MULTICENTRE STUDY OF NOMACOPAN IN PAEDIATRIC HAEMATOPOIETIC STEM-CELL TRANSPLANT ASSOCIATED THROMBOTIC MICROANGIOPATHY

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LIST OF ABBREVIATIONS

Abbreviation	Definition/Term	Abbreviation	Definition/Term
ADA	Anti-drug Antibody	MedDRA	Medical Dictionary for Regulatory Activities
ADR	Adverse Drug Reaction	MIDD	Model Informed Drug Development
AE	Adverse Event	NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
AESI	Adverse Event of Special Interest	NOAEL	No Observed Adverse Event Level
aHUS	atypical Haemolytic Uraemic Syndrome	NONMEM	Non-linear Mixed Effects Modelling
AUC	Area Under the Curve	OmCI	*Ornithodoros moubata* Complement Inhibitor
CFHRs	Complement Factor H-Related Proteins	PBS	Phosphate Buffered Saline
CRF	Case Report Form	PD	Pharmacodynamics
CRO	Contract Research Organisation	PI	Principal Investigator
ECG	Electrocardiogram	PIS	Patient Information Sheet
ELISA	Enzyme-linked Immunosorbent Assay	PK	Pharmacokinetic
eGFR	estimated Glomerular Filtration Rate	PNH	Paroxysmal Nocturnal Haemoglobinuria
FDA	Food and Drug Administration	PP	Per Protocol
GCP	Good Clinical Practice	PRBC	Packed Red Blood Cells
GI	Gastrointestinal		
GVHD	Graft versus Host Disease	qd	Every day
HLA	Human Leukocyte Antigen	*qs*	*quantum satis* (the amount which is enough)
HSCT	Haematopoietic Stem Cell Transplantation	RBC	Red Blood Cells
HSCT-TMA	Host Stem Cell Transplant Associated Thrombotic Microangiopathy	SAE	Serious Adverse Event
ICF	Informed Consent Form	*sc*	Subcutaneous
ICH	International Conference on Harmonisation	SUSAR	Suspected Unexpected Serious Adverse Reaction
IEC	Independent Ethics Committee	TCA	Terminal Complement Activation
IMP	Investigational Medicinal Product	TEAE	Treatment Emergent Adverse Event
ITT	Intention-to-Treat	TMA	Thrombotic Microangiopathy
iv	Intravenous	TTP	Thrombocytic Thrombocytopaenic Purpura
kDa	kiloDaltons	ULN	Upper Limit of Normal
LDH	Lactate Dehydrogenase	UPCR	Urine Protein Creatinine Ratio
LLN	Lower Limit of Normal	WFI	Water for Injection
LLOQ	Lower Limit of Quantification	WHO	World Health Organisation
LTB4	Leukotriene B4		

PROTOCOL SIGNATURE PAGE

Protocol Title:	Multicentre Study of nomacopan in Paediatric Haematopoietic Stem-Cell Transplant Associated Thrombotic Microangiopathy
Protocol Number:	AK901

Authorised Sponsor Representative Signature:

_____ _____

Signature: Date:

Dr Sanjeev K Khindri, MB, ChB, MRCP
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United Kingdom

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

_____ _____

Signature: Date:

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1 PROTOCOL SYNOPSIS

Name of Sponsor/Company:
Akari Therapeutics Plc

Name of Investigational Product:
nomacopan

Name of Active Ingredient:
nomacopan (rVA576)

Title of Study:
Multicentre Study of nomacopan in Paediatric Haematopoietic Stem-Cell Transplant Associated Thrombotic Microangiopathy

Phase of Development:
Pivotal Phase III

Study Design:
Open-label, multi-centre two-part study.

Part A: dose algorithm, safety and efficacy
To confirm the effective dosing and pharmacodynamic (PD) effect of nomacopan on terminal complement activity ablation in 7 paediatric patients with HSCT-TMA for 24 weeks.

Part B: safety and efficacy
Following dose algorithm confirmation in Part A, up to 65 paediatric HSCT-TMA patients will be enrolled to evaluate the efficacy of nomacopan using a composite primary efficacy endpoint at 4, 8, 12, 16, 20 and 24 weeks (±5 days) to assess if TMA is resolved. Treatment will be discontinued for patients who have achieved the primary endpoint at 4, 8, 12, 16, 20 or 24 weeks (±5 days) but may continue for all patients for longer if requested by the investigator on clinical grounds.

Objectives:

Part A (7 patients aged ≥ 0.5 to < 18 years, in three age range cohorts)

Dose algorithm confirmation:
- To confirm the effective dose of nomacopan for the ablation of terminal complement activity. The data derived from Part A of the trial will be used together with existing data for PK/PD simulation modelling to define an age-based dosing regimen to completely control terminal complement activity in paediatric patients treated with nomacopan in Part B.

Efficacy and Safety Objectives:
- Primary, secondary, safety and exploratory objectives as described under Part B.

Part B (up to 65 patients aged ≥ 0.5 to < 18 years)

Objectives:

Efficacy:
To determine that the age-based dosing regimen defined in Part A can completely control complement activity in paediatric patients treated with nomacopan.

Safety:
To evaluate safety and tolerability of nomacopan

Number of Patients (planned):
7 patients in Part A.
Up to 65 patients in Part B.

Inclusion and Exclusion Criteria

Inclusion:

1. Aged ≥ 0.5 and < 18 years at the time of diagnosis of TMA.
2. Undergone allogeneic or autologous HSCT.
3. TMA diagnosis within a year of their allogeneic or autologous HSCT.
4. Clinical diagnosis of TMA with all of the following diagnostic criteria:
   - elevated plasma sC5b-9 (80% or more of ULN)
   - Urine protein creatinine ratio > 2 mg/mg (demonstrated on two separate morning samples, at least one day apart)
   - elevated LDH (> ULN)
   - thrombocytopaenia (< 50,000 per mm^3)
   - low haemoglobin concentration (< LLN)

   or

   Histological diagnosis of TMA with evidence of complement deposition:
   - Urine protein creatinine ratio > 2 mg/mg (demonstrated on two separate morning samples, at least one day apart), and
   - elevated plasma sC5b-9 (80% or more of ULN)
5. Provision of written informed consent.
6. Provision of informed assent (where appropriate)

Exclusion:

1. Patients weighing less than 5 kg.
2. Patients with a positive direct Coombs' test.
3. Patients who do not receive nomacopan within 21 days of the initial diagnosis of TMA.
4. Patients having an active systemic or organ system bacterial or fungal infection or progressive severe infection (including unresolved or untreated *Neisseria meningitidis* infection and *E. coli* Shiga toxin) at the time of diagnosis of the TMA.
5. Grade 4 Acute GVHD (as per the Glucksberg grading system, see section 18.9).
6. Received eculizumab or any other complement blocker therapy at any time.
7. Known hypersensitivity to the active ingredient or excipients
8. Patients who are pregnant and/or breastfeeding. All females of childbearing potential require a negative pregnancy test at screening.

Study Procedures:
Part A

The ablating dosing regimens (Day 1, two doses, 12 hours apart) will be 1.7 mg/kg/12 hourly (aged ≥ 0.5 to < 2 years), 1.3 mg/kg/12 hourly (aged ≥ 2 to < 9 years) or 1.0 mg/kg/12 hourly (aged ≥ 9 to < 18 years), and the maintenance dosing regimen (Days 2 to Week 24, 12 hours apart) will be 0.30 mg/kg/12 hourly irrespective of age group.

The patients will undergo PK/PD monitoring to assess whether terminal complement activity is fully controlled on the starting dose (*ie* CH50 is below the lower limit of quantification (LLOQ), and unbound nomacopan ≥ 55 ng/mL in serum). If the CH50 is > 10 U Eq/mL and/or unbound nomacopan is < 55 ng/mL at any time from pre-dose on Day 7 onwards once the CH50 results have been received, a single ablating dose (as per age group described above) will be administered followed by an increased maintenance dose of 0.45 mg/kg/12 hourly from 12 hours after the ablating dose to the end of treatment.

If 7 days or more after dose escalation to 0.45 mg/kg/12 hourly, CH50 > 10 U Eq/mL and/or unbound nomacopan is < 55 ng/mL, a final higher maintenance dose escalation is permitted with a single ablating dose (as described above), followed 12 hours later by 0.60 mg/kg every 12 hours until the end of treatment.

The following PK/PD related measures will be assessed for up to 24 weeks (±5 days):
- Terminal complement activity (measured by CH50).
- Unbound nomacopan.
- Soluble C5b9 (sC5b9).
- Total C5.
- C3b.
- Anti-drug antibody (ADA).
- LDH.
- LTB4 (urine).

Efficacy and safety will be assessed for up to 24 weeks at 4, 8, 12, 16, 20 and 24 weeks (± 5 days).

All patients will have a safety follow up 30 days (±5 days) after last dose of nomacopan.

Except in exceptional circumstances, the treatment period with nomacopan within the study protocol will be for no longer than 24 weeks (± 5 days). Patients may come off the drug sooner if the primary endpoint has been met (one or both components) and the treating clinician considers there is no longer a need for continued treatment with nomacopan. Patients who have achieved the primary endpoint and have stopped receiving nomacopan will have no further scheduled visits until their follow-up visit, which would be 30 days after their last dose of nomacopan. All surviving patients who are no longer receiving nomacopan at 24 weeks will also attend the clinical visit at 24 weeks (± 5 days) for a physical examination and assessment of renal function.

The PK/PD data from all 7 patients in Part A, together with existing adult and paediatric data from HSCT-TMA patients treated with nomacopan, will be used to undertake planned compartmental mechanistic simulation modelling, agreed in advance with the FDA, to select the optimal dose regimen for Part B.

Part B

An age-based dosing regimen will be used, defined by analysis of Part A data. It is planned that the starting dose will be effective in all patients, but a single higher dosing regimen (to be determined after Part A) will be available in the unexpected event that CH50 is not < LLOQ and/or free nomacopan is < 55ng/mL at any time from Day 7 onwards.

All Part B patients will have the same efficacy and safety assessments and clinic visits as described above for Part A but with fewer PK/PD measures.

Duration of Treatment:

Part A

A total of 7 patients (three patients in the ≥ 0.5 to < 2 category, and four other patients with at least one aged ≥ 2 to < 9 years, and at least one aged ≥ 9 to < 18 years) will be included in Part A of the trial.

The treatment period for nomacopan will be for no longer than 24 weeks (± 5 days). Patients may come off the drug sooner if the primary endpoint has been met (one or both components) and the treating clinician considers there is no longer a need for continued treatment with nomacopan. All patients will have a safety follow-up 30 days (± 5 days) after the last dose of nomacopan. All surviving patients who are no longer receiving nomacopan at week 24 will attend the clinic for a physical examination and assessment of renal function at 24 weeks (± 5 days). The End of the Study will occur when all surviving patients have attended the long-term follow-up visit at two years after diagnosis of HSCT.

In exceptional circumstances where the investigator requests continuation of nomacopan beyond 24 weeks for clinical reasons, the Sponsor may agree with the investigator to supply nomacopan for an additional 12 week period only. Any patients on nomacopan after week 24 will have safety assessed every 4 weeks while on the drug and will attend a safety follow-up 30 days (± 5 days) after the last dose.

Part B

Following Part A, up to 65 HSCT-TMA paediatric patients (in any age category) will be enrolled in a 24-week study to evaluate efficacy and safety at 4, 8, 12, 16, 20 and 24 weeks (± 5 days).

The treatment period for nomacopan will be for no longer than 24 weeks (± 5 days). Patients may come off the drug sooner if the primary endpoint has been met (one or both components) and the treating clinician considers there is no longer a need for continued treatment with nomacopan. All patients will have a safety follow-up 30 days (± 5 days) after the last dose of nomacopan. All surviving patients who are no longer receiving nomacopan at Week 24 will attend the clinic for a physical examination and assessment of renal function at 24 weeks (± 5 days). The End of the Study will occur when all surviving patients have attended the long-term follow-up visit at two years after diagnosis of HSCT.

Long-term follow-up visits will be performed at one and two years after the HSCT.

In exceptional circumstances where the investigator requests continuation of nomacopan beyond 24 weeks for clinical reasons, the Sponsor may agree with the investigator to supply nomacopan for an additional 12 week period only. Any patients on nomacopan after Week

24 will have safety assessed every 4 weeks while on the drug and will attend a safety follow-up 30 days (± 5 days) after the last dose.

Criteria for Evaluation (Parts A and B):

Primary Endpoint

This is a composite primary endpoint:

- Independent of RBC transfusion† for ≥ 28 days immediately prior to any scheduled clinical visit up to Week 24

or

- Urine protein creatinine ratio ≤ 2 mg/mg maintained over ≥ 28 days immediately prior to any scheduled clinical visit up to Week 24

Secondary Endpoints

Efficacy:

- Percentage of patients who achieve the primary endpoint of urine protein creatinine ratio ≤ 2 mg/mg (the nephrotic threshold) for ≥ 28 days
- Platelet transfusion independence† for ≥ 28 days
- Plasma sC5b-9 ≤ ULN
- Lactate dehydrogenase (LDH) ≤ ULN
- Normalization of haptoglobin

sC5b-9, LDH and haptoglobin will be measured at the last efficacy assessment in the trial before nomacopan treatment is stopped.

†Transfusion independence is defined as no RBC or platelet transfusion attributable to, or required to manage, TMA. Transfusion required for causes other than TMA will not be considered within evaluation of endpoints.

The Sponsor will not make this evaluation. The investigator will decide if a transfusion is required for the management of TMA or is part of the management of other clinical events or part of a site clinical management policy (*eg* haemoglobin maintenance thresholds, infection management).

Safety:

- Safety and tolerability of nomacopan

Statistical Methods & Data Analysis:

Part A will recruit 7 patients, in three age range cohorts. The purpose of Part A is to confirm the effective maintenance dose of nomacopan for ablation of terminal complement activity, which will then be used in Part B.

For Part B it is assumed that the responder rate on nomacopan will be approximately 30% and the minimum acceptable responder rate is 15%. Up to 65 patients will be recruited which gives 79% power to reject the null hypothesis proportion, π_0, of less than 0.15 when the alternative hypothesis proportion, π_1, is 0.3 using an exact binomial test with a 2.5% one-sided significance level.

An interim analysis will be conducted when 40 patients have been recruited into Part B of the study and have either completed 24 weeks of the study or discontinued the study before

24 weeks. In order to stop the study early for demonstration of efficacy, based on an O'Brien-Fleming stopping rule, at an information fraction of 0.62 (40 of 65 patients), the significance level at the interim analysis needs to be 0.0044 (1 sided). To meet this significance level, at least 13 of the 40 patients (32.5%) will need to be responders. If the study is not stopped early, recruitment will continue and the final significance level, after 65 patients, will then need to be 0.024.

Consideration will be given to including Part A patients in the primary overall analysis; this will be discussed with the FDA at the end of Part A.

2 INTRODUCTION

This study will be conducted and completed per study protocol and the guidelines of Good Clinical Practice (GCP). Compliance with this standard provides public assurance that the rights, safety, and wellbeing of trial patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

2.1 OVERVIEW OF THE DISEASE: BACKGROUND OF THROMBOTIC MICROANGIOPATHY, TREATMENT OPTIONS AND UNMET NEED

Thrombotic microangiopathy (TMA) is a pathology that can manifest in a range of conditions and presentations but is generally characterised by clinical presentation of thrombocytopaenia, microangiopathic haemolytic anaemia, and organ injury. Haematopoietic stem cell transplantation (HSCT) is used as a therapy for various autoimmune diseases, inborn errors of metabolism and for some types of cancer. TMA following HSCT is a rare disease with a mortality rate of 33-90% despite treatment[1]. HSCT-TMA manifests with a variety of symptoms which may include thrombocytopaenia, haemolysis, schistocytes in peripheral blood, acute renal failure, mental status change, and involvement of other organs[2]. The process of HSCT involves the intravenous (*iv*) infusion of autologous or allogeneic stem cells to re-establish haematopoietic function in patients whose bone marrow or immune system is damaged, defective, or has been therapeutically ablated.

HSCT-TMA involves arteriolar thrombi associated with intimal swelling and fibrinoid necrosis of the vessel wall with thickening of arterioles and capillaries, endothelial swelling and detachment, and subendothelial accumulation of proteins and cell debris[3]. This results from tissue injury that causes a release of cytokines that damage the microvascular epithelium. Activation and consumption of platelet and coagulation factors lead to thrombosis and fibrin deposition[3]. Microangiopathic haemolytic anaemia and thrombocytopaenia result from damage to red blood cells caused by microthrombi or fibrin strands that obstruct the microcirculation[3]. The kidney is the most commonly affected organ due to the susceptibility of the glomerular circulation to endothelial damage and occlusion[4], but HSCT-TMA can also affect the lung, bowel, heart, and brain[5].

Diagnosis is based on normal coagulation, negative direct Coombs' test result on red blood cells (RBCs), presence of schistocytes, elevated serum lactate dehydrogenase (LDH) levels, concurrent renal or neurological dysfunction unexplained by other mechanisms, progressive anaemia, thrombocytopaenia, and decreased levels of serum haptoglobin[2,5,6]. Jodele *et al*, in a study conducted in children and young adults in 2014, proposed a 2-pronged approach to diagnosis that includes diagnosis by direct renal tissue biopsy and a compilation of clinical and laboratory values including, elevated serum LDH, proteinuria, hypertension, *de novo* thrombocytopaenia, *de novo* anaemia, presence of schistocytes, and concentration of soluble terminal complement complex (sC5b-9)[7]. Risk factors for HSCT-TMA include high-dose chemotherapy, radiation therapy during pre-conditioning, unrelated donor, human leukocyte antigen (HLA) mismatch, exposure to calcineurin inhibitors with or without concomitant exposure to sirolimus, graft-versus-host disease (GVHD), infections, and possibly complement protein polymorphisms[2,3,8-10].

HSCT-TMA is frequently, but not always, associated with terminal complement activation (TCA). Involvement of TCA can be detected by measuring elevated circulating sC5b-9 levels and/or complement product deposition in tissues, including renal tissues, which may be detected by tissue biopsy and immunofluorescence staining. It has been suggested that HSCT-TMA with clear evidence of complement activation, may be effectively treated by complement

inhibition[11]. Eculizumab, a complement component 5 (C5) blocking therapy, is being investigated as a treatment[7,12,13].

As reviewed by Choi *et al*, the prognosis of HSCT-TMA is currently very poor, with reported mortality rates as high as 90% in high-risk patients[1]. There is no approved therapy for HSCT-TMA, and despite current management of the disease which includes withdrawal of calcineurin inhibitors and/or co-therapy with sirolimus, and supportive care, such as dialysis, plasma exchange (PEX), transfusion of platelets and RBCs, and antihypertensive therapy[2,3,5], the mortality rates remain very high. The pathological process of microvascular thrombosis, consumptive thrombocytopaenia and microangiopathic haemolytic anaemia frequently lead to ischaemia and infarction in target organs, particularly the kidney and the brain although cardiac, gastrointestinal (GI), and other organ dysfunction can occur, all of which contribute to the high mortality rate. Mortality estimates from more recent published clinical studies range from 33%[7,14,15] to 90%[13] of patients treated for HSCT-TMA, suggesting that despite current treatment options, a novel therapy option is needed.

