Akari Therapeutics PLC

AK901

Multicentre Study of Nomacopan in Paediatric Haematopoietic Stem-Cell Transplant Associated Thrombotic Microangiopathy

Part A

18FEB2021

Statistical Analysis Plan

Final Version 1.0

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List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ATC	anatomical therapeutic chemistry
CRF	case report form
CTCAE	common terminology criteria for adverse events
ECG	electrocardiogram
ELISA	enzyme linked immunosorbent assay
GFR	glomerular filtration rate
GVHD	graft versus host disease
HSCT	haematopoietic stem cell transplantation
HSCT-TMA	host stem cell transplant associated thrombotic microangiopathy
ICF	informed consent form
ICH	international conference on harmonisation
LDH	lactate dehydrogenase
LTB4	leukotriene B4
MedDRA	medical dictionary for regulatory activities
PD	pharmacodynamics
PK	pharmacokinetic
PP	patient profile
PT	preferred term
RBC	red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TCA	terminal complement activation
TMA	thrombotic microangiopathy
ULN	upper limit of normal
UPCR	urine protein creatinine ratio
WHODRUG	world health organization drug dictionary

1. Introduction

This statistical analysis plan (SAP) describes the data presentations for Part A of the AK901 two-part study, based on protocol Version 2.0, dated 29APR2020. Part A of the study aims to confirm an effective dose algorithm of nomacopan in paediatric patients with Host Stem Cell Transplant Associated Thrombotic Microangiopathy (HSCT-TMA). Data derived in Part A will be combined with existing data for pharmacokinetic (PK) and pharmacodynamic (PD) simulation modelling, to define an age-based dosing regimen that will be used in Part B to evaluate the efficacy of nomacopan in paediatric patients.

All planned data presentations for Part A of this study will be contained in this SAP document. This SAP is based on International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 and E9 Guidelines. A separate SAP will be developed for Part B.

2. Objectives

2.1. Dose algorithm confirmation

- To confirm the effective dose of nomacopan for the ablation of terminal complement activity (TCA) in paediatric patients with HSCT-TMA

2.2. Efficacy and safety

- To define an age-based dosing regimen of nomacopan that can be used in Part B to completely control complement activity in paediatric patients
- To evaluate safety and tolerability of nomacopan

3. Investigational Plan

3.1. Overall Study Design and Plan

This is an open-label, multi-centre, two-part study in paediatric patients who have undergone allogeneic or autologous HSCT and developed HSCT-TMA within 100 days of diagnosed HSCT using an adapted version of the diagnostic criteria of the Bone Marrow Transplant Clinical Trials Network and International Working Group[1].

A total of seven patients will be recruited to Part A, in three age range cohorts: three patients aged ≥ 0.5 to < 2 years and four other patients with at least one aged ≥ 2 to < 9 years, and at least one aged ≥ 9 to < 18 years. Patients will be treated with nomacopan over a period of 24 weeks (± 5 days). All patients will have a safety follow-up 30 days (± 5 days) after the last dose of nomacopan, and long-term follow-up visits will be performed at one and two years after the HSCT. The end of the study will occur when all surviving patients have attended the long-term follow-up visit two years after diagnosis of HSCT, however Part A data will be analyzed once the last enrolled patient has attended Week 24 visit.

Patients may stop taking nomacopan sooner than 24 weeks if one or both components of the primary endpoint has been met (see section 3.2) and the treating clinician considers that there is no longer a need for the patient to be treated with study drug.

In exceptional circumstances, the investigator may request continuation of treatment with nomacopan beyond 24 weeks, for clinical reasons, and the sponsor may agree to supply the investigator with nomacopan for an additional 12-week period only. All patients that are treated after week 24 will undergo safety assessments every 4 weeks while on the drug, and then will attend a safety follow-up 30 days (± 5 days) after the last dose of nomacopan.

3.2. Study Endpoints

The data related to the endpoints listed below (which are the endpoints for Part B of the study) will be provided through Patient Profiles (PP) and individual patient listings.

