or more consecutive readings at any time by >40% above the lowest value recorded after commencement of Coversin treatment
- CH50 >10 CH50 U Eq/mL on or after Day 14 providing that the assay has been performed by the Central laboratory

If after changing dosing regimen the patient is still inadequately controlled on the basis of the CH50 result (i.e. CH50 >10 U Eq/mL), the Investigator should discuss with the Sponsor's Medical Director the possible withdrawal of the patient.

Any SAE will be report to the IRB/PB within 24 hours of occurrence. All Serious Adverse Event (SAE) reports will be sent from the Investigator to Akari Therapeutics via an Akari Therapeutics supplied SAE form after they are reported to the MSK IRB/PB.

Table A-12: AK585 Schedule of Events		60 mg followed by 30 mg 12hrs later						22.5 mg twice daily Initiation Phase											
Evaluation & Procedures	**Screening**	**Day 1 Intense Monitoring (Ablation)** *overnight stay*						**Day 2**		**Day 3**	**Day 7** (± 3 days)	**Day 14-15** (± 3days) **Intense Monitoring** *overnight stay*							**Day 21** (± 3 days)
	Up to -14 days	**Baseline Pre-60mg dose**	**3hrs Post 60mg dose**	**6hrs Post-60mg dose**	**9hrs Post-60mg dose**	**12hrs Pre-30mg dose[a]**	**18hrs Post-30mg dose[b]**	**24hrs Pre-22.5mg dose**	**36hrs Pre-22.5mg dose**	**48hrs Pre-22.5mg dose**	**Pre-22.5mg dose**	**Pre-22.5mg dose**	**3hrs Post-22.5mg dose**	**6hrs Post-22.5mg dose**	**9hrs Post-22.5mg dose**	**12hrs Pre-22.5mg dose[a]**	**18hrs Post-22.5mg dose[b]**	**24hrs Pre-22.5mg dose**	**Pre-22.5mg dose**
Eligibility, ICF & Medical History and demographics	x																		
Physical Examination [1]	x										x	x							x
Nasal & Throat Swabs [2]	x																		
Vital Signs [3] (including height & weight)	x	x						x		x	x	x						x	x
ECG [4]		x	x																
CH50 (PD)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Coversin Drug Level (PK)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Total C5		x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x
Antibodies (ADA)		x									x	x							x
LTB4		x		x		x		x	x		x	x							x
LDH Isoenzymes		x																	
FLAER		x																	
Meningitis prophylaxis [5]	As per site schedule																		
Chemistry including LDH	x	x								x	x	x							x
Hematology	x	x								x	x	x							x
Urinalysis		x				x		x		x	x	x							x
Pregnancy Test Monthly [6]	x	Serum																	
Questionnaire on Self Injection																			
EQ-5D-5L & FACIT		x									x	x							x
Drug Accountability											x	x							x
IMP administration (±1hr)		x				x		x	x	x	x	x				x		x	x
AEs & Concomitant Medications	x	x	x	x		x	x	x	x	x	x	x	x	x		x	x	x	x

Table A-1: AK585 Schedule of Events	**45 mg once daily Maintenance Phase**														
Evaluation & Procedures	**Day 29** (± 3days)	**Day 36-37** (± 3days) **Intense Monitoring** *overnight stay*							**Day 43** (± 3days)	**Day 60** (± 3days)	**Day 90** (±3days)	**Day 120** (±3days)	**Day 150**[d] (±3days)	**Day 180** (±3days) **Early Termination**	**Follow up Visit Day 210 (+5 days)**[e]
	Pre-45mg dose	**Pre-45mg dose**	**3hrs Post-45mg dose**	**6hrs Post-45mg dose**	**9hrs Post-45mg dose**	**12hrs Post-45mg dose**	**18hrs Post-45mg dose**	**24hrs Pre-45mg Dose**[c]	**Pre-45mg dose**	**Pre-45mg dose**	**Pre-45mg dose**	**Pre-45mg dose**	**Pre-45mg dose**	**Pre-45mg dose**	
Eligibility, ICF & Medical History										x [7]					
Physical Examination [1]	x	x								x	x	x	x	x	x
Nasal & Throat Swabs [2]															
Vital Signs [3] (including height & weight)	x	x						x		x	x	x	x	x	x
ECG [4]											x	x	x	x	
CH50	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Coversin Drug Level (PK)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Total C5	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Antibodies (ADA)	x	x								x		x		x	x
LTB4	x	x							x	x		x		x	x
LDH Isoenzymes											x			x	
FLAER														x	
Meningitis prophylaxis [5]	As per site schedule														
Chemistry (including LDH)	x	x							x	x	x	x	x	x	x
Hematology	x	x							x	x	x	x	x	x	x
Urinalysis	x	x								x	x	x	x	x	x
Pregnancy Test Monthly [6]	x									x	x	x	x	Serum	x
Questionnaire on Self Injection	x										x			x	
EQ-5D-5L & FACIT	x	x							x	x	x	x	x	x	
Drug Accountability	x	x							x	x	x	x	x	x	
IMP administration (±1hr)	x	x				x		x	x	x	x	x	x	x	
AEs & Concomitant Medications	x	x	x	x		x	x	x	x	x	x	x	x	x	x

[a] These samples are to be taken 12hrs after the first dose in the morning and pre-second dose of Coversin

[b] These samples are to be taken 18hrs post dose referring to the first Coversin dose given the morning before

[c] This sample is to be taken 24hrs after the last Coversin dose and prior to the next 24-hourly dose

[d] Day 150 – Investigator and patient to confirm if patient will continue onto the long-term safety trial or begin alternative treatment. At Day 181, the patient will enter the long-term safety trial on Coversin or begin alternative treatment and not enter the long-term safety trial.

[e] Safety follow up visit is not required if the patient is entering the long-term safety and efficacy trial.

(1) Physical Examination – Inclusive of vein assessment and injection site inspection.

(2) Nasal & Throat swabs - Any positive Neisseria sp. results will be grounds for excluding the patient from the trial, and will mandate special vigilance on the part the Investigator and all medical and nursing staff. Repeat throat and nasal swabs should then be taken at weekly intervals until the organism has been eradicated and prophylactic antibiotic cover should be maintained as per standard of care. The patient can then begin the trial.

(3) Vitals – Diastolic and Systolic blood pressure, pulse rate and oral temperature (weight only required at Screening, Baseline (pre-dose Day 1), Day 29 and Day 180 and height is only required at Baseline).

(4) Routine ECG at any time pre-dose within 7 days of the first dose, 1 hour after the first dose and at the conclusion of the study at Day 180. ECG – A pre-dose standard ECG can be done at any time within 7 days of the first dose and between 1 and 6 hours post-dose and at the end of the study.

(5) This Protocol is flexible and permits each site to follow their own standard of care procedures for Meningitis prophylaxis. It is expected that the patient will receive at least 14 days of an appropriate antibiotic post first dose of Coversin and no vaccines are to be given during the change from 12 hourly dosing to 24 hourly dosing.

(6) Serum Pregnancy test will be performed at Baseline and end of treatment Day 180 or early termination. Throughout treatment, monthly urine pregnancy tests will be performed.

Shipment of samples on a Friday are not permitted therefore a 3-day window is permitted for every visit

All blood draws should be performed immediately prior to the next dose of Coversin, except as noted for the additional PK sampling