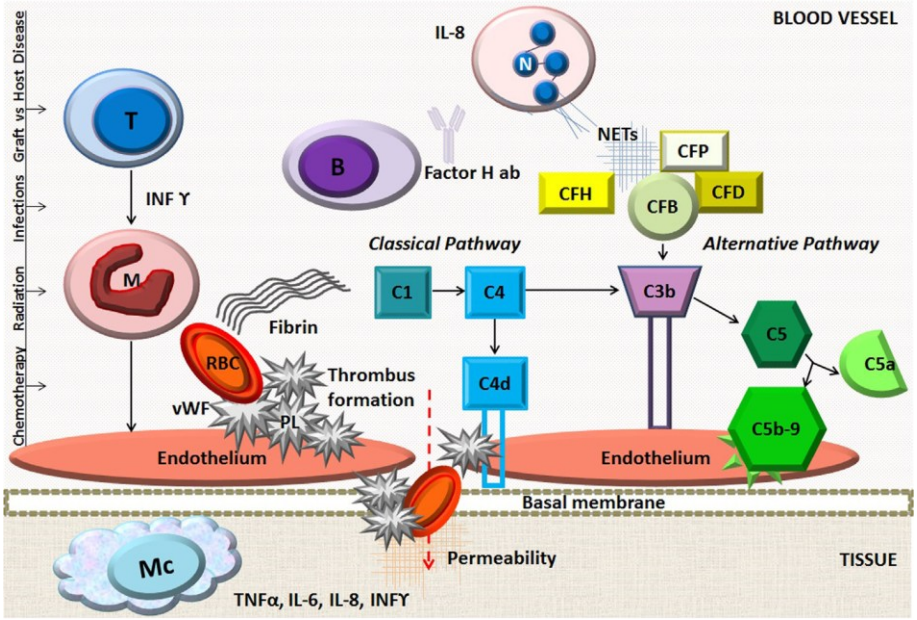
Unlike the complement component C5 blocking therapy eculizumab, nomacopan binds to complement C5 at a different site, though like eculizumab it prevents cleavage of C5 and formation of the active terminal complement products (C5a and C5b9), but nomacopan also binds tightly (K_D 0.2 nM) to the pro-inflammatory mediator leukotriene B4 (LTB4). Further, nomacopan is a small recombinant protein (16.7 kDa) and can be given by low-volume subcutaneous (*sc*) injection instead of *iv* infusion. As such, nomacopan may provide valuable therapy in the treatment of HSCT-TMA, a serious condition.

2.2 NOMACOPAN IN THROMBOTIC MICROANGIOPATHY

Although the exact pathophysiology remains unclear, complement activation or defects in its regulation appear to play a role in TMA following haematopoietic stem cell transplantation since the regulation of complement activation is critical in maintaining endothelial cell integrity[16]. Complement activation, including C4d deposition in tissues, has been demonstrated in the renal arterioles and other organs of patients with HSCT-TMA[17]. Mutations in complement proteins including complement factor H-related proteins (CFHRs) 1 and 3 and auto-antibodies to CFHR that may predispose to development of HSCT-TMA have also been reported in patients[8,9].

The complement cascade has three activation pathways (classical, lectin, and alternative). Activated complement generates three major types of effectors: anaphylatoxins (C3a & C5a), opsonins (C3b, iC3b, & C3d), and the terminal complement complex (C5b-9). There is strong evidence that C5b-9 formation is associated with TMA. Elevated levels of C5a and soluble C5b-9 (sC5b9) have been reported in related TMAs, notably thrombotic thrombocytopaenic purpura (TTP) and atypical haemolytic uremic syndrome (aHUS)[18,19]. Nomacopan inhibits all three complement activation pathways, as it acts after the convergence of the pathways after the formation of C3 convertase. Nomacopan acts by preventing C5 activation thereby preventing formation of the terminal complement complex and the potent anaphylatoxin C5a while preserving the immune clearance and opsonization functions that depend on C3b. Nomacopan also exhibits very tight binding to LTB4 (K_D 0.2 nM), a potent chemoattractant and activator of myeloid cells, particularly, neutrophils. Nomacopan captures LTB4 within an internal binding cavity, which prevents binding of LTB4 to its two G protein-coupled receptors BLT1 and BLT2 and thereby prevents leukocyte activation and recruitment and inhibits inflammation.

Figure 1
HSCT-TMA Pathogenesis



Source: Jodele 2018[20]

The development of HSCT-TMA and the chain of events in the disease pathology are described in Figure 1. C5-inhibiting therapy with eculizumab may be effective in treating HSCT-TMA[7,12,13,21]. Jodele *et al* provide evidence of a role of complement activation in HSCT-TMA from a prospective study of subjects undergoing HSCT who had elevated sC5b-9 (evidence of complement activation) and proteinuria at the time of TMA diagnosis[22]. These patients had a 1-year survival of < 20%, whereas subjects with normal sC5b-9 and no proteinuria had a survival of 100%[22]. Additionally, mutations in genes responsible for complement activation have been identified at a significantly higher rate in stem cell recipients with HSCT-TMA compared to those patients without HSCT-TMA[10]. Because of the association found with complement activation, Jodele *et al* treated six children with severe HSCT-TMA with the complement inhibitor eculizumab and achieved TMA resolution in four patients; the other two critically ill patients were not able to reach therapeutic eculizumab levels and did not survive[7].

LTB4, which is also inhibited by nomacopan, is not known to play a role in the pathology of HSCT-TMA. However, in the context of Figure 1, it is notable that LTB4 can induce expression of IL-8[23], can play a role in thrombus formation[24], and has been shown by Akari to activate endothelial cells *in vitro* leading to deposition of C5b9 when cells are exposed to serum taken from patients with active aHUS (data on file, unpublished).

As such, nomacopan is expected to be efficacious in the treatment of HSCT-TMA, a serious condition with a high mortality whose pathology is driven by complement activation.

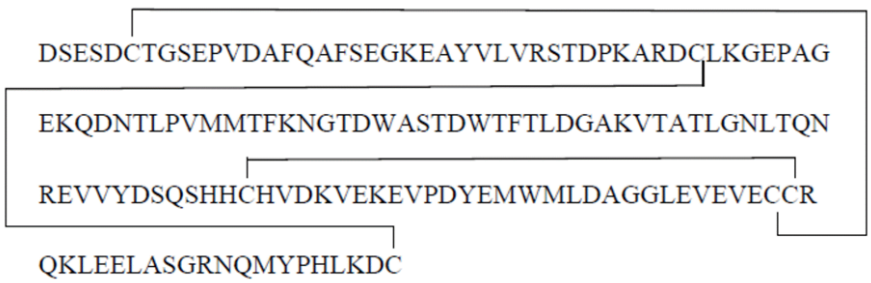
3 PRIOR EXPERIENCE WITH THE INVESTIGATIONAL PRODUCT

3.1 INVESTIGATIONAL PRODUCT

Nomacopan is a small protein molecule derived from a native protein found in the saliva of the *Ornithodoros moubata* tick. Profound complement component 5 (C5) inhibition occurs following nomacopan administration. A surface-active site on the protein binds complement C5 with high affinity (K_D 1.0 x 10^{-9} M by surface plasmon residence)[25] preventing cleavage of C5 by C5 convertase to the active fragments C5a and C5b, and subsequent formation of the terminal complement complex[26]. Nomacopan also exhibits very tight binding to LTB4 (K_D 0.2 nM by fluorescence titration), a potent chemoattractant and activator of myeloid cells, particularly, neutrophils. Nomacopan captures LTB4 within an internal binding cavity, which prevents binding of LTB4 to its two G protein-coupled receptors BLT1 and BLT2 and thereby prevents leukocyte activation and recruitment and inhibits inflammation.

The molecular mass of nomacopan, as predicted by molecular modelling and confirmed by mass spectrometry, is 16.786 kDa. Nomacopan is not glycosylated. The amino acid sequence showing disulphide bridges is shown in Figure 2.

Figure 2
Nomacopan Amino Acid Sequence



Recombinant nomacopan drug product is formulated as a lyophilized powder for reconstitution for subcutaneous (*sc)* injection. The lyophilised formulation is presented in 6 mL Type I glass vials containing lyophilized powder comprised of sodium phosphate buffered saline (PBS) and 18 mg nomacopan per vial with no additional additives, preservatives, or stabilizers. The vials are stored at 2-8ºC. The drug product is reconstituted with 0.6 mL of sterile water for injection (WFI), to create a solution of 30 mg/mL nomacopan in PBS pH 7.2 (Table 1).

Table 1
Recombinant nomacopan Drug Product Formulated as a Lyophilized Powder for Reconstitution for Subcutaneous Injection

Ingredient	Amount per vial (mg)
nomacopan	18
Disodium hydrogen orthophosphate dihydrate	0.45
Sodium dihydrogen orthophosphate dihydrate	1.30
NaCl	4.34
NaOH/HCL to adjust to pH 7.2 ± 0.2	q.s.

q.s. = quantum satis

After reconstitution, the drug will normally be injected immediately. **Only if absolutely needed** the drawn-up syringe may be stored between 2-8ºC for up to 24 hours at pharmacy or in a secure environment and checked for clarity immediately prior to use. The extractable volume from each vial using a standard syringe is ≥ 0.5 mL, permitting administration of 15 mg nomacopan per vial.

3.2 SUMMARY OF RELEVANT NON-CLINICAL AND CLINICAL STUDIES

3.2.1 Non-clinical

There is no animal model of HSCT-TMA in which to test the efficacy of nomacopan. However, complement is believed to have a causative role in exacerbating the pathology of HSCT-TMA shown by means of an association between disease severity and sC5b9 levels[7,11]. Since nomacopan has been shown to treat various diseases driven by complement in both nonclinical and clinical studies it may be an effective therapy for HSCT-TMA.

Similar to eculizumab, nomacopan inhibits all three C activation pathways (classical, alternative, and lectin), as it acts after the convergence of these activation pathways. Nomacopan prevents the generation of C5 activation and formation of the terminal complement complex and the anaphylatoxin C5a while preserving the immune clearance and opsonization functions that depend on C3b. As such it is expected to be efficacious in the treatment of HSCT-TMA, a serious condition with a high mortality whose pathology may be driven by complement activation.

The dose-response relationship of inhibition of TCA by nomacopan when administered to animals has been examined in 3 studies:

1. Nomacopan was administered to C5 sufficient and C5 deficient mice by *iv* bolus and TCA measured by lytic assay[27]. The data showed that in C5 sufficient mice, complement was fully ablated within minutes of *iv* administration and gradually returned to normal levels within 24 hours. In C5 deficient mice, nomacopan is very rapidly cleared from circulation, whereas in the presence of C5, nomacopan has a prolonged half-life due to its tight binding to C5. The half-life of nomacopan bound to C5 was estimated at 30 hours in rats.
2. In a study to investigate complement C5 inhibition (VA002-REP-001), nomacopan was administered by slow *iv* infusion into the jugular vein of Sprague-Dawley rats (6 groups with 2 rats/group) over a 12-hour period at doses of 1, 5, 10, 50, and 500 µg/kg/hour, and serial blood samples were taken from the tail artery. The study demonstrated a dose-response relationship between concentration/kg/hour and inhibition of TCA measured by lytic assay. Approximately 75% inhibition of activity was observed at 5 hours at a dose of 100 mg/kg/hour, and approximately 97% inhibition was observed at 2 hours at 500 µg/kg/hour.
3. In a 28-day toxicology study (S54790), nomacopan was administered to cynomolgus monkeys by daily *sc* injection. The onset and offset of TCA was assessed by CH50 ELISA. The onset of inhibition of TCA was faster in cynomolgus monkeys than in humans where, in monkeys, nomacopan *sc* caused full complement blockade within 1 hour of the first dose of 4.8 mg/kg. The daily 4.8mg/kg dose sustained total complement blockade at trough for 28 days. The lower 0.5 mg/kg dose produced approximately 90% blockade after 4 hours and about 80% inhibition at trough for 28 days.

While not specific to HSCT-TMA, these animal data provide support for the terminal complement inhibitory activity also observed in humans that is believed to be relevant to the pathology of HSCT-TMA.

3.2.2 Clinical

Nomacopan has not yet been studied in patients with HSCT-TMA in a clinical trial.

3.3 PREVIOUS EXPERIENCE IN PATIENTS

Goodship *et al* reported on the first HSCT-TMA patient treated with nomacopan for HSCT-TMA[28]. The 3-year old boy underwent a HLA-matched unrelated HSCT and subsequently developed TMA with microangiopathic haemolytic anaemia and hypertension. He was treated with eculizumab for 10 weekly infusions with no clinical improvement and was later found to be resistant to eculizumab due to an amino acid polymorphism in C5 that reduces eculizumab binding to the complement protein. To determine whether C5 could be blocked by nomacopan, ascending doses of eculizumab and nomacopan were added to patient serum and pooled control serum and TCA was assessed. Nomacopan at 15 µg/mL was found to completely block TCA in both patient and control serum, whereas eculizumab decreased complement activity by a maximum of approximately 75%. Having shown that nomacopan but not eculizumab can fully inhibit C5 activation *in vitro*, the patient was then treated with nomacopan and showed some initial improvement including reduced gastrointestinal bleeding. However, the patient's condition worsened, and he died two weeks after he received his last daily dose of nomacopan. During the 58 days that the patient received nomacopan, there were no adverse events and no injection site reactions. Low titre non-neutralizing anti-nomacopan antibodies were detected after 14 days of treatment.

An additional seven "specials" patients who received nomacopan presented *in extremis*. All 7 of those treated in 2018/2019 had elevated sC5b9 and proteinuria (high risk group) and all presented with TMA more than six months after HSCT, whereas in work undertaken by Jodele *et al* it is evident that when patients are closely monitored for signs and symptoms of TMA the majority of patients (92%) develop TMA within 100 days of transplant, and early diagnosis and treatment of TMA is thought necessary to provide patients with the best chance of survival[22]. However, a small but important number of patients may develop TMA for up to year after HSCT and benefit from treatment. Clinical performance of the first two paediatric HSCT-TMA patients treated with nomacopan was reported at a UK Bone Marrow Transplant meeting. Both patients received nomacopan for 56 days and showed a strong clinical response to treatment indicated by resolution of haemolytic anaemia, thrombocytopaenia, schistocytes and hypertension. One patient made a complete recovery and stopped receiving nomacopan the other died of lung complications considered unrelated to the drug.

3.3.1 Summary of Known and Potential Risks and Benefits to Human Patients

To date (August 2021), nomacopan has been administered by subcutaneous (*sc)* injection or ophthalmic (eye drops) routes to 97 subjects (32 healthy volunteers and 65 patients) - see Table 2. Fifty-six of the subjects are adults in clinical trials, and eight were children who received compassionate use nomacopan under a UK "specials licence".

Nomacopan was administered to 16 healthy male subjects in a Phase Ia single ascending dose study (VA576), 16 healthy male subjects in a Phase Ib 7-day repeat dose study (AK577), one eculizumab-resistant PNH patient in a Phase II study (AK578), eight PNH patients in the Phase II study (AK579), one eculizumab resistant PNH patient in AK585, nine PNH patients in

AK580, nine bullous pemphigoid patients in AK801, and using ophthalmic eye drops six patients with atopic keratoconjunctivitis.

Additionally, nine complex paediatric HSCT-TMA patients with advanced disease were treated with subcutaneous nomacopan using a compassionate use/ "specials" licence or on a named patient basis.

In all these subjects, nomacopan has generally been found to be well tolerated.

Table 2
Total Number of Subjects Exposed to Nomacopan in Clinical Trials & as Named Patients (07 Aug 2021)

Study	Phase	Number of Subjects	Indication/route of admin *sc* = subcutaneous *O* = ophthalmic eye drops
Healthy Volunteers			
VA576	Ia	16	Healthy volunteer, *sc*
VA577	Ib	16	Healthy volunteer, *sc*
Total Volunteers		32	
Patients			
AK578	II	1	PNH, *sc*
AK579	II	8	PNH, *sc*
AK580	III	9	PNH, *sc*
AK585	II	1	PNH (ongoing), *sc*
AK801	II	9	Bullous pemphigoid (ongoing), *sc*
AK701	II	6	Atopic keratoconjunctivitis (ongoing: LSLV complete: CSR being written), *O*
Compassionate use/Specials licence named patients		8	HSCT-TMA pediatric, *sc*
Compassionate use/Investigator-initiated program		23	Covid-19 pneumonia, *sc*
Total Patients		65	
Overall Total		97	

In the Phase Ia trial (VA576) four mild, non-serious AEs were reported in three subjects (two active and one placebo) but a causal relationship to the study drug was not established. There was no dose relationship, and the AEs were mild and self-limiting.

In the Phase Ib trial (VA577), an AE was reported which the investigator considered was not study drug related. This patient was assessed by the investigator as having rhabdomyolysis and stopped treatment after the third dose of nomacopan. The patient also experienced asymptomatic raised creatinine kinase and serum myoglobin levels which the investigator considered were related to the administration of ciprofloxacin as a prophylactic antibiotic during the trial. Twenty-two other non-serious, mild/moderate AEs were reported in this trial in seven patients, all of which resolved without treatment.

In the Phase II trial (AK578) the only PNH subject who was enrolled and completed the study benefited from nomacopan and currently continues therapy on nomacopan twice daily in Study AK581 (15 mg every 12 hours). The drug was generally well-tolerated. Overall, two SAEs occurred within this study. The patient had breakthrough haemolysis (worsening of PNH

symptoms presenting with fatigue and dark urine) on Day 5 of treatment before full control of the disease had been achieved. The investigators considered that this SAE was unrelated to nomacopan. The second SAE was a lung infection in which the patient presented with fever and cough. This SAE was assessed as not related to nomacopan. No other significant findings arose from this study.

Overall, nomacopan was well tolerated in the Phase II AK579 trial. There were no drug related SAEs and few drug related AEs other than mild to moderate injection site reactions. SAEs were reported in two patients. One patient had an SAE of staphylococcal infection, and another patient had SAEs of angina pectoris, lethargy and dyspnoea. All four SAEs resolved during the study and were considered to be not related to nomacopan. The most frequently reported nomacopan-related AEs were injection site reactions (*eg* erythema, pruritis, bruising, pain, swelling, discharge, hypersensitivity, induration, or haematoma), which were reported in six out of the eight patients enrolled.

In the Phase III trial (AK580) in PNH, three patients experienced four SAEs. One patient had two SAEs of cholelithiasis and haemoglobinuria (associated with worsening of PNH). A second patient had an episode of catheter site infection and a third had an episode of viral gastroenteritis. These events were assessed as not being related to nomacopan, and all resolved. One patient had two SAEs of neutropenic sepsis and haemolysis during screening and were not randomised into the study. This study has finished.

Three SAEs were reported in Study AK585 in one patient (002-001) Grade 3 febrile neutropaenia, Grade 3 device-related infection and Grade 3 urinary tract infection. None of these events was assessed as related to nomacopan. All SAEs resolved. The study is ongoing.

In the Phase II trial (AK801) in BP, three patients each had one non-related SAE. One patient had an episode of a localised (knee) infection that had not resolved by the end of study. The other two patients had a single episode of condition (*ie* BP) aggravated with both resolving. This study has finished.

In the Phase II, randomised and placebo controlled trial in SACK (AK701), six patients received nomacopan whilst six received placebo. There were no SAEs. The study has finished.

Patients in the PNH trials AK578, AK579, AK580 and AK585 were eligible to continue treatment with nomacopan within the long-term safety study (AK581). Three of fifteen patients experienced a total of 13 SAEs during the study. One patient experienced an episode of an *E. coli* UTI that was considered possibly related to nomacopan. Based on a history of previous recurrent UTIs that usually resolved with oral antibiotics, the sponsor did not consider this a related event. This patient also had three other SAEs. One patient had two unrelated SAEs whilst the another had six unrelated SAEs. Only one of these events (pulmonary hypertension had not resolved). The study has finished.

In all clinical trials to date nomacopan has been well tolerated and there have been no serious drug-related adverse events, no suspected unexpected serious adverse reactions (SUSARs) and no treatment emergent adverse events other than mild to moderate injection site reactions. These have been of a comparable type and severity to those seen with other subcutaneously administered drugs (*eg* insulin) and are not considered to be drug related. The most frequently reported TEAE is injection site discomfort, erythema, redness or pain.

3.3.2 Summary of Experience with 9 Compassionate Use/Named Patient Paediatric HSCT/TMA Patients

Despite the fact that nomacopan has not been studied to date in patients with HSCT-TMA in a clinical trial, it has been used to treat a paediatric patient in 2013[28] and seven paediatric HSCT-TMA patients in 2018/2019 under a specials license in the United Kingdom.

The ablating and maintenance dose regimens used for treatment of the 7 paediatric HSCT patients in 2018/2019 resulted in a reduction in TCA measured by enzyme-linked immunosorbent assay (ELISA) to < 8 CH50 U Eq/mL, corresponding to > 90% reduction in TCA compared to baseline. The data demonstrate that TCA is quickly controlled by the ablating doses used (within 24 hours) and most patients remain fully controlled on the daily dosing regimen.

Free nomacopan concentrations were also measured. The data show that, with one exception, the ablating and maintenance doses used maintained free nomacopan levels above the calculated concentration required to ensure complete inhibition of TCA.

The 8 "specials" patients who received nomacopan presented *in extremis*. All 7 of those treated in 2018/2019 had elevated sC5b9 and proteinuria (high risk group) and all presented with TMA more than six months after HSCT, whereas in work undertaken by Jodele *et al* it is evident that when patients are closely monitored for signs and symptoms of TMA the majority of patients (92%) develop TMA within 100 days of transplant, and early diagnosis and treatment of TMA is thought necessary to provide patients with the best chance of survival[22]. However, a small but important number of patients may develop TMA for up to year after HSCT and benefit from treatment.

3.3.3 Anti-drug Antibodies

Nomacopan is a xenologous protein with the recombinant protein originally derived from a cDNA encoding a tick salivary protein. In the AK577 healthy volunteer study, ADAs were detected in two of four subjects dosed with nomacopan for 21 days and in none of the subjects dosed with nomacopan for 7 days. The antibodies were of low titre and did not neutralise the complement inhibitory activity of nomacopan. The eculizumab resistant PNH patient who had been receiving nomacopan for more than 21 months in Study AK578 first had detectable ADA at Day 16, which peaked at Day 60 and declined thereafter. All patients (n=8) in AK579 developed detectable ADAs, which were first detectable between Day 14 to Day 90. Again, the antibodies were of low titre and did not neutralise the complement inhibitory activity of nomacopan.

The appearance of ADA does not appear to be associated with an increase in the rate or severity of injection site reactions.

The most compelling data supporting that the human ADA are non-neutralising is that in PNH patients from trials AK578, AK579, AK581 and AK585, over a daily dosing period of years, TCA has been found to be below the lower limit of quantification at all time points after Day 1 of nomacopan dosing. Furthermore, ADA are not associated with a decrease in the concentration of unbound nomacopan in patients.

Experience with nomacopan to date appears similar to patient experience with other parasite derived therapeutic molecules, such as the leech-derived anticoagulant hirudin, where the majority of patients develop detectable ADA which have no effect on the inhibitory function of the protein[29].

3.4 DESCRIPTION OF AND JUSTIFICATION OF ROUTE OF ADMINISTRATION, DOSAGE REGIMEN AND TREATMENT PERIOD

Empirical data from the completed Phase 1 trials AK576 (MAD) and AK577 (SAD), and from the Phase 2/3 PNH trials AK579, AK580 and AK585 indicated that in 50-100 kg adults a fixed subcutaneous (*sc*) ablating dose of 60 mg followed by 30 mg 12 hours later and a fixed *sc* maintenance dose of 22.5 mg twice daily, 30 mg once daily, or 45 mg once daily inhibits systemic TCA measured by CH50 ELISA to less than the assays lower limit of quantification (LLOQ) which is 10 CH50 U Eq/mL.

Pharmacokinetic and pharmacodynamic (PK/PD) data have also been obtained from 7 UK paediatric HSCT-TMA patients treated in 2018/2019 on a named patient basis with daily *sc* administration of nomacopan for durations of between one week to 56 days. Intensive PK/PD measurements of free nomacopan and TCA were taken on Day 1 of dosing and at various intervals thereafter.

Using this data AKARI has developed a mechanistic PK/PD model to describe and understand the dynamics of the nomacopan-complement C5 system following single and multiple *sc* doses in humans. The model uses non-linear mixed effects modelling (NONMEM) methodology and describes the dynamics of free nomacopan concentrations and total TCA in plasma. The model has been used to understand adult dosing in particular the proportion of patients who will have their TCA essentially fully inhibited by the ablating and fixed maintenance *sc* dosing regimens (this is described in the Investigator's Brochure).

Working with the FDA as part of their Model Informed Drug Development (MIDD) programme, the PK/PD model has been refined and extended to evaluate and select age based mg/kg dosing regimens to ablate complement. With the three paediatric age categories defined as: Category 1, ≥ 0.5 to < 2 years; Category 2, ≥ 2 to < 12 years; and Category 3, ≥ 12 to < 18 years. The latest PK/PD model (Run6_023) utilizes data from 31 adults and 7 paediatric HSCT-TMA patients dosed with nomacopan.

The model includes inter-individual variability on clearance rate of nomacopan (CL_{nom}), volume of intravascular compartment for C5 and nomacopan (V_{int}), rate constant for transfer of nomacopan from *sc* injection site to intravascular compartment (Ka), and concentration of free nomacopan in intravascular compartment at which CH50 is reduced to 50% of baseline value (EC50). These are the 4 parameters where inter-individual variability was demonstrated to be the most significant and was quantified during the model-building process. The model also includes a description of the influence of maturation of the estimated glomerular filtration rate (eGFR) on clearance of nomacopan.

Based on the model's outputs, paediatric ablation and maintenance dosing will use *sc* injections of nomacopan twice a day (12 hours apart) to ensure total inhibition of TCA, with the three age categories receiving ablating doses between 1.0 and 1.7 mg/kg, and an initial maintenance dose of 0.30 mg/kg (see Table 3 and text below for details).

As described in more detail below, these dosing regimens are predicted to ablate TCA measured by CH50 ELISA within 18 hours of the first dose of nomacopan and maintain CH50 < 3% of baseline in approximately 99% of patients.

To select age based dosing regimens for Part A of the trial the model was used to simulate a range of ablating doses and maintenance doses in 1000 virtual paediatric patients randomly sampled from the NHANESIII database[30].

The ablating dose predicted to reduce TCA to 3% or less of baseline by 18h in 97.5% of the paediatric patients in each age category was determined (Table 3). Similarly, the 12-hourly maintenance dose predicted to reduce TCA to 3% or less of baseline value in 99% of the paediatric patients at steady state in each age category was selected as the standard starting dose - this turned out to be 0.3 mg/kg in all three age categories (Table 3).

Larger simulations (10000 virtual paediatric patients) were undertaken to identify those few patients whose TCA is not essentially fully inhibited on the starting dose. Further maintenance dose simulations in this subset of patients were undertaken to identify two dose escalations for patients for whom the standard maintenance dosing regimen (0.3 mg/kg) fails to provide sufficient complement inhibition at steady state. With failure to provide sufficent terminal complement inhibition defined as CH50 U Eq/mL ≥ 10 or concentration of free nomacopan < 55µg/L. The simulations suggested maintenance dose escalations to either 0.45 mg/kg or 0.6 mg/kg (the highest permitted 12-hourly dose) should provide near complete control of systemic TCA in almost all patients.

Table 3
Summary of Recommended Paediatric Dosing Regimens

Age Range (Years)	Recommended Ablation Dosing Regimen	Recommended Maintenance Dosing Regimen
≥ 0.5 to < 2	1.7 mg/kg at 0 and 12 h	0.30 mg/kg at 24 h, & every 12 h thereafter
≥ 2 to < 12	1.3 mg/kg at 0 and 12 h	0.30 mg/kg at 24 h, & every 12 h thereafter
≥ 12 to < 18	1.0 mg/kg at 0 and 12 h	0.30 mg/kg at 24 h, & every 12 h thereafter

To simulate PK/PD exposure metrics during maintenance dosing at steady state, 1000 virtual paediatric patients were randomly sampled from the NHANESIII database[30]. Simulations were executed using Run6_023 with inclusion of inter-individual variability for CL_{nom}, V_{int}, Ka and EC50. The Ka value used was that for diseased subjects, since during model refinement Ka was found to be significantly lower in diseased adult and paediatric subjects than in healthy subjects. C5 concentration and CH50 at baseline in each virtual patient were sampled from log-normal distributions with means and standard deviations estimated from the baseline C5 concentration and CH50 from all subjects (n = 38) in the nomacopan PK/PD modelling data file. Steady state values were assured by running the simulation through 21 days of dosing.

All exposure metrics listed in Table 4 are quoted as geometric mean, with exception of T_{max} which is given as median. Values in parentheses give the range from the 5th to 95th percentile of the results from the 1000 virtual patients. The median is preferred to the arithmetic mean because PK-related parameters except T_{max} are log normally distributed.

Table 4 shows that at steady state nomacopan administered subcutaneously enters paediatric patients circulation relatively rapidly with free nomacopan levels peaking ($T_{max,ss}$) about 3.5 hour after administration depending on the age category. Once it has entered the circulation, free nomacopan has a short half-life when it is not bound to C5 (estimated at less than 30 minutes in man), the level of free nomacopan then declines to C_{min} immediately prior to the next dose. The relatively prolonged action of the drug is due to the gradual entry of nomacopan from the sc site of administration into the circulation.

When considering nomacopan dosing regimens, a critical value is the lowest concentration of free nomacopan that ensures that C5 that is essentially completely bound by nomacopan which therefore cannot be activated by the alternative and classical/lectin complement C5 convertases. This threshold concentration of free nomacopan that inhibits TCA by 95% is estimated at a

geometric mean of 12.1µg/L in both adults and pediatrics. To maintain control of TCA by 95% or more (free C5 less than 5% of baseline at trough) this threshold value must be exceeded at C_{min} *ie* immediately before receiving the next dose. Table 4 (last row) shows that the majority (> 97.9%) of both adult and paediatric patients exceed the threshold.

Thus at the recommended dosing for adult and paediatric patients, at steady state nomacopan 0.3 mg/kg should provide full control of TCA in paediatric patients.

A second consideration in selection of dose is to ensure that the concentration of nomacopan stays above the threshold that inhibits TCA by 95% even when the drug is not administered at exactly the same time each day. As shown in Table 4 in paediatric patients at steady state the median time until free C5 exceeds 5% (equivalent to TCA of 5%) is between 51 and 57 hours (age dependent) in pediatrics with 5th to 95th centile range of 28 to 116 hours. Thus, on the recommended doses most patients have a window of at least 3 hours each day in which to dose themselves to maintain essentially complete control of complement activity.

Table 4
Paediatric PKPD Exposure Metrics

Paediatric PKPD exposure metrics, drug concentration thresholds for inhibition, duration of action and proportion of population expected to have TCA inhibited by more than 95% for three age cohorts dosed with age specific ablating doses and a fixed maintenance dose of 0.3mg/kg

	Age Category 1 (≥ 0.5 to < 2 years) Ablating 1.7 mg/kg	**Age Category 2** (≥ 2 to < 9 years) Ablating 1.3 mg/kg	**Age Category 3** (≥ 9 to < 18 years) Ablating 1.0 mg/kg
Free nomacopan Cmax,ss [µg/L]	166.3 (81.1 - 350.2)	152.7 (71.3 - 310.4)	152.6 (72.9 - 325.3)
Free nomacopan Tmax,ss [h]	3.4 (3.2 - 3.7)	3.3 (3.1 - 3.6)	3.3 (3.1 - 3.5)
Free nomacopan Cmin,ss [µg/L]	119.7 (56.2 - 256.4)	109.3 (48.9 - 229.8)	112.7 (52.6 - 243.4)
Threshold of free nomacopan that inhibits C5 by 95% (at steady state) [µg/L]	12.11 (12.00 - 12.22)	12.12 (12.01 - 12.20)	12.13 (12.03 - 12.21)
Elapsed time after dose administration until free C5 concentration exceeds 5% of baseline value [h]	51.3 (28.9 - 98.5)	51.6 (27.6 - 97.3)	57.3 (31.4 - 115.6)
Simulated percent of patient population with free C5 < 5% of baseline at steady state trough [%]	100.0	100.0	100.0

Once daily repeat dose toxicology studies in mice (1, 3 and 6 months) and NHP (1 month) have been performed using doses of up to 6.5 mg/kg (mouse, 6 months) and 4.8mg/kg (NHP, 1 month). On a weight basis, this is 22 times (mice) and 16 times (NHP) more nomacopan as a single dose than the starting paediatric maintenance dose of 0.3mg/kg. To determine actual exposure to nomacopan, empirical data on free drug levels and TCA in the NHP dosed at 4.8 mg/kg qd for 28 days was used re-parameterise the human PK/PD model for nomacopan permitting an estimate of free nomacopan C_{max}, and C_{min}. Comparison of these values with the same values derived from paediatric patients under the dosing regimen proposed for AK580 showed that C_{max} of free nomacopan is similar (circa 1.6 times higher in NHP than paediatric patients), and thus the 1 month toxicology findings in non-human primates provide a valid reference for anticipated safety paediatric patients (Table 5).

Table 5
Safety Factor Calculation - maintenance dosing

PK Parameter	Non-Human Primate*	Paediatric Human	Minimum Safety Factor
$C_{max,ss}$ [µg/L]	267.4 (236.0 - 302.5)	152.6 - 166.3 (71.3 - 350.2)	1.61
$C_{min, ss}$ [µg/L]	49.6 (38.3 - 61.5)	109.3 – 119.7 (48.9 – 256.4)	0.41

**NHP predictions made with an earlier version of PKPD model*

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. However, Akari recognise that this exposure data is important and have undertaken a study in the same strain of mice as used for the long-term mouse toxicology studies to evaluate PKPD. The expectation from these studies is that mice dosed *sc* 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 nomacopan by mice. When they have been processed, these data will be presented in the Investigator's Brochure.

The duration of dosing with nomacopan in the paediatric HSCT-TMA study is expected to be no longer than the longest repeat dose toxicology study in mice (6 months). In man, 9 PNH patients have been chronically dosed with nomacopan for more than 2 years each and the drug has been safe and well tolerated. HSCT-TMA patients will be dosed with the drug until the treating clinician considers there is no further need for treatment with nomacopan or for up to a maximum 24 weeks. In studies with eculizumab for treatment of HSCT-TMA, if patients resolve the clinical symptoms of TMA they usually do so within 2 - 4 months of starting treatment.

4 TRIAL OBJECTIVES AND ENDPOINTS

4.1 TRIAL OBJECTIVES

Part A (7 patients aged ≥ 0.5 to < 18 years, in three age range cohorts)

Dose algorithm confirmation:

- To confirm the effective dose of nomacopan for ablation of TCA. The data derived from Part A of the trial will be used together with existing data for PK/PD simulation modelling to define an age-based dosing regimen to completely control complement activity in paediatric patients treated with nomacopan in Part B.

Efficacy:

- Primary, secondary, safety and exploratory objectives as described under Part B.

Part B (up to 65 patients aged ≥ 0.5 to < 18 years)

Objectives:

Efficacy:
- To determine that the age-based dosing regimen defined in Part A can completely control complement activity in paediatric patients treated with nomacopan.

Safety:
- To evaluate safety and tolerability of nomacopan

4.2 ENDPOINTS (PARTS A AND B)

4.2.1 Composite Primary Endpoint

- RBC transfusion independence† for ≥ 28 days immediately prior to any scheduled clinical visit up to Week 24
  or
- Urine protein creatinine ratio ≤ 2 mg/mg for ≥ 28 days immediately prior to any scheduled clinical visit up to Week 24

4.2.2 Secondary Endpoints (Efficacy)

- Percentage of patients who achieve the primary endpoint of urine protein creatinine ratio ≤ 2 mg/mg (the nephrotic threshold) for ≥ 28 days
- Platelet transfusion independence† for ≥ 28 days.
- Plasma sC5b-9 ≤ ULN
- Lactate dehydrogenase (LDH) ≤ULN
- Normalization of haptoglobin

The sC5b-9, LDH and haptoglobin will be measured at the last efficacy assessment in the trial before nomacopan treatment is stopped.

†Transfusion independence is defined as no RBC or platelet transfusion attributable to, or required to manage, TMA. Transfusion required for causes other than TMA will not be considered within evaluation of endpoints.

4.2.3 Safety Endpoints

- Safety and tolerability of nomacopan

4.2.4 Exploratory Endpoints

- Overall survival at Week 24 after the first dose of nomacopan, and at one year and two years after HSCT.
- To evaluate the percentage of patients with urine protein creatinine ratio ≤ 1.5 mg/mg for ≥ 28 days.
- To evaluate the percentage of patients with urine protein creatinine ratio ≤ 1 mg/mg for ≥ 28 days.

- Renal function monitoring (urea, serum creatinine, urine protein creatinine ratio, proteinuria < 30 mg/dL, and eGFR) at baseline and at one year and two years after HSCT.

5 TRIAL POPULATION

This is a study in paediatric patients who have undergone allogeneic or autologous HSCT and develop HSCT-TMA within 1 year of HSCT diagnosed using an adapted version of the diagnostic criteria of the Bone Marrow Transplant Clinical Trials Network and International Working Group[6].

5.1 INCLUSION CRITERIA

1. Aged ≥ 0.5 and < 18 years at the time of diagnosis of TMA.
2. Undergone allogeneic or autologous HSCT.
3. TMA diagnosis within a year of their allogeneic or autologous HSCT.
4. Clinical diagnosis of TMA with all of the following diagnostic criteria:
   - elevated plasma sC5b-9 (80% or more of ULN)
   - Urine protein creatinine ratio > 2 mg/mg (demonstrated on two separate morning samples, at least one day apart)
   - elevated LDH (> ULN)
   - thrombocytopaenia (< 50,000 per mm^3)
   - low haemoglobin concentration (< LLN)

   or

   Histological diagnosis of TMA with evidence of complement deposition:
   - Urine protein creatinine ratio > 2 mg/mg (demonstrated on two separate morning samples, at least one day apart), and
   - elevated plasma sC5b-9 (80% or more of ULN)
5. Provision of written informed consent.
6. Provision of informed assent (where appropriate).

5.2 EXCLUSION CRITERIA

1. Patients weighing less than 5 kg.
2. Patients with a positive direct Coombs' test.
3. Patients who do not receive nomacopan within 21 days of the initial diagnosis of TMA.
4. Patients having an active systemic or organ system bacterial or fungal infection or progressive severe infection (including unresolved or untreated Neisseria meningitidis infection and *E. coli* Shiga toxin) at the time of diagnosis of the TMA.
5. Grade 4 Acute GVHD (as per the Glucksberg grading system, see section 18.9).
6. Received eculizumab or any other complement blocker therapy at any time.
7. Known hypersensitivity to the active ingredient or excipients.
8. Patients who are pregnant and/or breastfeeding. All females of childbearing potential require a negative pregnancy test at screening.

5.3 CONCOMITANT THERAPY

At screening, the PI will ask the patient about any medication that are currently ongoing. During the course of the study the PI should discuss medications at each visit. All concomitant

medications, including herbal and vitamin supplements, must be recorded into the electronic case report form (eCRF). Diary cards will be provided for patients on nomacopan not being treated in hospital.

In addition, the use of immunosuppressant compounds administered since the diagnosis of TMA up to the baseline visit (even if they are not currently prescribed) will be recorded.

5.3.1 Prohibited Medications

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

- *eculizumab (Soliris®), ravulizumab (Ultomiris®) or any other investigational drug that acts directly on the complement system*
- *Chemotherapeutic agents (not including methotrexate – see permitted medicines below)*
- *Therapeutic Plasma Exchange*
- *rituximab or any other CD20 blocking agent*

Permitted medications: *Prophylaxis for GVHD that is standard of care. This includes: methotrexate, mycophenolate mofetil, corticosteroids and calcineurin inhibitors (ciclosporin, tacrolimus, sirolimus)*

If any patient has been found to have taken any of these prohibited medications during this trial, they should be withdrawn immediately, treatment with nomacopan stopped, and a follow-up visit performed 30 days after receiving the last dose of nomacopan. Withdrawn patients will not be replaced.

5.4 MENINGITIS PROPHYLAXIS

It is known that TCA is important in protection against infection by gram negative bacteria especially *Neisseria*[31]. Patients taking part in previous trials (in adults) of complement C5 inhibitors were found to be at greater risk of *Neisseria* infection, particularly meningococcal infection[32], and prophylactic treatment is now usual when complement C5 inhibitors are used.

All patients in the study must therefore receive antimicrobial therapy appropriate for *N meningitidis* prophylaxis. This should be commenced, at the latest, on the day of first study drug administration and be continued for 7 days after the last dose of nomacopan.

In this study, patients will have received or be receiving immunosuppression therapy, and *N. meningitidis* immunisation should only be used when the investigator evaluates that immune function would be adequate for immunisation to be effective, with a positive risk benefit ratio.

If required in the investigator's judgement, it is suggested that an initial dose of a quadrivalent meningitis vaccine and/or Bexsero® vaccine may be given once the patient is fully stabilised on nomacopan therapy. 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/available, it may be omitted.

5.5 CONTRACEPTION

There are no specific, identified risks to mother or foetus from nomacopan 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 nomacopan 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 nomacopan 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 nomacopan on body weight, food intake, mating activity, fertility and mating, pregnancy or uterine implantation. There were no findings at necropsy considered to be related to nomacopan and group mean ovary and testes weights for animals given the test item were similar to controls. Until the reproductive toxicology studies are completed, patients being treated with nomacopan 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 nomacopan. Females of child-bearing potential are considered those who have had menarche.
Two or more of the following methods are acceptable and must include at least one barrier method:

- 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. Any female patient who becomes pregnant during the course of the trial will be withdrawn from the trial.

5.5.1 Exposure of Partners During the Study

There is a risk of drug exposure through ejaculate 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 nomacopan administration.

5.5.2 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 nomacopan administration.

6 TRIAL DESIGN AND PROCEDURES

6.1 TRIAL DESIGN

This is an open-label, multi-centre, two-part study.

Part A: dose algorithm, safety and efficacy
To confirm the effective paediatric dosing, by measuring the pharmacokinetic (PK) and pharmacodynamic (PD) effect of nomacopan (drug levels, complete inhibition of TCA and control of sC5b-9 levels) and clinical safety in 7 paediatric patients with HSCT-TMA for 24 weeks.

Part B: safety and efficacy
Following dose algorithm confirmation after Part A, up to 65 HSCT-TMA patients will be enrolled in a 24 weeks study to evaluate the efficacy and safety of nomacopan at 4, 8, 12, 16, 20 and 24 weeks (± 5 days).

6.2 DOSING SCHEME

Nomacopan is provided as an 18 mg/vial powder for solution for injection. The product will be administered *sc* twice daily. Indwelling *sc* catheter systems may be used for administration if preferred to individual injections.

The child's weight taken at Day 1 will determine the dose calculations for the study. For children in the youngest two cohorts (≥ 0.5 to < 2 years, and ≥ 2 to < 9 years), the dose will be re-calculated at the **week 8** and **week 16** visits using the child's new weight measured at that visit.

Part A

The following starting dosing regimens (Table 6) will be used for patients in Part A, dependent on age category:

Table 6
Starting Dose for Patients in Part A

Age Category	Ablating Dose Day 1; two doses 12 hours apart	Maintenance Dose Day 2 to End of Treatment; 12 hours apart
≥ 0.5 to < 2 years	1.7 mg/kg	0.30 mg/kg
≥ 2 to < 9 years	1.3 mg/kg	0.30 mg/kg
≥ 9 to < 18 years	1.0 mg/kg	0.30 mg/kg

The dosing regimens shown above are predicted to ablate TCA (measured by CH50 ELISA) within 18 hours of the first dose of nomacopan and maintain CH50 < 3% of baseline in approximately 99% of patients.

The patients will undergo PK/PD monitoring to assess whether TCA is fully controlled on the starting dose (*ie* CH50 is below LLOQ, and unbound nomacopan ≥ 55 ng/mL in serum).

The predicted maintenance dose for all three age groups is 0.30 mg/kg, and it is anticipated that this dose will normally fully inhibit TCA.

Dose Escalation

If required, the dose will be escalated if, at pre-dose on Day 7 or after, provided the CH50 results have been received, CH50 > 10 U Eq/mL and/or unbound nomacopan in serum is < 55 ng/mL. Dose escalation will consist of a **single ablating dose**, followed by a higher 0.45

mg/kg 12 hourly dose (for all age categories) **starting from 12 hours after the ablating dose** (Table 7).

Table 7
Initial Dose Increase for Part A

Age Category	Ablating Dose	Maintenance Dose
	Day 1 of change to higher dosing; one dose then maintenance	12 hours after ablating dose until End of Treatment; 12 hours apart
≥ 0.5 to < 2 years	1.7 mg/kg	0.45 mg/kg
≥ 2 to < 9 years	1.3 mg/kg	0.45 mg/kg
≥ 9 to < 18 years	1.0 mg/kg	0.45 mg/kg

If 7 days or more after dose escalation to 0.45 mg/kg, pre-dose CH50 > 10 U Eq/mL and/or unbound nomacopan in serum is < 55 ng/mL, a final higher dose escalation to 0.60 mg/kg is permitted (Table 8). Dose escalation will consist of a **single ablating dose**, followed by a higher 0.6 mg/kg 12-hourly dose (for all age categories) **starting from 12 hours after the ablating dose**.

Table 8
Second Dose Increase for Part A

Age Category	Ablating Dose	Maintenance Dose
	Day 1 of change to higher dosing; one dose then maintenance	12 hours after ablating dose until End of Treatment; 12 hours apart
≥ 0.5 to < 2 years	1.7 mg/kg	0.60 mg/kg
≥ 2 to < 9 years	1.3 mg/kg	0.60 mg/kg
≥ 9 to < 18 years	1.0 mg/kg	0.60 mg/kg

In the exceptional situation that the unbound nomacopan in serum is < 30 ng/mL on the starting maintenance dose (0.3 mg/kg), the investigator and Sponsor may agree to escalation of the dose from 0.3 mg/kg straight to 0.6 mg/kg (bypassing the 0.45 mg/kg) which is the highest permitted maintenance dose.

Dose assessments with changing weight measurements

For children in the youngest two cohorts (≥ 0.5 to < 2 years, and ≥ 2 to < 9 years), the dose will be re-calculated at the **week 8** and **week 16** visits using the child's new weight measured at that visit. The new adjusted dose should be given after all study procedures have been performed. This new adjusted dose will **not** require an ablating dose.

Part B

All patients in Part B will receive an ablating dose of nomacopan on Day 1 and then receive the dosing regimen defined following Part A of the study. It is planned that the starting dose will be effective in all patients, but a single higher dosing regimen (to be determined after Part A) will be available in the unexpected event that CH50 is not < LLOQ and/or free nomacopan is <55 ng/mL at any time from Day 7 onwards.

6.3 BLOOD SAMPLE VOLUMES FOR PAEDIATRIC PATIENTS

The volume of blood taken from patients in this study will be monitored very carefully.

Calculations of blood volumes that may be taken from the youngest female patient permitted to enter the trial are provided in Section 18, Appendix 18.8. The 6-month-old female would have an average weight of 7.3 kg and an average blood volume of 584 mL. The greatest relative amount of blood would be taken in the unlikely event that the patient received two dose increases as permitted in Part A of the protocol.

Older patients and Part B patients (who will have PKPD sampled less frequently) will have a smaller % of their blood sampled.

To ensure compliance with guidelines, sites will monitor and record the total blood volume taken during this trial.

6.4 TRIAL OVERVIEW, PROCEDURES AND PATIENT COMPLIANCE (PARTS A AND B)

Initiation of nomacopan treatment will be at the investigator's clinic with nurses administering the *sc* injections initially. Prior to discharge (if any), the nurses will train the patient (or the individual who will be administering the drug) on how to store, prepare and administer nomacopan, as well as guidance on what to do if a dose is missed. Patients will be provided with diary cards to complete when administering study drug at home.

Study drug will be administered 12 hours apart, with a morning and an evening dose.

The treatment period for nomacopan will be no longer than 24 weeks. Patients may come off the drug sooner if one or both components of the primary endpoint have been met and the treating clinician considers there is no longer a need for continuing treatment with nomacopan. These patients who have stopped nomacopan will complete the end of study assessments and are then required to attend the 30-day follow-up visit, the 24-week visit (limited assessments) and the year 1 and 2 visit.

Patients who have achieved one or both components of the primary endpoint prior to week 24 but who remain treated with nomacopan will continue to receive 4-weekly assessments until Week 24 and are required to attend the 30-day follow up visits and attend the year 1 and 2 visits.

In exceptional circumstances where the investigator requests continuation of nomacopan beyond 24 weeks for clinical reasons, the Sponsor may agree to supply nomacopan for an additional 12 week period. Any patients on nomacopan after week 24 will have safety assessed every 4 weeks while on the drug and will attend a safety follow-up 30 days (± 5 days) after the last dose (see SOEs in Appendix 18.7).

6.4.1 Screening (up to 21 days, Parts A and B)

The maximum period between the screening visit and starting study drug is 21 days. However, the intent is to start study drug as soon as possible once diagnosis of HSCT-TMA has been confirmed.

At the screening visit the following assessments will be performed:

A record of all screened patients will be kept, with the date the screening assessment was performed, and whether or not the patient was eligible. If the patient was not eligible for study entry, or did not wish to participate, the reason will be recorded. Informed consent will be obtained and where appropriate, informed assent will be obtained.

Medical History & Prior Medication (including transfusions): any relevant medical history and prior medications along with start and stop dates (if appropriate) will be recorded.

Details of all RBC or platelet transfusions given in the 30 days prior to enrolment should also be recorded. It should be determined whether these transfusions were TMA-related.

Demography: date of birth, sex, race and ethnicity will be recorded.

Physical Exam: a physical exam will be performed, and any abnormal results recorded along with an assessment of the clinical significance of any abnormality. A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological system, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes, and extremities. If clinically significant, further details should be provided. An assessment of GVHD will also be performed.
ECG: 12-lead ECG at screening only. Findings to be recorded as clinically significant or non-clinically significant.

Vital signs: weight, height, temperature, pulse rate, respiratory rate and systolic and diastolic blood pressures will be recorded. Vital signs are to be taken while the subject is in a supine position, having rested in this position for at least five minutes. Measurements are to be repeated if clinically significant changes are observed or a machine error occurs.

Nasal and throat swabs: nasal and throat swabs will be taken locally, and assays performed to identify any active infection. Results from the swabs will not be used to confirm eligibility for study entry.

Blood samples: blood samples for haematology and chemistry will be taken for assay at the local laboratory, and blood samples for direct Coombs' Test, ADAMTS13, sC5b-9 and a serum pregnancy test for all females of childbearing potential will be taken for assay at the local or central laboratory.

Urine samples: urine samples (morning urine) will be taken for urine protein creatinine ratio (UPCR) and protein.

Adverse events: once the informed consent form is signed all adverse events beyond that point will be recorded.

6.4.2 Part A

Day 1 Pre-dose: Physical examination (including GVHD assessment) and vital sign assessment will be performed, and any adverse events and concomitant medications recorded. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, anti-drug antibodies (ADA), LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine), for UPCR and protein will also be performed.

Additional blood samples for efficacy (CH50) and PK assessments will be taken at 3 and 6 hours after the first ablating dose, and at 12 hours (immediately prior to the second ablating dose of nomacopan). If the 12-hour samples cannot be taken for logistical reasons, then 9-hour samples can be taken. Any AEs and concomitant medications will be recorded at these time points.

An additional vital sign assessment will be performed at 12 hours (immediately prior to the administration of the second ablating dose of nomacopan). Any AEs and concomitant medications will be recorded.

Day 2: Immediately prior to the morning study drug administration, vital signs (temperature, pulse rate, respiratory rate and systolic and diastolic blood pressures) will be recorded. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5 and sC5b-9. Urinalysis (morning urine), for UPCR and protein will also be performed. Any AEs and concomitant medications will be recorded.

Additional blood samples for efficacy (CH50) and free nomacopan levels (PK) assessments will be taken at 6 and 12 hours after the morning dose. If the 12-hour samples cannot be taken for logistical reasons, then 9-hour samples can be taken. Any AEs and concomitant medications will be recorded at these time points.

Day 3: Immediately prior to the morning study drug administration, samples will be taken for CH50 and free nomacopan levels (PK). These samples will NOT be taken for the youngest age cohort. Any AEs and concomitant medications will be recorded.

Day 4: Immediately prior to the morning study drug administration, pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK) and total C5, sC5b-9. Urinalysis (morning urine), for UPCR and protein will also be performed. Any AEs and concomitant medications will be recorded.

Day 7 (± 1 day): Immediately prior to the morning study drug administration physical examination (including GVHD assessment) and vital sign assessment will be performed, and pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, anti-drug antibodies (ADA), LTB4 (urine), sC5b-9, and C3b will be taken. Urinalysis (morning urine), for UPCR and protein will also be performed. Any AEs and concomitant medications will be recorded.

Additional blood samples for efficacy (CH50) and PK assessments will be taken at 3, 6, 12 hours after the morning dose, (immediately prior to the next dose of nomacopan). In the youngest age cohort samples will be taken pre-dose at 3 and 12 hours only. If the 12-hour samples cannot be taken for logistical reasons, then 9-hour samples can be taken. Any AEs and concomitant medications will be recorded at these time points.

Drug accountability to be undertaken.

Day 11 (± 1 day): Immediately prior to the morning study drug administration a vital sign assessment and urinalysis (morning urine), for UPCR and protein will also be performed. Any AEs and concomitant medications will be recorded.

Day 14 (± 1 day): Immediately prior to the morning study drug administration, pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, anti-drug antibodies (ADA), LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine), for UPCR and protein will also be performed. AEs and concomitant medications will be recorded, and drug accountability undertaken.

Week 4 (Day 28 (± 5 days)): Prior to the morning dose a physical examination (including GVHD assessment) and vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine),

sC5b-9, and C3b. Urinalysis (morning urine), for UPCR and protein will also be performed. A urine pregnancy test for females of childbearing potential will be taken.

Any AEs and concomitant medications will be recorded, and drug accountability undertaken.

Additional blood samples for CH50 and PK assessments will be taken at 3, 6 and 12 hours (immediately prior to the next dose of nomacopan) after the morning dose. In the youngest age cohort samples will be taken pre-dose at 3 and 12 hours only. If the 12-hour samples cannot be taken for logistical reasons, then 9-hour samples can be taken. Any AEs and concomitant medications will be recorded at these time points.

Week 8 (± 5 days): Prior to the morning dose a physical examination (including GVHD assessment) and vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine), for UPCR and protein will also be performed. A urine pregnancy test for females of childbearing potential will be taken.

Any AEs and concomitant medications will be recorded, and a drug accountability undertaken.

For children in the youngest two cohorts (≥ 0.5 to < 2 years, and ≥ 2 to < 9 years), the dose will be re-calculated using the child's new weight measured at that visit. The new adjusted dose should be given after all study procedures have been performed. This new adjusted dose will **not** require an ablating dose.

Week 12 (± 5 days): Prior to the morning dose a physical examination (including GVHD assessment) and vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine), for UPCR and protein will also be performed. A urine pregnancy test for females of childbearing potential will be taken.

AEs and concomitant medications will be recorded, and a drug accountability undertaken.

Week 16 (± 5 days): Prior to the morning dose a physical examination (including GVHD assessment) and vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine), for UPCR and protein will also be performed. A urine pregnancy test for females of childbearing potential will be taken.

AEs and concomitant medications will be recorded, and drug accountability undertaken.

For children in the youngest two cohorts (≥ 0.5 to < 2 years, and ≥ 2 to < 9 years), the dose will be re-calculated using the child's new weight measured at that visit. The new adjusted dose should be given after all study procedures have been performed. This new adjusted dose will **not** require an ablating dose.

Week 20 (± 5 days): Prior to the morning dose a physical examination (including GVHD assessment) and vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine), for UPCR and protein will also be performed. A urine pregnancy test for females of childbearing potential will be taken.

AEs and concomitant medications will be recorded, and drug accountability undertaken.

Week 24 (± 5 days) - the last dosing day: Prior to the morning dose a physical examination (including GVHD assessment) and vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine), for UPCR and protein will also be performed. A urine pregnancy test for females of childbearing potential will be taken.

Any AEs and concomitant medications will be recorded, and drug accountability undertaken.

Week 24 (± 5 days). Limited assessments – for all patients who completed dosing with nomacopan before 24 weeks and completed end of study procedures: A physical examination and vital sign assessment will be performed (including GVHD assessment), blood samples for haematology and chemistry, and urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded. If the patient received study drug less than a week prior to this visit, then samples for CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b will also be taken.

Safety Follow-up - 30 days (±5 days) after the last dose of nomacopan: The patient will attend the clinic for a physical examination (including GVHD assessment), assessment of vital signs, and blood samples will be taken for haematology, chemistry. Urinalysis (morning urine), for UPCR and protein will also be performed. A urine pregnancy test for females of childbearing potential will be performed. AEs and concomitant medications will be recorded.

One Year (post-HSCT) Follow-up (± 5 days): The patient will attend the clinic for a physical exam (including GVHD assessment), assessment of vital signs, and urinalysis (morning urine) for UPCR and protein will also be performed. If the patient has died, the date and cause of death will be recorded.

Two Year (post-HSCT) Follow-up (± 5 days): The patient will attend the clinic for a physical exam (including GVHD assessment), assessment of vital signs, and urinalysis (morning urine), for UPCR and protein will also be performed. If the patient has died, the date and cause of death will be recorded.

Unscheduled Visits: A physical exam (including GVHD assessment) and vital sign assessment will be performed, and urinalysis (morning urine) for UPCR and protein will also be performed. Any AEs and concomitant medications will be recorded. Any other procedures are at the Investigators discretion.

Early Withdrawal: Should a patient be withdrawn from the study, all end of study procedures should be performed.

6.4.3 Part B

Day 1 Pre-dose: A physical examination (including GVHD assessment) and vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded.

An additional vital sign assessment will be performed at 12 hours (immediately prior to the administration of the second ablating dose of nomacopan). Any AEs and concomitant medications will be recorded.

Day 2: Immediately prior to the morning study drug administration, vital signs (temperature, pulse rate, respiratory and systolic and diastolic blood pressures) will be recorded. Pre-dose samples for CH50, nomacopan drug levels (PK), total C5 and sC5b-9. Urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded.

Day 7 (± 1 day): Immediately prior to the morning study drug administration a physical exam (including GVHD assessment) and a vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded, and drug accountability undertaken.

Day 14 (± 1 day): Immediately prior to the morning study drug administration a physical exam (including GVHD assessment) and a vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded, and drug accountability undertaken.

Week 4 (± 5 days)): Immediately prior to the morning study drug administration a physical exam (including GVHD assessment) and a vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded, and drug accountability undertaken. A urine pregnancy test for females of childbearing potential will be taken.

Week 8 (± 5 days): Immediately prior to the morning study drug administration a physical exam (including GVHD assessment) and a vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded, and drug accountability undertaken. A urine pregnancy test for females of childbearing potential will be taken.

Week 12 (± 5 days): Immediately prior to the morning study drug administration a physical exam (including GVHD assessment) and a vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded, and drug accountability undertaken. A urine pregnancy test for females of childbearing potential will be taken.

Week 16 (± 5 days): Immediately prior to the morning study drug administration a physical exam (including GVHD assessment) and a vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded, and drug accountability undertaken. A urine pregnancy test for females of childbearing potential will be taken.

Week 20 (± 5 days): Immediately prior to the morning study drug administration a physical exam (including GVHD assessment) and a vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded, and drug accountability undertaken. A urine pregnancy test for females of childbearing potential will be taken.

Week 24 (± 5 days) - the last dosing day: Immediately prior to the morning study drug administration a physical exam (including GVHD assessment) and a vital sign assessment will be performed. Pre-dose samples for haematology, chemistry, CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b. Urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded, and drug accountability undertaken. A urine pregnancy test for females of childbearing potential will be taken.

Week 24 (± 5 days), Limited assessments – for all patients who completed dosing with nomacopan before 24 weeks and completed all the final study procedures: A physical examination (including GVHD assessment) and a vital sign assessment will be performed. Blood samples for haematology and chemistry, and urinalysis (morning urine) for UPCR and protein will also be performed. Any AEs and concomitant medications will be recorded. If the patient received study drug less than a week prior to this visit, then samples for CH50, nomacopan drug levels (PK), total C5, ADA, LTB4 (urine), sC5b-9, and C3b) will also be taken.

Safety Follow-up - 30 days (± 5 days) after the last dose of nomacopan: The patient will attend the clinic for a physical examination (including GVHD assessment), assessment of vital signs, and blood samples will be taken for haematology, chemistry, and urinalysis (morning urine) for UPCR and protein will also be performed. A urine pregnancy test for females of childbearing potential will be performed. Any AEs and concomitant medications will be recorded, and drug accountability undertaken.

One Year (post-HSCT) Follow-up (± 5 days): The patient will attend the clinic for a physical exam (including GVHD assessment), assessment of vital signs, and urinalysis (morning urine) for UPCR and protein will also be performed. If the patient has died, the date and cause of death will be recorded.

Two Year (post-HSCT) Follow-up (± 5 days): The patient will attend the clinic for a physical exam, (including GVHD assessment) assessment of vital signs, and urinalysis (morning urine), for UPCR and protein will also be performed. If the patient has died, the date and cause of death will be recorded.

Unscheduled Visits: A physical examination (including GVHD assessment) and vital sign assessment will be performed, and urinalysis (morning urine), for UPCR and protein will also be performed. Any AEs and concomitant medications will be recorded. Any other procedures are at the Investigators discretion.

Early Withdrawal: Should a patient be withdrawn from the study all end of study procedures should be performed.

6.4.4 Dose Increase Part A – if required

Day n: Prior to the ablating dose, samples for CH50, nomacopan drug levels (PK) and urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded.

Additional blood samples for CH50 and nomacopan drug levels (PK) will be taken at 3, 6 and 12 hours (*ie* immediately prior to the second dose of nomacopan) after the first ablating dose. AEs and concomitant medications will be recorded.

Day n+1: Prior to the maintenance dose, samples for CH50, nomacopan drug levels (PK) and urinalysis (morning urine) for UPCR and protein will also be performed.

Additional blood samples for CH50 and nomacopan drug levels (PK) will be taken at 6 and 12 hours after the first morning maintenance dose. AEs and concomitant medications will be recorded.

Day n+2: Prior to the maintenance dose, samples for CH50, nomacopan drug levels (PK) and urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded.

Day n+6 (± 1 day): Prior to the maintenance dose, samples for haematology and chemistry, CH50, nomacopan drug levels (PK) and urinalysis (morning urine) for UPCR and protein will also be performed.

Additional blood samples for CH50 and nomacopan drug levels (PK) will be taken at 3, 6 and 12 hours (*ie* immediately prior to the second dose of nomacopan) after the first morning maintenance dose. Drug accountability to be undertaken. AEs and concomitant medications will be recorded.

6.4.5 Dose Increase Part B – if required

Day n: Prior to the ablating dose, samples for CH50, nomacopan drug levels (PK) and urinalysis (morning urine) for UPCR and protein will also be performed. AEs and concomitant medications will be recorded.

Additional blood samples for CH50 and nomacopan drug levels (PK) will be taken at 12 hours prior to the administration of the maintenance dose. AEs and concomitant medications will be recorded.

Day n+1: Prior to the maintenance dose, samples for CH50, nomacopan drug levels (PK) and urinalysis (morning urine), for UPCR and protein will also be performed. AEs and concomitant medications will be recorded.

Day n+6 (± 1 day): Prior to the maintenance dose, samples for haematology and chemistry, CH50, nomacopan drug levels (PK) and urinalysis (morning urine) for UPCR and protein will also be performed. Drug accountability to be undertaken. Any AEs and concomitant medications will be recorded.

6.5 LOCAL LABORATORY TESTS

Part A and Part B

The specified times and measurements of clinical chemistry, haematology and urinalysis are the same in Part A and Part B of the trial.

6.5.1 Clinical Chemistry Part A and Part B

All samples will be taken as per the Schedule of Events in Section 18.

The clinical chemistry parameters to be assessed at each specified time point are sodium, potassium, calcium, phosphate, urea, creatinine (including eGFR calculation), ALT, AST, LDH, GGT, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, and c-reactive protein.

All of the above parameters will be assessed by the local laboratory.

eGFR will be calculated by sites using the NIDDK eGFR calculator for children which uses the Schwartz calculation[33]. The calculation is different depending on the units used for reporting creatinine calculations at the local lab.

For mg/dL, use: eGFR (mL/min/1.73 m²) = (0.41 × Height in cm) / Creatinine in mg/dL [https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators/children-conventional-units].

For µmol/L, use: eGFR (mL/min/1.73 m²) = (36.2 × Height in cm) / Creatinine in µmol/L [https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators/children-si-units].

6.5.2 Haematology Part A and Part B

All samples will be taken as per the Schedule of Events in Section 18.

The haematology parameters to be assessed at each specified time point are haemoglobin, haematocrit, total WBC, neutrophils, lymphocytes, monocytes, basophils, eosinophils, RBC, platelets, reticulocytes, haptoglobin and MCV.

All of the above parameters will be assessed by the local laboratory.

The Coombs' test and ADAMTS13 test are required for screening.

6.5.3 Urinalysis Part A and Part B

All samples will be taken as per the Schedule of Events in Section 18.

The urinalysis parameters to be assessed at each time point are UPCR and protein.

The above parameters will be assessed by the local laboratory.

6.6 CENTRAL LABORATORY TESTS

6.6.1 Pharmacodynamics (PD) - CH50

TCA will be measured from serum by CH50 ELISA which measures formation of the terminal complement complex. All samples will be taken as per the Schedule of Events in Section 18.

6.6.2 Pharmacokinetics (PK)

Unbound nomacopan concentration will be measured from serum by ELISA. All samples will be taken as per the Schedule of Events in Section 18.

6.6.3 Total C5, sC5b-9 and C3b Assays

All samples will be taken as per the Schedule of Events in Section 18. All sC5b-9 samples will be analysed centrally and measured in plasma.

6.6.4 LTB4 (urinary)

All urine samples will be taken as per the Schedule of Events in Section 18.
For determination of urinary LTB4, 24-hour urine samples will be collected. Patients should NOT be catheterised specifically to allow for the collection of this urine sample. For patients who are not catheterised (for other medical reasons), all urine samples should be collected over the defined 24-hour period. In younger children, where possible, urine from diapers/nappies should be collected.

6.6.5 Anti-drug Antibodies

All samples will be taken as per the Schedule of Events in Section 18.

6.7 BLOOD TRANSFUSIONS

Transfusion independence is defined as no RBC or platelet transfusion attributable to, or required to manage, TMA. Transfusion required for causes other than TMA will not be considered within evaluation of endpoints.

The Sponsor will not make this evaluation. The investigator will decide if a transfusion is required for the management of TMA or is part of the management of other clinical events or part of a site clinical management policy (*eg* haemoglobin maintenance thresholds, infection management), and this assessment will be recorded on the CRF.

Details of all RBC or platelet transfusions given in the 30 days prior to enrolment should also be recorded. It should be determined whether these transfusions were TMA-related.

6.8 OTHER ASSESSMENTS

6.8.1 Pregnancy Test

All females who are of childbearing potential must have a serum negative pregnancy test at screening. Where a site is not able to perform a serum pregnancy, a urine pregnancy test will be acceptable. This test will be performed at the local or central laboratory. A urine pregnancy test will be performed every 4 weeks on all females of childbearing potential. The patient will be discontinued from the study if she becomes pregnant during the study and will be followed up for health and condition of the baby for **1 year** after the childbirth.

6.9 SAFETY ASSESSMENTS

6.9.1 Adverse Events

All clinical AEs, defined in Section 8.1 occurring from when the patient has signed the ICF to the follow-up period (30 days after last dose of nomacopan), whether observed by the investigator or reported by the patient, will be recorded on the AE eCRF page. Medical conditions (including laboratory values/vital signs that are out of range and found clinically significant) that exist prior to informed consent will be recorded as part of medical history, unless there is a deterioration of the pre-existing condition after baseline, in which case it would be an reported as an AE.

All laboratory values and vital signs should be reviewed by the investigator to determine clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings should be reported as AEs if they are symptomatic, lead to study drug discontinuation, require corrective treatment, or are clinically significant in the opinion of the investigator.

All SAEs are to be reported according to the procedures in Section 8. Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary signs or symptoms as the AE or SAE term with additional details included in the SAE narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report as individual entries of AE or SAE. For events that are serious due to hospitalisation, the reason for hospitalisation must be reported as the SAE (diagnosis or symptom requiring hospitalisation). Pre-planned (prior to signing the ICF) procedures or hospitalisations for pre-existing conditions which do not worsen in severity should not be reported as SAEs (see Section 8 for Definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE. In addition, any serious, untoward event that may occur subsequent to the reporting period that the investigator assesses as related to study drug should also be reported and managed as an SAE.

At each visit, the investigator should determine whether any AEs have occurred by evaluating the patient. AEs may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 8. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature.

Investigators should follow patients with AEs until the event has resolved or the condition has stabilized. Unresolved drug related AEs, including significant abnormal laboratory values at the end of the study, should be followed until resolution or until no longer clinically relevant.

6.9.2 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
Past (or plans for future) surgeries	Alcohol use or substance abuse
Neurological/psychiatric	Haematological/lymphatic
Abdominal/urogenital	Endocrine/metabolic

Medications	Smoking
Allergies/drug sensitivities	Dialysis History

Details of all RBC or platelet transfusions given in the 30 days prior to enrolment should be recorded. It should be determined whether these transfusions were TMA-related.

6.9.3 Physical Examination

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological system, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes, and extremities. A GVHD assessment will also be performed during the physical examination using the Glucksberg assessment (Appendix 18.9).

6.9.4 Vital Signs

Vital sign measurements will be recorded for pulse rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Vital signs are to be taken while the subject is in a supine position, having rested in this position for at least five minutes. Measurements are to be repeated if clinically significant changes are observed or a machine error occurs.

6.9.5 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures at the timepoints specified in the schedule of events.

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

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

6.10 MISSED DOSES

A missed dose is defined as a dose not taken either two hours before or after the time the patient would normally dose. For example, for a dose scheduled at 07:00 am, the dose can be administered between 05:00 am and 09:00 am. However, it is recommended that the patient is normally given their doses at the same time each day.

- If a dose is missed between 2 and 6 hours after the time the patient should have had a scheduled dose, the missed dose should be given as soon as possible. Subsequent doses should continue at the normal schedule.
- If a dose is missed between 6 and 12 hours after the time the patient should have had a scheduled dose, the missed dose should not be given. Instead the patient should be given

a single ablating dose. The next scheduled dose should be missed, and then subsequent maintenance doses should continue at the normal scheduled times.

- If two consecutive doses have been missed, the patient should receive a single ablating dose, and subsequent maintenance doses should continue at the normal schedule. The reasons for the missed doses should be discussed, and consideration should be given to preventing any further missed doses and maintaining compliance with the protocol.

7 REASON FOR WITHDRAWAL/EARLY DISCONTINUATION

7.1 TERMINATION OR SUSPENSION OF THE STUDY

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

- Safety concerns *eg* due to occurrence of many serious adverse drug reactions (ADRs)
- Achieving the purpose of the study is considered impossible *eg* due to inadequate recruitment of patients
- The planned interim analysis in Part B suggests lack of efficacy of the study drug

The Sponsor may prematurely terminate or suspend the study as well 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 (ICH) GCP has not been followed.

If the study is prematurely terminated or suspended, the Sponsor should promptly inform the Investigators. The investigator should promptly inform the participating patients and change the study medication to other appropriate therapy(ies). All supplies must be returned.

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 (*eg* occurrence of many SAEs).

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

The Sponsor will notify Regulatory Authorities, as appropriate of premature terminations. The investigator should promptly inform the corresponding Ethics Committee.

7.2 WITHDRAWAL CRITERIA

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

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

If an enrolled patient has a positive ADAMTS13 test (< 10%) returned from their screening assessment, the patient should be withdrawn from the study and appropriate treatment for TTP should be commenced.

In the event of the premature withdrawal of a patient from the trial, all end of study procedures should be performed. In addition, the patient should return for a follow up safety assessment after 30 days.

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 stabilises, and any interventions required to resolve or stabilise the event will be recorded in the eCRF.

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

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

8 SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable 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.

8.1.2 Adverse Drug Reaction (ADR)

All untoward and unintended responses to an investigational medicinal product 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 ADRs.

8.1.3 Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information that is available (*eg* in the IB for an unauthorized investigational medicinal product or the Summary of Product Characteristics for an authorized product).

8.1.4 Serious Adverse Event or Serious Adverse Reaction

Any untoward medical occurrence or effect at any dose that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital abnormality / birth defect.

NOTE: Other events that may not result in death, are not life threatening, or do not require hospitalisation, 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, hyporeactivity or hyperventilation, or convulsions.

Note: Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

All SAEs will be reported to the Sponsor (or designee) within 24 hours of notice of occurrence. The Sponsor (or 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.

8.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information that is available (*eg* in the IB for an unapproved investigational product or the Summary of Product Characteristics for an authorized product).

8.1.6 Treatment Emergent Adverse Events (TEAEs)

Treatment emergent adverse events (TEAEs) are undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment.

8.1.7 Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical concern given the IMP's mechanism of action and knowledge of similar products. Ongoing or additional monitoring and immediate rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterise and understand them. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (*eg* regulators) might also be warranted.

For this study, 'serious gram-negative infections' will be considered an AESI. That is, any infection with a proven culture of a gram-negative organism that meets the SAE criteria.

8.2 PROCEDURES FOR RECORDING OF SAFETY EVENTS

8.2.1 General

All adverse events occurring during the study (from the time point of signing of the ICF until the patients' 30-day follow up visit) 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/grading (by CTCAE criteria),
- 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 using the CTCAE criteria (version 5).
General guidance of CTCAE severity assessment:

Grade	Definition
Grade 1	**Mild;** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	**Moderate;** minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living
Grade 3	**Severe or medically significant** but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living
Grade 4	**Life-threatening** consequences; urgent intervention indicated.
Grade 5	**Death** related to AE.

Further guidance should be consulted on the below URL link:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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

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

The degree of certainty with which an AE is attributed to IMP administration (or alternative causes, *eg* natural history of the underlying disease, concomitant therapy, *etc.*) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the IMP,
- Whether reactions of a similar nature have been previously observed with the IMP or this class of drug,
- A temporal relationship to IMP administration, terminating with IMP withdrawal or recurring on re-challenge,
- Alternative cause.

At the last scheduled visit, the investigator shall instruct each patient to report any subsequent event(s) that the patient, or their 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.

8.2.2 Pre-existing Conditions

For the purposes of this study a pre-existing condition means a diagnosed, clinically significant finding, symptom or laboratory abnormality present at screening. 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.

8.2.3 Overdose

All overdoses with or without associated symptoms, should be reported as AEs on the appropriate eCRF page. An overdose is defined as a dose greater than the total ablating dose that patients receive on Day 1 of the study in any 12-hour period. If sequelae meeting the criteria for a SAE have occurred in association with the overdose, the case must be reported immediately, within 24 hours.

Action to be taken, if any, in event of an overdose should be discussed with the Sponsor's medical representative at the earliest opportunity. However, in animal toxicology, no adverse events have been observed following single *iv* doses of approximately 50 times the human therapeutic dose, so no specific toxicity is anticipated. There are no known antidotes to nomacopan, and observation and supportive treatment are the only recommended measures. An assessment of whether the overdose was accidental or intentional should be recorded. If the overdose was a suicide attempt, this fact should be clearly stated. The AEs and SAEs that occur as a result of an overdose should be recorded on the eCRF.

8.2.4 Pregnancy

Nomacopan 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 pregnancy tests may be negative during the first few weeks, pregnancy may later be confirmed by an ultrasound examination. If at least one of the above-mentioned examinations is positive, administration of the IMP must be stopped, and the patient must be immediately withdrawn from the study. All pregnancies (even if suspected) must be reported on the appropriate eCRF page and Pregnancy Form to the pharmacovigilance provider of the Sponsor within 24 hours of the investigator becoming aware of the pregnancy (or suspected pregnancy). In any case each pregnancy must be followed until its resolution (either by birth of a child or abortion) and the eCRF page and Pregnancy Form has to be updated.

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

E-mail: safety@akaritx.com

8.2.5 Transfusions

Overnight stays for transfusion do not need to be reported as SAEs.

As all patients are anticipated to be hospitalised at the start, and potentially for the duration of the study, existing hospitalisation will not automatically be regarded as an SAE. Planned visits to hospital for routine follow up and planned medical care will not be regarded as an SAE.

On the other hand, progression of the underlying disease (at investigator's discretion) or potential complications have to be reported as AEs.

8.3 Reporting Procedures for Serious Adverse Events

Any SAE occurring during the study has to be managed by established standard 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 withdrawn from the study, or not.

All SAEs, irrespective of their causality, must be notified to the pharmacovigilance provider 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 centre during the initiation visit, and sent by e-mail to:

E-mail: safety@akaritx.com

The provided information shall contain as much detail regarding the event as 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 8.2.1. Where applicable, information from relevant hospital records or autopsy reports should be obtained and provided to Akari Therapeutics Plc.

8.4 Expedited Safety Reporting

Any SAE, 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 (IRBs) 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 hospitalisation or prolongation of hospitalisation 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 the Sponsor or contracted parties including the Contract Research Organisation (CRO) and the Pharmacovigilance Provider.

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

8.5 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.

9 STATISTICS

9.1 STATISTICAL DESIGN

The study is divided into two parts. Both parts are single arm, and open-labelled. The design of Part A is based on pragmatic considerations based on generating adequate data to confirm the paediatric dose algorithm; the design of Part B is based on determining if the responder rate obtained using the given dosing algorithm is at least 15%. Consideration will be given to including Part A patients in the primary overall analysis; this will be discussed with the FDA at the end of Part A.

9.2 SAMPLE SIZE CONSIDERATIONS

Part A will recruit 7 patients, in three age range cohorts (≥ 0.5 to < 2 years, ≥ 2 to < 9 years, and ≥ 9 to < 18 years). The purpose of Part A is to confirm the effective maintenance dose of nomacopan for ablation of TCA. This dose will then be used in Part B.

For Part B it is assumed that the responder rate on nomacopan will be approximately 30% and the minimum acceptable responder rate is 15%. Up to 65 patients will be recruited which gives 79% power to reject the null hypothesis proportion, π_0, of less than 0.15 when the alternative hypothesis proportion, π_1, is 0.3 using an exact binomial test with a 2.5% one-sided significance level.

An interim analysis will be conducted when 40 patients have been recruited into Part B of the study and have either completed 24 weeks of the study or discontinued the study before 24 weeks. In order to stop the study early for demonstration of efficacy, based on an O'Brien-Fleming stopping rule, at an information fraction of 0.62 (40 of 65 patients), the significance level at the interim analysis needs to be 0.0044 (1 sided). To meet this significance level, at least 13 of the 40 patients (32.5%) will need to be responders. If the study is not stopped early, recruitment will continue and the final significance level, after 65 patients, will then need to be 0.024.

9.3 ANALYSIS SETS

9.3.1 Safety Analysis Set (SAS)

All patients in Part A and in Part B who receive any dose of nomacopan. The data from patients in both parts of the study will be combined together for summaries of safety.

9.3.2 Full Analysis Set (Intention-to-treat)

All patients in Part B who receive any dose of nomacopan. The primary efficacy analyses will be based on only the Part B patients although additional summary results will be included that also combine Part A and Part B together.

9.3.3 Per Protocol (PP) Analysis Sets

All patients in Part B who do not have major protocol deviations, die of causes that are considered not to be related to TMA (as determined by the review committee) or who on later analysis were considered not to have had TMA at the time that treatment with nomacopan was initiated.

9.4 STATISTICAL ANALYSIS

9.4.1 Overview

A detailed statistical analysis plan (SAP) will be written before any patients are recruited into Part B of the trial (but may be written whilst Part A is ongoing). The protocol explains the key elements of data presentation and analysis.

Part A patients will have their data summarised separately to Part B patients – although for key endpoints, summary Tables combining data from Parts A and B will also be included.

At a minimum, analyses of all 7 patients until week 12 of dosing will be completed before Part B starts.

9.4.2 Disposition of Study Patients

Summaries showing the number of patients recruited into Parts A and B separately, the number and percentage of patients discontinuing Part A or Part B and the reasons for discontinuation (as collected on the eCRF) will be produced.

The number and percentage of patients included in each analysis set will be summarized by Parts A and B and overall for all recruited patients.

A listing of patients excluded from the PP set and the reason for exclusion will be provided.

9.4.3 Baseline

Demographic and baseline characteristics will be listed for Part A patients (sub-identified by age cohort) and Part B patients separately. Summary Tables will be produced for Part B patients.

The following demographic and baseline characteristics will be summarized:

age, gender, race, ethnicity, weight, temperature, pulse rate, systolic and diastolic blood pressures, transfusion history (number of units of PRBCs and platelets transfused, along with corresponding Hb concentration and platelet count) and sC5b-9 concentration.

9.4.4 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint for Part B is:

> independence of RBC transfusion[†] for ≥ 28 days immediately prior to any scheduled clinical visit up to Week 24
> **or**
> urine protein creatinine ratio ≤ 2 mg/mg, maintained over a ≥ 28-day period immediately prior to any scheduled clinical visit up to Week 24

[†]Transfusion independence is defined as no RBC or platelet transfusion attributable to, or required to manage, TMA. Transfusions required for causes other than TMA will not be considered within the evaluation of the primary efficacy endpoints.

The number and proportion of patients fulfilling this composite endpoint will be reported, along with a 95% confidence interval for the proportion and an exact binomial test of the null hypothesis that the responder rate is 0.15 vs. alternative hypothesis that the responder rate is 0.15 or above.

Supporting analyses will be performed on the individual components of the composite endpoint: 95% confidence intervals for each of the rates of RBC infusion independence and urine protein creatinine ratio ≤ 2 mg/mg will be reported. In addition, 95% confidence intervals will be given for the responder rate based on pooling Part A and Part B patients together.

9.4.5 Secondary Endpoints Analysis

The proportions of patients meeting each of the following criteria will be reported, along with a 95% confidence interval for the proportions:

- Percentage of patients who achieve the primary endpoint of urine protein creatinine ratio ≤ 2 mg/mg (the nephrotic threshold) for ≥ 28 days,
- platelet transfusion† independence for ≥ 28 days,
- sC5b-9 ≤ ULN,
- lactate dehydrogenase (LDH) ≤ ULN and
- normalization of haptoglobin - (only in a subset of patients where haptoglobin was abnormal at baseline.

The sC5b9, LDH and haptoglobin secondary endpoints will be measured at the last efficacy assessment in the trial before nomacopan treatment is stopped.

These results will be reported for patients in Part B of the study, and for the combined Part A and Part B patient group.

9.4.6 Exploratory Endpoints

- Overall survival at Week 24 after the first dose of nomacopan, and at 1 year and 2 years after HSCT will be analysed by - Kaplan Meier survival curves. Overall survival is calculated as the time from first dose of nomacopan to death. Overall survival as time from HSCT to death will also be analysed by Kaplan Meier methods. From these survival curves, the respective 24-week, 1-year and 2-year survival rates will be reported.

For the following exploratory endpoints, 95% confidence intervals for rates (percentages) will be reported.

- Percentage of patients with urine protein creatinine ratio ≤ 1.5 mg/mg for ≥ 28 days.
- Percentage of patients with urine protein creatinine ratio ≤ 1 mg/mg for ≥ 28 days.
- To evaluate renal function (urea, serum creatinine, urine protein creatinine ratio, proteinuria < 30 mg/dL and eGFR) at baseline and at 1 year and 2 years after HSCT.

These results for all exploratory endpoints will be reported for patients in Part B of the study, and for the combined Part A and Part B patient group.

9.4.7 Subgroup Analysis

The primary and secondary endpoints will also be reported in subgroups based on degree of elevation of sC5b-9 categorised as below or above the median.

9.4.8 Interim Analysis

One interim analysis will take place when 40 Part B patients have been recruited into the study and have either completed 24 weeks of the study or discontinued the study before 24 weeks. This analysis will only include Part B patients. An O'Brien-Fleming stopping rule, at an information fraction of 0.62 (40 of 65 patients), will be used. At the time of the interim analysis, to stop the study early, the 1-sided P-value needs to be less than 0.0044. To meet this significance level, at least 13 of the 40 patients (32.5%) will need to be responders. Methods of primary efficacy analysis endpoint (see Section 9.4.4) will be used for the interim analysis on 40 patients.

If the study does not meet statistical significance at this time, the one-sided P-value needed at the final analysis with all 65 patients will be 0.024.

9.4.9 Safety Analysis strategy for laboratory and clinical safety data

Analysis of all safety data will be performed on the Safety Analysis Set. Adverse events (AEs) and medical history will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). New or worsening AEs after dosing of investigational product will be summarized by system organ class, preferred term, and treatment. Listings of subjects who have an SAE or who discontinue from the study due to an AE will be provided. AEs leading to withdrawal will be summarized for Part A and Part B.

Summary statistics for laboratory values will be provided at baseline, post-baseline visits, and for changes from baseline to post-baseline for Part A and Part B. Vital signs parameters will be summarized similarly. Occurrence of significant laboratory abnormalities will be summarized for Part A and Part B. Physical examination and urine pregnancy tests data will be listed.

10 DATA HANDLING AND SOURCE DOCUMENTS

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

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

Direct access to these documents must be guaranteed by the investigator or their designee, or the study coordinator, who must provide support at all times for these activities.
The nature and location of all sources of original data required to complete the eCRF will be identified by the CRO and the site staff.

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

study site as necessary. The database will be quality assured and will be available for analysis according to the Statistical Analysis Plan.

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

10.1 INFORMED CONSENT PROCEDURES

Written informed consent expresses the understanding and agreement of fully informed parent(s) or legal guardian(s) to permit the child to enter into this study. In addition, it also means the assent (the affirmative agreement) of the child to participate in this study, where the child is able (old enough) to provide assent. Lack or absence of agreement or disagreement must not be interpreted as assent.

For the sake of simplicity in this protocol, references to the patient can also mean references to the legal guardian where appropriate.

10.2 PROTOCOL DEVIATIONS

The investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favourable opinion by the independent ethics committee (IEC).

A protocol deviation to eliminate any apparent immediate hazard to a patient(s) may be implemented immediately. The Sponsor, Competent Authorities and the IEC must be notified of the deviation and reason. The Sponsor must be notified of all intended or unintended deviations to the protocol (*eg* inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

If a patient received at least one dose of study medication but was subsequently determined to be ineligible or to have received the wrong dose or investigational treatment, all appropriate safety and early termination procedures should be performed, with data collected for inclusion in the safety and efficacy analysis, as appropriate. The protocol deviation should be appropriately documented.

The investigator should notify the IEC of deviations from the protocol in accordance with local procedures. The Competent Authorities should also be notified of any protocol deviation performed to protect the patients against any immediate hazard which meets the definition of an urgent safety measure.

10.3 SUBJECT CONFIDENTIALITY

The investigators and the Sponsor will preserve the confidentiality of all patients taking part in the study, in accordance with GCP and local regulations.

The investigator must ensure that the patient's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor or designee, subjects should be identified by a unique

subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor or designee (*eg* signed ICF) should be kept in strict confidence by the investigator.

In compliance with applicable regulations and ICH GCP guidelines, it is required that the investigator and institution permit authorised representatives of the company, of the regulatory agency(s), and the IEC direct access to review the patient's original medical records for verification of study-related procedures and data. The investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the patient.

11 DRUG ACCOUNTABILITY AND COMPLIANCE

11.1 ACCOUNTABILITY PROCEDURES

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

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

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

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

Patients are required to return used and unused vials to the clinical unit if at some point during the study they are discharged from hospital. 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.

11.2 COMPLIANCE

Reasonable levels of compliance are assumed as a condition of entry to the study. For each patient, a reconciliation will be made between the number of vials recorded to have been used, the number of vials actually used (number of vials returned empty), and the number of vials that should have been used according to the dosing record. As an additional measure of compliance, all empty nomacopan vials will be returned to the clinical unit. At the end of the study, all unused vials may be returned to the Sponsor or representative.

12 QUALITY CONTROL AND ASSURANCE

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

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

14 FINANCING, INDEMNITY AND INSURANCE

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

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

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

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

15 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 Plc for review and comment before its submission to the journal. In cases where Akari Therapeutics Plc considers that the proposed publication contains information which should be protected as valuable confidential

information or is out of compliance with applicable laws and regulations, Akari Therapeutics Plc reserves the right to delay submission to the journal, until the required deletion or amendment of the confidential information from the proposed publication has been done.

16 STUDY RECORD RETENTION

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

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

All correspondence (*eg* with the Sponsor, or designee, EC) 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.

16.1 CLINICAL STUDY REPORT

The results of this clinical study must be summarised by the Sponsor (or designee) and a final audited report must be retained on file. This report will include discussions on the study objectives, methodology, findings and conclusions. The 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 CSR. The report must be archived with all other study documents.

16.2 HANDLING AND RETENTION OF BLOOD AND PATHOLOGICAL SAMPLES

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

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18 APPENDICES

18.1 SCHEDULE OF EVENTS PART A (FIRST 4 WEEKS)

Evaluation & Procedures	Screening	Day 1 Intense Monitoring				Day 2 Intense Monitoring			Day 3	Day 4	Day 7 Intense Monitoring (± 1 day)				Day 11 (± 1 day)	Day 14 (± 1 day)	Week 4 Intense Monitoring (± 5 days)			
	Up to -21 days	Pre-dose	3 hrs	6 hrs	12 hrs Predose	Pre-dose	6 hrs	12 hrs	Pre-dose	Pre-dose	Pre-dose	3 hrs	6 hrs	12 hrs Predose	Pre-dose	Pre-dose	Pre-dose	3 hrs	6 hrs	12 hrs Predose
Eligibility & ICF	x																			
Medical History	x																			
Demographics	x																			
Physical Exam[1]	x	x									x						x			
ADAMTS13[2]	x																			
Coombs' Test[2] & ECG[3]	x																			
Nasal & Throat Swabs[4]	x																			
Vital signs[5]	x	x			x	x					x				x		x			
CH50[6]		x	x	x	x	x	x	x	X[15]	x	x[14]	x[14]	x[14, 15]	x[14]		x	x	x	X[15]	x
PK[6]		x	x	x	x	x	x	x	X[15]	x	x[14]	x[14]	x[14, 15]	x[14]		x	x	x	X[15]	x
Total C5[6]		x				x				x	x					x	x			
Antibodies[6]		x									x					x	x			
Urinary LTB4[6]		x									x					x	x			
sC5b-9[6,7]	x[7]	x				x				x	x					x	x			
C3b[6]		x									x					x	x			
Chemistry[2,8]	x	x				x				x	x					x	x			
Haematology[2,9]	x	x				x				x	x					x	x			
Urinalysis[2,10]	x	x				x				x	x				x	x	x			
Pregnancy test[11]	x[12]																x[13]			
Drug Accountability											x					x	x			
AEs & Con Meds	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x

[1] *A physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological & cardiovascular systems, lungs, abdomen (liver & spleen), lymph nodes & extremities. A GVHD assessment will also be performed.*

[2] *Local laboratory.*

[3] *12-lead ECG.*

[4] *Nasal & throat swab results prior to first dose is not an entry requirement. Meningitis prophylaxis with vaccines will be in accordance with the investigator's judgement & local guidelines.*

[5] *Vital signs: pulse rate, systolic & diastolic blood pressure, respiratory rate, & body temperature. Vital signs are to be taken after the subject has been supine for at least 5 minutes. Measurements should be repeated if clinically significant changes are observed or a machine error occurs. In addition, weight should be measured every 4 weeks, and height at screening and Week 24.*

[6] *Central laboratory. For the 24 hours urine (LTB4) - in non-catheterised patients all urine samples over the period should be collected, as completely as possible. For younger children, urine from diapers/nappies should be collected if feasible.*

[7] *Plasma sC5b-9 is mandatory before study entry and may be performed more frequently than shown at the investigator's discretion.*

[8] *Liver function, Renal function including eGFR Calculation & LDH.*

[9] *Including haptoglobin.*

[10] *Urinalysis: UPCR &Protein.*

[11] *For females of childbearing potential.*

[12] *Serum pregnancy test.*
[13] *Urine pregnancy test.*
[14] *A dose increase CANNOT be given until Day 7 PK/PD results are available.*
[15] *These samples will NOT be taken in the youngest age cohort.*

18.2 SCHEDULE OF EVENTS PART A (WEEK 8 ONWARDS)

Evaluation & Procedures	Week 8[14] (± 5 days)	Week 12 (± 5 days)	Week 16[14] (± 5 days)	Week 20 (± 5 days)	End of Treatment Week 24[11], (± 5 days)	Safety Follow-up (30 days after last dose)	1 Year Post HSCT follow-up (± 5 days)	2 Years Post HSCT follow-up[12] (± 5 days)	Early Withdrawal	Unscheduled Visit
	Pre-dose	**Pre-dose**	**Pre-dose**	**Pre-dose**	**Pre-dose**	(± 5 days)				**Pre-dose**
Medical History										
Demographics										
Physical Exam[1]	x	x	x	x	x	x	x	x	x	x
Coombs' Test & ECG[16]										
Nasal & Throat Swabs										
Vital signs[3]	x	x	x	x	x	x	x	x	x	x
CH50[4]	x	x	x	x	x[13]				x	
PK[4]	x	x	x	x	x[13]				x	
Total C5[4]	x	x	x	x	x[13]				x	
Antibodies[4]	x	x	x	x	x				x	
Urinary LTB4[4]	x	x	x	x	x[13]				x	
sC5b-9[4,5]	x	x	x	x	x[13]				x	
C3b[4]	x	x	x	x	x[13]				x	
Chemistry[2,6]	x	x	x	x	x	x			x	
Haematology[2,7]	x	x	x	x	x	x			x	
Urinalysis[2,8]	x	x	x	x	x	x	x	x	x	x[13]
Pregnancy test[9]	x[10]	x[10]	x[10]	x[10]	x[10]	x[10]			x[10]	
Drug Accountability	x	x	x	x	x				x	
AEs & Con Meds	x	x	x	x	x	x	x[15]	x[15]	x	x
Overall survival status							x	x		

[1] *A physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological & cardiovascular systems, lungs, abdomen (liver & spleen), lymph nodes & extremities. A GVHD assessment will also be performed.*

[2] *Local laboratory.*

[3] *Vital signs: pulse rate, systolic & diastolic blood pressure, respiratory rate, & body temperature. Vital signs are to be taken after the subject has been supine for at least 5 minutes. Measurements should be repeated if clinically significant changes are observed or a machine error occurs. In addition, weight should be measured every 4 weeks, and height at screening and Week 24.*

[4] *Central laboratory. For the24 hours urine (LTB4)- in non-catheterised patients all urine samples over the period should be collected, as completely as possible. For younger children, urine from diapers/nappies should be collected if feasible.*

[5] *Plasma sC5b-9 is mandatory before study entry and may be performed more frequently than shown at the investigator's discretion.*

[6] *Liver function, Renal function including eGFR calculation & LDH.*

[7] *Including haptoglobin.*

[8] *Urinalysis: UPCR & Protein.*

[9] *For females of childbearing potential.*

[10] *Urine pregnancy test.*

[11] *Patients who meet the primary endpoint before week 24 and who stop drug must attend the Week 24 visit and 30 day safety visit after last dose.*

[12] *End of Study is two years after of HSCT.*

[13] *Samples for PK and efficacy measurements (free nomacopan, CH50, total C5, LTB4(urine), sC5b-9, and C3b) will only be taken if patient received study drug < 1 week prior to this visit.*

[14] *For children in the youngest two cohorts (≥ 0.5 to < 2 years, and ≥ 2 to < 9 years), the dose will be re-calculated at the **week 8** and **week 16** visits using the child's new weight measured at that visit. The new adjusted dose should be given after all study procedures have been performed. This new adjusted dose will **not** require an ablating dose.*

[15] *Only SAEs considered possibly related or related to nomacopan to be reported at these visits.*
[16] *12-lead ECG*

18.3 SCHEDULE OF EVENTS PART A (DOSE INCREASE)

Evaluation & Procedures	Day n Dose Increase[7] Intense Monitoring. (single ablation dose followed by increased maintenance dose 12 hrs later)				Day n+1 Intense Monitoring			Day n+2	Day n+6 Intense Monitoring (± 1 day)				Proceed to Next Scheduled Visit
	Pre-dose	3 hrs	6 hrs	12 hrs Pre-dose	Pre-dose	6 hrs	12 hrs	Pre-dose	Pre-dose	3 hrs	6 hrs	12 hrs Pre-dose	
Eligibility & ICF													Scheduled visits according to 18.1 and 18.2 will continue as scheduled. If a PKPD visit that is scheduled due to a dose increase coincides with 18.1 or 18.2 scheduled visit the visits will be combined.
Medical History													
Demographics													
Physical Exam[1]													
Coombs' Test & ECG[8]													
Nasal & Throat Swabs													
Vital signs													
CH50[3]	x	x	x	x	x	x	x	x	x	x	x	x	
PK[3]	x	x	x	x	x	x	x	x	x	x	x	x	
Chemistry[2,4]									x				
Haematology[2,5]									x				
Urinalysis[2,6]	x												
Urine pregnancy test													
Drug Accountability												x	
AEs & Con Meds	x	x	x	x	x	x	x	x	x	x	x	x	
Overall survival status													
Long term follow-up													

[1] *A physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological & cardiovascular systems, lungs, abdomen (liver & spleen), lymph nodes & extremities. A GVHD assessment will also be performed.*
[2] *Local laboratory.*
[3] *Central laboratory.*
[4] *Liver function, Renal function including eGFR calculation & LDH.*
[5] *Including haptoglobin.*
[6] *Urinalysis: UPCR & Protein*
[7] *Dose Increase 1 is a maintenance dose of 0.45 mg/kg and Dose Increase 2 is a maintenance dose of 0.60 mg/kg.*
[8] *12-lead ECG*

18.4 SCHEDULE OF EVENTS PART B (FIRST 12 WEEKS)

Evaluation & Procedures	Screening	Day 1 (ablation dose followed by maintenance dose 12 hours later)		Day 2	Day 7 (± 1 day)	Day 14 (± 1 day)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)
	Up to -21 days	Pre-dose	12 hrs Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose
Eligibility & ICF	x								
Medical History	x								
Demographics	x								
Physical Exam[1]	x	x			x	x	x	x	x
ADAMTS13	x								
Coombs' Test[2] & ECG[13]	x								
Nasal & Throat Swabs[3]	x								
Vital signs[4]	x	x	x	x	x	x	x	x	x
CH50[5]		x		x	x	x	x	x	x
PK[5]		x		x	x	x	x	x	x
Total C5[5]		x		x	x	x	x	x	x
Antibodies[5]		x			x	x	x	x	x
Urinary LTB4[5]		x			x	x	x	x	x
sC5b-9[5,6]	x	x		x	x	x	x	x	x
C3b[5]		x			x	x	x	x	x
Chemistry[2,7]	x	x			x	x	x	x	x
Haematology[2,8]	x	x			x	x	x	x	x
Urinalysis[2,9]	x	x		x	x	x	x	x	x
Pregnancy test[10]	x[11]						x[12]	x[12]	x[12]
Drug Accountability					x	x	x	x	x
AEs & Con Meds	x	x	x	x	x	x	x	x	x
Overall survival status									
Long term follow-up									

[1] *A physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological & cardiovascular systems, lungs, abdomen (liver & spleen), lymph nodes & extremities. A GVHD assessment will also be performed.*

[2] *Local laboratory.*

[3] *Nasal & throat swab results prior to first dose is not an entry requirement. Meningitis prophylaxis with vaccines will be in accordance with the investigator's judgement & local guidelines.*

[4] *Vital signs: pulse rate, systolic & diastolic blood pressure, respiratory rate, & body temperature. Vital signs are to be taken after the subject has been supine for at least 5 minutes. Measurements should be repeated if clinically significant changes are observed or a machine error occurs. In addition, weight should be measured every 4 weeks, and height at screening and Week 24.*

[5] *Central laboratory. For the 24 hours urine (LTB4) - in non-catheterised patients all urine samples over the period should be collected, as completely as possible. For younger children, urine from diapers/nappies should be collected if feasible.*

[6] *Plasma sC5b-9 is mandatory before study entry and may be performed more frequently than shown at the investigator's discretion.*

[7] *Liver function, Renal function including eGFR calculation & LDH.*

[8] *Including haptoglobin.*

[9] *Urinalysis: UPCR & Protein.*

[10] *For females of childbearing potential.*

[11] *Serum pregnancy test, where available.*

[12] *Urine pregnancy test.*

[13] *12-lead ECG.*

18.5 SCHEDULE OF EVENTS PART B (WEEK 16 ONWARDS)

Evaluation & Procedures	Week 16 (± 5 days)	Week 20 (± 5 days)	End of Treatment Week 24[11] (± 5 days)	Safety Follow-up (30 days after last dose)	1 Year Post HSCT follow-up (± 5 days)	2 Years Post HSCT follow-up (± 5 days)	Early Withdrawal	Unscheduled Visit
	Pre-dose	**Pre-dose**	**Pre-dose**	(± 5 days)				
Eligibility & ICF								
Medical History								
Demographics								
Physical Exam[1]	x	x	x	x	x	x	x	x
Coombs' Test & ECG								
Nasal & Throat Swabs								
Vital signs[2]	x	x	x	x	x	x	x	x
CH50[3]	x	x	x[12]				x	
PK[3]	x	x	x[12]				x	
Total C5[3]	x	x	x[12]				x	
Antibodies[3]	x	x	x[12]				x	
Urinary LTB4[3]	x	x	x[12]				x	
sC5b-9[3,4]	x	x	x[12]				x	
C3b[3]	x	x	x[12]				x	
Chemistry[5,6]	x	x	x	x			x	
Haematology[5,7]	x	x	x	x			x	
Urinalysis[5,8]	x	x	x	x	x	x	x	x
Pregnancy test[9]	x[10]	x[10]	x[10]	x[10]			x[10]	
Drug Accountability	x	x	x	x			x	
AEs & Con Meds	x	x	x	x	X[13]	X[13]	x	x
Overall survival status					x	x		
Long term follow-up[11]					x	x		

[1] *A physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological & cardiovascular systems, lungs, abdomen (liver & spleen), lymph nodes & extremities. A GVHD assessment will also be performed.*

[2] *Vital signs: pulse rate, systolic & diastolic blood pressure, respiratory rate, & body temperature. Vital signs are to be taken after the subject has been supine for at least 5 minutes. Measurements should be repeated if clinically significant changes are observed or a machine error occurs. In addition, weight should be measured every 4 weeks, and height at screening and Week 24.*

[3] *Central laboratory. For the 24 hours urine (LTB4) -in non-catheterised patients all urine samples over the period should be collected, as completely as possible. For younger children, urine from diapers/nappies should be collected if feasible.*

[4] *Plasma sC5b-9 is mandatory before study entry and may be performed more frequently than shown at the investigator's discretion.*

[5] *Local laboratory.*

[6] *Liver function, Renal function including eGFR calculation & LDH.*

[7] *Including haptoglobin.*

[8] *Urinalysis: UPCR & Protein.*

[9] *For females of childbearing potential.*

[1] *Urine pregnancy test.*

[11] *Patients who meet the primary endpoint before week 24 and who stop drug must attend the Week 24 visit and the 30 day safety visit after last dose.*

[12] *Samples for PK and efficacy measurements (free nomacopan, CH50, total C5, ADA, LTB4(urine), sC5b-9, and C3b) will only be taken if patient received study drug < 1 week prior to this visit.*

[13] *Only SAEs considered possibly related or related to nomacopan to be reported at these visits.*

18.6 SCHEDULE OF EVENTS PART B (DOSE INCREASE)

Evaluation & Procedures	Day n Dose Increase[7] (single ablation dose followed by increased maintenance dose 12 hrs later)		Day n+1	Day n+6 (± 1 day)	Proceed to Next Scheduled Visit
	Pre-dose	12 hrs pre-dose	Pre-dose	Pre-dose	
Eligibility & ICF					Scheduled visits according to 18.4 and 18.5 will continue as scheduled. If a PKPD visit that is scheduled due to a dose increase coincides with 18.4 or 18.5 scheduled visit the visits will be combined.
Medical History					
Demographics					
Physical Exam[1]					
Coombs' Test & ECG[8]					
Nasal & Throat Swabs					
Vital signs					
CH50[3]	x	x	x	x	
PK[3]	x	x	x	x	
Chemistry[2,4]				x	
Haematology[2,5]				x	
Urinalysis[2,6]	x		x	x	
Urine pregnancy test					
Drug Accountability				x	
AEs & Con Meds	x	x	x	x	

[1] *A physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological & cardiovascular systems, lungs, abdomen (liver & spleen), lymph nodes & extremities. A GVHD assessment will also be performed.*
[2] *Local laboratory.*
[3] *Central laboratory.*
[4] *Liver function, Renal function including eGFR calculation & LDH.*
[5] *Including haptoglobin.*
[6] *Urinalysis: UPCR & Protein.*
[7] *Dose increase 1 is a maintenance dose of 0.45 mg/kg and Dose increase 2 is a maintenance dose of 0.60 mg/kg.*
[8] *12-lead ECG.*

18.7 SCHEDULE OF EVENTS PARTS A AND B (TREATMENT EXTENSION)

Evaluation & Procedures	Week 24	Week 28	Week 32	End of Study Treatment (Extension Period)	Safety Follow-up, 1 Year and 2 Years
		Pre-dose	Pre-dose	Pre-dose	
	As per Week 24 Visit in 18.2 or 18.5				As per 18.2 or 18.5
Eligibility & ICF					
Medical History					
Demographics					
Physical Exam[1]		x	x	x	
Coombs' Test & ECG[10]					
Nasal & Throat Swabs					
Vital signs[2]		x	x	x	
CH50[3]		x	x	x	
PK[3]		x	x	x	
Total C5[3]		x	x	x	
Antibodies[3]		x	x	x	
Urinary LTB4[3]		x	x	x	
sC5b-9[3,4]		x	x	x	
C3b[3]		x	x	x	
Chemistry[5,6]		x	x	x	
Haematology[5,7]		x	x	x	
Urinalysis[5,8]		x	x	x	
Urine pregnancy test[9]		x	x	x	
Drug Accountability		x	x	x	
AEs & Con Meds		x	x	x	

[1] *A physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological & cardiovascular systems, lungs, abdomen (liver & spleen), lymph nodes & extremities. A GVHD assessment will also be performed.*
[2] *Vital signs: pulse rate, systolic & diastolic blood pressure, respiratory rate, & body temperature. Vital signs are to be taken after the subject has been supine for at least 5 minutes. Measurements should be repeated if clinically significant changes are observed or a machine error occurs. In addition, weight should be measured every 4 weeks, and height at screening and Week 24.*
[3] *Central laboratory. For the 24 hours urine (LTB4) - in non-catheterised patients all urine samples over the period should be collected, as completely as possible. For younger children, urine from diapers/nappies should be collected if feasible.*
[4] *plasma sC5b-9 is mandatory before study entry and may be performed more frequently than shown at the investigator's discretion.*
[5] *Local laboratory.*
[6] *Liver function, renal function including eGFR calculation & LDH.*
[7] *Including haptoglobin.*
[8] *Urinalysis: UPCR & Protein.*
[9] *For females of childbearing potential.*
[10] *12-lead ECG.*

18.8 TOTAL BLOOD VOLUME CALCULATIONS

In the tables that follow we present data on the % of blood sampled at each time point in Part A of the trial for the youngest female patient (average weight of 7.3 kg and an average blood volume of 584 mL) permitted to enter the trial. Older patients and the Part B patients (who will have PKPD sampled less frequently) will have a smaller % of their blood sampled.

Table 9
Part A Dosing for youngest female patient –
maintenance dose agreed with the FDA as part of Model Informed Drug Development

6-month-old Female Average Weight (WHO) - 7.3 kg Average Blood Volume - 584 mL			Volume of Blood Parameter (mL)							Total Blood Volume (mL)	Total Blood Volume in 24 hours (mL)	% of Average Blood Volume for 6-month-old Female in 24-hour period
Study Visit	Study Day	Hour	Hem/Chem	Coombs'	Pregnancy	ADAMTS13	sC5b-9	CH50 + PK + ADA + C5	C3b			
Screening	-21	-	2	1	2	1.8	1			7.8	7.8	1.3
Day 1 Intensive	1	0 3 6 12	2				1	3.5 2.5 2.5 2.5	2	8.5 2.5 2.5 2.5	16.0	2.7
Day 2	2	0 6 12	2				1	2.5 2.5 2.5		5.5 2.5 2.5	10.5	1.8
Day 4	4	0	2				1	2.5		5.5	5.5	0.9
Day 7 Intensive	7	0 3 12	2				1	3.5 2.5 2.5	2	8.5 2.5 2.5	13.5	2.3
Day 14	14	0	2				1	3.5	2	8.5	8.5	1.5
Week 4 Intensive	28	0 3 12	2				1	3.5 2.5 2.5	2	8.5 2.5 2.5	13.5	2.3
Week 8	56	0	2				1	3.5		6.5	6.5	1.1
Week 12	84	0	2				1	3.5		6.5	6.5	1.1
Week 16	112	0	2				1	3.5		6.5	6.5	1.1
Week 20	140	0	2				1	3.5		6.5	6.5	1.1
Week 24	168	0	2				1	3.5		6.5	6.5	1.1
30 Day F-U	198	0	2							2.0	2.0	0.3

Table 10
Part A Dose Increase 1 for youngest female patient
to maintenance dose of 0.45 mg/kg/12 hours – if required

6-month-old Female Average Weight (WHO) - 7.3 kg Average Blood Volume - 584 mL			Volume of Blood Parameter (mL)							Total Blood Volume (mL)	Total Blood Volume in 24 hours (mL)	% of Average Blood Volume for 6-month-old Female in 24-hour period
Study Visit	Study Day	Hour	Hem/Chem	Coombs'	Pregnancy	ADAMTS13	sC5b-9	CH50 + PK + ADA + C5	C3b			
Screening	-21	-	2	1	2	1.8	1			7.8	7.8	1.3
Day 1 Intensive	1	0 3 6 12	2				1	3.5 2.5 2.5 2.5	2	8.5 2.5 2.5 2.5	16.0	2.7
Day 2	2	0 6 12	2				1	2.5 2.5 2.5		5.5 2.5 2.5	10.5	1.8
Day 4	4	0	2				1	2.5		5.5	5.5	0.9
Day n Dose Increase	7	0 3 12	2				1	3.5 2.5 2.5	2	8.5 2.5 2.5	13.5	2.3
Day n+1	8	0 6 12						2.5 2.5 2.5		2.5 2.5 2.5	7.5	1.2
Day n+2	9	0						2.5		2.5	2.5	0.4
Day n+6	13	0 3 6 12	2					2.5 2.5 2.5 2.5		4.5 2.5 2.5 2.5	12.0	2.1
Day 14	14	0	2				1	3.5	2	8.5	8.5	1.5
Week 4 Intensive	28	0 3 12	2				1	3.5 2.5 2.5	2	8.5 2.5 2.5	13.5	2.3
Week 8	56	0	2				1	3.5		6.5	6.5	1.1
Week 12	84	0	2				1	3.5		6.5	6.5	1.1
Week 16	112	0	2				1	3.5		6.5	6.5	1.1
Week 20	140	0	2				1	3.5		6.5	6.5	1.1
Week 24	168	0	2				1	3.5		6.5	6.5	1.1
30 Day F-U	198	0	2							2.0	2.0	0.3

Table 11
Part A Dose Increase 2 for youngest female patient
to maintenance dose of 0.60 mg/kg/12 hours – if required

6-month-old Female Average Weight (WHO) - 7.3 kg Average Blood Volume - 584 mL			Volume of Blood Parameter (mL)							Total Blood Volume (mL)	Total Blood Volume in 24 hours (mL)	% of Average Blood Volume for 6-month-old Female in 24-hour period
Study Visit	Study Day	Hour	Hem/Chem	Coombs'	Pregnancy	ADAMTS13	sC5b-9	CH50 + PK + ADA + C5	C3b			
Screening	-21	-	2	1	2	1.8	1			7.8	7.8	1.3
Day 1 Intensive	1	0 3 6 12	2				1	3.5 2.5 2.5 2.5	2	8.5 2.5 2.5 2.5	16.0	2.7
Day 2	2	0 6 12	2				1	2.5 2.5 2.5		5.5 2.5 2.5	10.5	1.8
Day 4	4	0	2				1	2.5		5.5	5.5	0.9
Day n Dose Increase 1	7	0 3 12	2				1	3.5 2.5 2.5	2	8.5 2.5 2.5	13.5	2.3
Day n+1	8	0 6 12						2.5 2.5 2.5		2.5 2.5 2.5	7.5	1.3
Day n+2	9	0						2.5		2.5	2.5	0.4
Day n+6	13	0 3 6 12	2					2.5 2.5 2.5 2.5		4.5 2.5 2.5 2.5	12.0	2.1
Day n Dose Increase 2	14	0 3 6 12	2				1	3.5 2.5 2.5 2.5	2	8.5 2.5 2.5 2.5	16.0	2.7
Day n+1	15	0 6 12						2.5 2.5 2.5		2.5 2.5 2.5	7.5	1.3
Day n+2	16	0						2.5		2.5	2.5	0.4
Day n+6	20	0 3 6 12	2					2.5 2.5 2.5 2.5		4.5 2.5 2.5 2.5	12	2.1
Week 4 Intensive	28	0 3 12	2				1	3.5 2.5 2.5	2	8.5 2.5 2.5	13.5	2.3
Week 8	56	0	2				1	3.5		6.5	6.5	1.1
Week 12	84	0	2				1	3.5		6.5	6.5	1.1
Week 16	112	0	2				1	3.5		6.5	6.5	1.1
Week 20	140	0	2				1	3.5		6.5	6.5	1.1
Week 24	168	0	2				1	3.5		6.5	6.5	1.1
30 Day F-U	198	0	2							2.0	2.0	0.3

18.9 ACUTE GVHD GRADING

(Glucksberg-Seattle, adapted from: Przepiorka D, Weisdorf D, Martin P, *et al*. 1994 Consensus conference on acute GVHD grading. *Bone Marrow Transplant. 1995;15:825–828*)

	Skin	Gastrointestinal (output/day)	Liver
Grade 0	No Rash	Child: <10 mL/kg/day Adult (if over 50kg): <500 mL/day	Bilirubin <2 mg/dL Or Bilirubin <34 µmol/L
Grade 1	Rash <25% Body Surface Area	Child: 10-19.9 mL/kg/day Or persistent nausea/vomiting Adult (if over 50kg): 500-1000 mL/day Or persistent nausea/vomiting	Bilirubin 2-3 mg/dL Or Bilirubin 34-51 µmol/L
Grade 2	Rash 25-50% Body Surface Area	Child: 20–30 mL/kg/day Adult (if over 50kg): 1001-1500 mL/day	Bilirubin 3.1-6 mg/dL Or Bilirubin 52-102 µmol/L
Grade 3	Rash >50% Body Surface Area	Child: >30 mL/kg/day Adult (if over 50kg): >1500 mL/day	Bilirubin 6.1-15 mg/dL Or Bilirubin 103-255 µmol/L
Grade 4	Generalised erythroderma and bullae formation	Severe abdominal pain with or without ileus Or Grossly bloody diarrhoea	Bilirubin >15 mg/dL Or Bilirubin >255 µmol/L

	Skin	Gastro-intestinal	Liver
Grade 1	1-2	0	0
Grade 2	3	1	1
Grade 3	0-3	2-3	2-4
Grade 4	4	4	0-4

18.10 SUMMARY OF MAIN CHANGES AND JUSTIFICATION - VERSION 2.0 - VERSION 3.0

- **Change 1: Title Page and Protocol Signature page– Authorised Signatories and Sponsor's Medical Expert**

Previous text:

AUTHORISED SIGNATORIES:	Dr James Fettiplace MBBS
SPONSOR'S MEDICAL EXPERT	Dr James Fettiplace MBBS

Updated text:

AUTHORISED SIGNATORIES:	**Dr Sanjeev K Khindri, MB, ChB, MRCP**
SPONSOR'S MEDICAL EXPERT	**Dr Sanjeev K Khindri, MB, ChB, MRCP** **Senior Medical Director**

Justification:
Change in the sponsor's medical expert and authorised signatory

- **Change 2: Inclusion Criterion #4, Secondary Endpoint, Central Laboratory Tests:**

*Previous text (**Synopsis, Section 5.1**):*

4. Clinical diagnosis of TMA with all of the following diagnostic criteria:
   - elevated serum C5b-9 (80% or more of ULN for age)
   - Urine protein creatinine ratio > 2 mg/mg (demonstrated on two separate morning samples, at least one day apart)
   - elevated LDH (> ULN)
   - thrombocytopaenia (< 50,000 per mm^3)
   - low haemoglobin concentration (< LLN)

   or
   Histological diagnosis of TMA with evidence of complement deposition:
   - Urine protein creatinine ratio > 2 mg/mg (demonstrated on two separate morning samples, at least one day apart), and

   elevated serum C5b-9 (80% or more of ULN for age)

*Updated text (**Synopsis, Section 5.1**):*

4. Clinical diagnosis of TMA with all of the following diagnostic criteria:
   - elevated **plasma** ~~serum~~ **s**C5b-9 (80% or more of ULN ~~for age~~)
   - Urine protein creatinine ratio > 2 mg/mg (demonstrated on two separate morning samples, at least one day apart)
   - elevated LDH (> ULN)
   - thrombocytopaenia (< 50,000 per mm^3)
   - low haemoglobin concentration (< LLN)

   or
   Histological diagnosis of TMA with evidence of complement deposition:

- Urine protein creatinine ratio > 2 mg/mg (demonstrated on two separate morning samples, at least one day apart), and

elevated ~~serum~~ **plasma s**C5b-9 (80% or more of ULN ~~for age~~)

*Previous text (**Secondary Endpoints – Synopsis, Section 4.2.2**):*

- Percentage of patients who achieve the primary endpoint of urine protein creatinine ratio ≤ 2 mg/mg (the nephrotic threshold) for ≥ 28 days
- Platelet transfusion independence† for ≥ 28 days
- Serum sC5b-9 ≤ ULN
- Lactate dehydrogenase (LDH) ≤ ULN
- Normalization of haptoglobin

*Updated text (**Secondary Endpoints– Synopsis, Section 4.2.2**):*

- Percentage of patients who achieve the primary endpoint of urine protein creatinine ratio ≤ 2 mg/mg (the nephrotic threshold) for ≥ 28 days
- Platelet transfusion independence† for ≥ 28 days
- **Plasma** ~~Serum~~ sC5b-9 ≤ ULN
- Lactate dehydrogenase (LDH) ≤ ULN
- Normalization of haptoglobin

*Previous text (**Section 6.6.3 – Total C5, sC5b-9 and C3b assay**):*

All samples will be taken as per the Schedule of Events in Section 18. The screening sC5b-9 sample can be analysed locally or centrally for a quicker turnaround. All sC5b-9 samples that follow will be sent to a central laboratory.

*Updated text (**Section 6.6.3 – Total C5, sC5b-9 and C3b assay**):*

All samples will be taken as per the Schedule of Events in Section 18. ~~The screening sC5b-9 sample can be analysed locally or centrally for a quicker turnaround. All sC5b-9 samples that follow will be sent to a central laboratory.~~ All sC5b-9 samples will be analysed centrally and measured in plasma.

Justification:
To ensure a comparable assessment of soluble C5b9 (sC5b9) from clinical sites in both the USA and Europe we are now planning to use a single lab (Cincinnati Children's Hospital, CCH) for measurement of sC5b9 from all sites. CCH requires plasma rather than serum for use in their validated sC5b9 assay. The change from collecting serum to collecting plasma from patients does not present any safety issues as the mode (IV draw) and frequency is not changed by collecting plasma-EDTA rather than serum. The change to measurement of sC5b9 from plasma-EDTA rather than serum also has no impact on assessment of the secondary endpoint of "Serum sC5b9 < ULN" as the endpoint is a relative one. Thus it does not make a difference whether sC5b9 is measured from serum or plasma as if the sC5b9 is normalised at the end of nomacopan treatment patients achieve the endpoint *ie* patients join the trial with sC5b9 >ULN and to achieve the secondary endpoint must have sC5b9 < ULN at the last efficacy assessment in the trial before nomacopan treatment is stopped.

C5b-9 is a cell surface protein/biomarker and as we are measuring the circulating *ie* soluble C5b-9 in plasma, we have added sC5b-9 to provide clarity. We have made this change consistently throughout the protocol.

We are not aware of any age-specific reference ranges for sC5b-9 and therefore have modified the inclusion criterion to >80% of ULN without adjusting for age. Furthermore, as all samples are being analysed at a single central laboratory in a Children's Hospital, the laboratory's reference range will be applied across the overall study population.

- **Change 3: Inclusion Criterion #6**

*Previous text (**Synopsis, Section 5.1**):*
6. Provision of informed assent

*Updated text (**Synopsis, Section 5.1**):*
6. Provision of informed assent **(where appropriate)**

Justification:
To clarify that informed assent will not be taken from all participants but only where appropriate.

- **Change 4: Other Assessments - Pregnancy Test– Screening**

*Previous text (***Section 6.4.1 & 6.8.1**):

Blood samples: blood samples for haematology and chemistry will be taken for assay at the local laboratory, and blood samples for direct Coomb's Test, ADAMTS13, sC5b-9 and a serum pregnancy test for all females of childbearing potential will be taken for assay at the local or central laboratory.

*New text (***Section 6.4.1 & 6.8.1**):

Blood samples: blood samples for haematology, chemistry and direct Coombs' Test will be taken at the local laboratory. ADAMTS13 and sC5b-9 will be performed at a central laboratory. All females who are of childbearing potential must have a serum negative pregnancy test at screening. Where a site is not able to perform a serum pregnancy, a urine pregnancy test will be acceptable. This test will be performed at the local or central laboratory.

Justification:
Based on the outcome of ongoing feasibility and conduct of pre-study site selection visits, it has come to light that some sites will not be able to perform a serum pregnancy test, therefore, at these sites a urine pregnancy test will be acceptable.

- **Change 5: Section 6.4.2 Part A - Day 1, Day 2, Day 7, Week 4, Dose Increase (n, n+1, n+6) Pre-dose**

New text:

If the 12-hour samples cannot be taken for logistical reasons, then 9-hour samples can be taken.

Justification:
Based on the outcome of ongoing feasibility and conduct of pre-study site selection visits, it is come to light that many sites may not be able to perform the 12-hour blood draw as stipulated in the protocol. The issue has arisen from the opening times of laboratories and resourcing of site staff to

centrifuge and prepare the tubes for storage. Therefore, in these circumstances, a 9-hour sample is acceptable. The site should note and specify where this occurs.

- **Change 6: Section 6.4.2 Part A - Day 3**

New text:

These samples will NOT be taken for the youngest age cohort.

Justification:
In order to minimise the volume of blood drawn over any given 24-hour period and across the entire study, a trough sample will not be taken on Day 3. Trough samples are taken at other timepoints over the course of the study; therefore, the overall assessment of PK/PD will not be negatively impacted.

- **Change 7: Section 6.4.2 Part A - Day 7 (+/- 1 day), Week 4 (Day 28 (+/- 5 days)**

Previous text:

Additional blood samples for CH50 and PK assessments will be taken at 3, 6 and 12 hours (immediately prior to the next dose of nomacopan) after the morning dose. Any AEs and concomitant medications will be recorded at these time points.

New text:

Additional blood samples for CH50 and PK assessments will be taken at 3, 6 and 12 hours (immediately prior to the next dose of nomacopan) after the morning dose. In the youngest age cohort, samples will be taken pre-dose at 3 and 12 hours only. If the-12 hour samples cannot, be taken for logistical reasons, then 9-hour samples can be taken.

Justification:
In order to minimise the volume of blood drawn over any given 24-hour period and across the entire study, a 6-hour sample will not be taken on Day 7 and Week 4. With the evaluation of PK/PD at 3 and 12 hours the overall assessment of PK/PD will not be negatively impacted.

- **Change 8: Section 6.5.2 Haematology for Part A and Part B**

Previous text:

The haematology parameters to be assessed at each specified time point are haemoglobin, haematocrit, total WBC, neutrophils, RBC, platelets, reticulocytes, haptoglobin and MCV.

Updated text:

The haematology parameters to be assessed at each specified time point are haemoglobin, haematocrit, total WBC, neutrophils, **lymphocytes, monocytes, basophils, eosinophils**, RBC, platelets, reticulocytes, haptoglobin and MCV.

Justification:
A full white blood cell panel was missing and therefore has been added.

- **Change 9: Section 6.6.2 Pharmacokinetics (PK)**

Previous text:

Unbound nomacopan concentration will be measured from plasma-EDTA by ELISA. All samples will be taken as per the Schedule of Events in Section 18.

Updated text:

Unbound nomacopan concentration will be measured from **serum** ~~plasma-EDTA~~ by ELISA. All samples will be taken as per the Schedule of Events in Section 18.

Justification:
Plasma-EDTA sample for measurement of unbound nomacopan is incorrect. Our validated assay for measurement of unbound nomacopan requires a serum sample.

- **Change 10: Section 6.6.4 LTB4 (urinary)**

New text:

For determination of urinary LTB4, 24-hour urine samples will be collected. Patients should NOT be catheterised specifically to allow for the collection of this urine sample. For patients who are not catheterised (for other medical reasons), all urine samples should be collected over the defined 24-hour period. In younger children, where possible, urine from diapers/nappies should be collected.

Justification:
New text added to clarify that LTB4 will measured in a 24-hour urine sample and that patients should NOT be catheterised specifically to collect this sample. In addition, guidance has been provided on collecting urine from diapers/nappies in the youngest patients (where possible).

- **Change 11:– ALL Schedule of events Part A and Part B and Dose Calculation Tables**

The schedule of events and dose calculation tables have been updated to reflect the above changes.

18.11 SUMMARY OF MAIN CHANGES AND JUSTIFICATION – VERSION 3.0 - VERSION 4.0

- **Change 1:– Inclusion Criterion #3**

*Previous text (**Synopsis, Section 5.1**):*

3. TMA diagnosis within 100 days of their first allogeneic or autologous HSCT.

Updated text:

3. TMA diagnosis within ~~100 days~~ **a year** of their ~~first~~ allogeneic or autologous HSCT.

Justification:
In paediatric patients, whilst transplant associated TMA (TA-TMA) typically occurs early after allogenic HSCT with a median diagnosis of between 35 and 47 days and approximately 90 % occur within 100 days, a small but important number of patients develop TMA up to a year after HSCT. In addition, TMA can develop after any HSCT, whether this is the first or subsequent/sequential transplant, indeed may be more common after second or subsequent transplants. Based on this data and taking into account advise received from our investigators, we have revised the eligibility criteria to allow the recruitment of patients with TA-TMA that occurs within a year of any HSCT and not limited only to that occurring after the first transplant.

- **Change 2:– Exclusion Criterion #3**

*Previous text (**Synopsis, Section 5.2, 18-Schedule of Events, Blood Volume Tables**):*

3. Patients who do not receive nomacopan within 14 days of the initial diagnosis of TMA.

Updated text:

3. Patients who do not receive nomacopan within ~~14~~ **21** days of the initial diagnosis of TMA.

Justification:
Whilst it is important to identify and initiate treatment with nomacopan for TMA as soon as possible, given diagnostic and logistical challenges to complete all diagnostic tests and those to establish eligibility, we have, considered advice from our investigators and propose to allow for a screening window of up to 21 days, although a concerted effort to randomise eligible patients as soon as possible will be made.

- **Change 3:– Summary of known and potential risks and benefits to human patients**

*Previous text (**Section 3.3.1**):*

To date (August 2019), nomacopan has been administered by subcutaneous (*sc)* injection or ophthalmic (eye drops) routes to 64 subjects (32 healthy volunteers and 32 patients) - see Table 2. Fifty-six of the subjects are adults in clinical trials, and eight were children who received compassionate use nomacopan under a UK “specials licence”.

Nomacopan was administered to 16 healthy male subjects in a Phase Ia single ascending dose study (VA576), 16 healthy male subjects in a Phase Ib 7-day repeat dose study (AK577), one eculizumab-resistant PNH patient in a Phase II study (AK578), eight PNH patients in the Phase II study

(AK579), one eculizumab resistant PNH patient in AK585, five PNH patients in AK580, six bullous pemphigoid patients in AK801, and using ophthalmic eye drops three patients with atopic keratoconjunctivitis.

Additionally, eight complex paediatric HSCT-TMA patients with advanced disease were treated with subcutaneous nomacopan using a compassionate use/ "specials" licence.

In all of these subjects, nomacopan has generally been found to be well tolerated.

Table 12
Total Number of Subjects Exposed to Nomacopan in Clinical Trials & as Named Patients (07 Aug 2019)

Study	Phase	Number of Subjects	Indication/route of admin *sc* = subcutaneous *O* = ophthalmic eye drops
Healthy Volunteers			
VA576	Ia	16	Healthy volunteer, *sc*
VA577	Ib	16	Healthy volunteer, *sc*
Total Volunteers		32	
Patients			
AK578	II	1	PNH, *sc*
AK579	II	8	PNH, *sc*
AK580	III	5	PNH (ongoing), *sc*
AK585	II	1	PNH, *sc*
AK801	II	6	Bullous pemphigoid (ongoing), *sc*
AK701	II	3	Atopic keratoconjunctivitis (ongoing), *O*
Compassionate use/Specials licence named patients		8	HSCT-TMA Pediatric, *sc*
Total Patients		32	
Overall Total		64	

In the Phase Ia trial (VA576) four mild, non-serious AEs were reported in three subjects (two active and one placebo) but a causal relationship to the study drug was not established. There was no dose relationship and the AEs were mild and self-limiting.

In the Phase Ib trial (VA577), an AE was reported which the investigator considered was not study drug related. This patient was assessed by the investigator as having rhabdomyolysis and stopped treatment after the third dose of nomacopan. The patient also experienced asymptomatic raised creatinine kinase and serum myoglobin levels which the investigator considered were related to the administration of ciprofloxacin as a prophylactic antibiotic during the trial. Twenty-two other non-serious, mild/moderate AEs were reported in this trial in seven patients, all of which resolved without treatment.

In the Phase II trial (AK578) the only PNH subject who was enrolled and completed the study benefited from nomacopan and currently continues therapy on nomacopan twice daily in Study AK581 (15 mg every 12 hours). The drug was generally well-tolerated. Overall, two SAEs occurred within this study. The patient had breakthrough haemolysis (worsening of PNH symptoms presenting with fatigue and dark urine) on Day 5 of treatment before full control of the disease had

been achieved. The investigators considered that this SAE was unrelated to nomacopan. The second SAE was a lung infection in which the patient presented with fever and cough. This SAE was assessed as not related to nomacopan. No other significant findings arose from this study.

Overall, nomacopan was well tolerated in the Phase II AK579 trial. There were no drug related SAEs and few drug related AEs other than mild to moderate injection site reactions. SAEs were reported in two patients. One patient had an SAE of staphylococcal infection, and another patient had SAEs of angina pectoris, lethargy and dyspnoea. All four SAEs resolved during the study and were considered to be not related to nomacopan. The most frequently reported nomacopan-related AEs were injection site reactions (*eg* erythema, pruritis, bruising, pain, swelling, discharge, hypersensitivity, induration, or haematoma), which were reported in six out of the eight patients enrolled.

Two SAEs have been reported in Study AK580, neutropenic sepsis and haemolysis. Neither of these events was assessed as related to nomacopan, and they have both resolved. This study is ongoing.

Three SAEs were reported in Study AK585 in one patient (002-001) Grade 3 febrile neutropaenia, Grade 3 device-related infection and Grade 3 urinary tract infection. None of these events was assessed as related to nomacopan. All SAEs resolved. The study has finished.

One non-related SAE has been reported in Study AK801 (condition aggravated). The SAE resolved. This study is ongoing.

Patients in the PNH trials AK578, AK579, AK580 and AK585 are eligible to continue treatment with nomacopan within the long-term safety study (AK581). To date (August 2019) 10 patients have entered the AK581 study only four of whom have experienced treatment related AEs to date. These were mostly injection site reactions which have all resolved.

In all clinical trials to date nomacopan has been well tolerated and there have been no serious drug-related adverse events, no suspected unexpected serious adverse reactions (SUSARs) and no treatment emergent adverse events other than mild to moderate injection site reactions. These have been of a comparable type and severity to those seen with other subcutaneously administered drugs (*eg* insulin) and are not considered to be drug related. The most frequently reported TEAE is injection site discomfort, erythema, redness or pain.

Updated text:

Commented [RV1]: Hard to see what the changes are, perhaps we can bold the text in the updated text?

To date (August **2021**), nomacopan has been administered by subcutaneous (*sc)* injection or ophthalmic (eye drops) routes to **97** subjects (32 healthy volunteers and **65** patients) - see Table 2. Fifty-six of the subjects are adults in clinical trials, and eight were children who received compassionate use nomacopan under a UK “specials licence”

Nomacopan was administered to 16 healthy male subjects in a Phase Ia single ascending dose study (VA576), 16 healthy male subjects in a Phase Ib 7-day repeat dose study (AK577), one eculizumab-resistant PNH patient in a Phase II study (AK578), eight PNH patients in the Phase II study (AK579), one eculizumab resistant PNH patient in AK585, **nine** PNH patients in AK580, **nine** bullous pemphigoid patients in AK801, and using ophthalmic eye drops **six** patients with atopic keratoconjunctivitis.

Additionally, **nine** complex paediatric HSCT-TMA patients with advanced disease were treated with subcutaneous nomacopan using a compassionate use/ "specials" licence **or on a named patient basis**.

In all **~~of~~** these subjects, nomacopan has generally been found to be well tolerated.

Table 13
Total Number of Subjects Exposed to Nomacopan in Clinical Trials & as Named Patients (07 Aug 2021)

Study	Phase	Number of Subjects	Indication/route of admin *sc* = subcutaneous *O* = ophthalmic eye drops
Healthy Volunteers			
VA576	Ia	16	Healthy volunteer, *sc*
VA577	Ib	16	Healthy volunteer, *sc*
Total Volunteers		32	
Patients			
AK578	II	1	PNH, *sc*
AK579	II	8	PNH, *sc*
AK580	III	**9**	PNH, **~~(ongoing)~~**, *sc*
AK585	II	1	PNH **(ongoing)**, *sc*
AK801	II	**9**	Bullous pemphigoid (ongoing), *sc*
AK701	II	**6**	Atopic keratoconjunctivitis (ongoing: **LSLV complete: CSR being written**), *O*
Compassionate use/ /Specials licence named patients		8	HSCT-TMA Pediatric, *sc*
Compassionate use/Investigator-initiated program		**23**	**Covid-19 pneumonia, *sc***
Total Patients		**65**	
Overall Total		**97**	

In the Phase Ia trial (VA576) four mild, non-serious AEs were reported in three subjects (two active and one placebo) but a causal relationship to the study drug was not established. There was no dose relationship, and the AEs were mild and self-limiting.

In the Phase Ib trial (VA577), an AE was reported which the investigator considered was not study drug related. This patient was assessed by the investigator as having rhabdomyolysis and stopped treatment after the third dose of nomacopan. The patient also experienced asymptomatic raised creatinine kinase and serum myoglobin levels which the investigator considered were related to the administration of ciprofloxacin as a prophylactic antibiotic during the trial. Twenty-two other non-serious, mild/moderate AEs were reported in this trial in seven patients, all of which resolved without treatment.

In the Phase II trial (AK578) the only PNH subject who was enrolled and completed the study benefited from nomacopan and currently continues therapy on nomacopan twice daily in Study AK581 (15 mg every 12 hours). The drug was generally well-tolerated. Overall, two SAEs occurred within this study. The patient had breakthrough haemolysis (worsening of PNH symptoms presenting with fatigue and dark urine) on Day 5 of treatment before full control of the disease had been achieved. The investigators considered that this SAE was unrelated to nomacopan. The

second SAE was a lung infection in which the patient presented with fever and cough. This SAE was assessed as not related to nomacopan. No other significant findings arose from this study.

Overall, nomacopan was well tolerated in the Phase II AK579 trial. There were no drug related SAEs and few drug related AEs other than mild to moderate injection site reactions. SAEs were reported in two patients. One patient had an SAE of staphylococcal infection, and another patient had SAEs of angina pectoris, lethargy and dyspnoea. All four SAEs resolved during the study and were considered to be not related to nomacopan. The most frequently reported nomacopan-related AEs were injection site reactions (*eg* erythema, pruritis, bruising, pain, swelling, discharge, hypersensitivity, induration, or haematoma), which were reported in six out of the eight patients enrolled.

In the Phase III trial (AK580) in PNH, three patients experienced four SAEs. One patient had two SAEs of cholelithiasis and haemoglobinuria (associated with worsening of PNH). A second patient had an episode of catheter site infection and a third had an episode of viral gastroenteritis. These events were assessed as not being related to nomacopan, and all resolved. One patient had two SAEs of neutropenic sepsis and haemolysis during screening and were not randomised into the study. This study has finished.

Three SAEs were reported in Study AK585 in one patient (002-001) Grade 3 febrile neutropaenia, Grade 3 device-related infection and Grade 3 urinary tract infection. None of these events was assessed as related to nomacopan. All SAEs resolved. The study **is ongoing**.

In the Phase II trial (AK801) in BP, three patients each had one non-related SAE. One patient had an episode of a localised (knee) infection that had not resolved by the end of study. The other two patients had a single episode of condition (*ie* BP) aggravated with both resolving. This study has finished.

In the Phase II, randomised and placebo controlled trial in SACK (AK701), six patients received nomacopan whilst six received placebo. There were no SAEs. The study has finished.

Patients in the PNH trials AK578, AK579, AK580 and AK585 were eligible to continue treatment with nomacopan within the long-term safety study (AK581). **Three of fifteen patients experienced a total of 13 SAEs during the study. One patient experienced an episode of an *E. coli* UTI that was considered possibly related to nomacopan. Based on a history of previous recurrent UTIs that usually resolved with oral antibiotics, the sponsor did not consider this a related event. This patient also had three other SAEs. One patient had two unrelated SAE whilst the another had six unrelated SAEs. Only one of these events (pulmonary hypertension had not resolved). The study has finished.**

In all clinical trials to date nomacopan has been well tolerated and there have been no serious drug-related adverse events, no suspected unexpected serious adverse reactions (SUSARs) and no treatment emergent adverse events other than mild to moderate injection site reactions. These have been of a comparable type and severity to those seen with other subcutaneously administered drugs (*eg* insulin) and are not considered to be drug related. The most frequently reported TEAE is injection site discomfort, erythema, redness or pain.

Justification:
Updated safety information on completed and ongoing studies in line the most recent DSUR 07 Aug 2021