3.2.1. Primary Endpoint

This is a composite primary endpoint:

- Red blood cell (RBC) transfusion independence for ≥ 28 days immediately prior to any scheduled clinical visit up to Week 24

or

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

3.2.2. Secondary Endpoints

Efficacy:

- Percentage of patients who achieve the primary endpoint of UPCR ≤ 2 mg/mg (the nephrotic threshold) for ≥ 28 days
- Platelet transfusion independence for ≥ 28 days
- Serum sC5b-9 ≤ upper limit normal (ULN) at final efficacy assessment
- Lactate dehydrogenase (LDH) ≤ ULN at final efficacy assessment
- Normalization of haptoglobin at final efficacy assessment (to be analyzed only in a subset of patients where haptoglobin was abnormal at baseline)

Safety:

- Safety and tolerability of nomacopan

3.3.3. Exploratory Endpoints

- Overall survival at Week 24 after the first dose of nomacopan, and at one year and two years post HSCT
- Percentage of patients with UPCR ≤ 1.5 mg/mg for ≥ 28 days
- Percentage of patients with UPCR ≤ 1 mg/mg for ≥ 28 days
- Renal function monitoring at baseline and at one year and two years post HSCT

3.3. Treatments

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

The following dose regimens will be given to patients in Part A, dependent on age category:

Age Category	Ablating Dose	Maintenance Dose
	Day 1; two doses 12 hours apart	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

3.4. Dose Adjustment/Modifications

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.

Dose can be escalated at two different timepoints, as described in section 6.2 of the protocol.

4. General Statistical Considerations

Only Patient Profiles (PP) and individual subject data listings will be created for Part A of the study. Although most information presented on these outputs will be taken directly from the case report forms (CRFs), other outcomes will have to be derived.

Separate PPs will be created for each patient. Data within the PPs will be grouped in different sections and displayed by data type where the following data types will be included: demographics and baseline characteristics, disease history – HSCT/HSCT-TMA and justification for inclusion in the study – and general medical history, prior medications, concomitant medications, exposure and adherence to nomacopan, blood and platelet transfusions, UPCR data, achievement status of the primary and secondary endpoints, survival status, safety and tolerability of nomacopan treatment and PKPD parameters. Details on the specific data types are provided from section 5.

Along with standard study information such as sponsor and protocol number, the following information will be presented in the header of the PP: patient ID, age at screening, sex, weight at baseline and clinical site.

For Part A, baseline will be defined as the last valid assessment before the first nomacopan dose. For most endpoints, baseline will be Day 1 Pre-dose assessment.

Study day will be counted from the date of first nomacopan dose (Day 1).

Imputation of partial dates will not be applied to the outputs, as dates in there will be presented as given in the database, however if events need to be categorized to certain periods depending on the occurrence date (e.g. if a historical medication was taken prior to / on or post HSCT), then the rules used to handle partial dates are described in Section 6.1.

Source data verification will be used to review the data entered in the CRF and data will only be considered final once it is 100% verified.

All analyses will be conducted using SAS Version 9.4 or higher.

4.1. Sample Size

Part A will recruit 7 patients, in three age range cohorts (three patients in the ≥ 0.5 to < 2 years category, and four other patients with at least one aged ≥ 2 to < 9 years, and at least one aged ≥ 9 to < 18 years).

4.2. Randomization, Stratification, and Blinding

This is a one-arm, open-label study. No randomization, stratification or blinding measures will be applied.

4.3. Analysis Set

For Part A, all patients for whom a signed informed consent/assent form (ICF) was obtained are considered enrolled and are part of the Enrolled Analysis Set. Those will be the patients present in the data reporting described in this SAP. No other analysis sets are applicable for Part A.

5. Demographics and Baseline Characteristics

5.1. Demographics

Per CRF, age can be collected either in months or in years. In case age is given in months, it will be presented in the outputs as the number of complete years and the number of months (e.g. 15 months will be displayed as 1 year, 3 months). If the patient is younger than one year, age will be displayed in months only (e.g. 10 months).

5.2. Disease History

The following information will be provided in the PPs: HSCT subtype, reason for HSCT, date of HSCT, donor type, stem cell source, date of HSCT-TMA diagnosis, time between HSCT and HSCT-TMA diagnosis (in days), details of HSCT-TMA diagnostic criteria, justification for inclusion (screening results for serum sC5b-9, UPCR, LDH, haemoglobin, Coomb's test, GVHD and pregnancy test) and time between HSCT-TMA diagnosis and start of nomacopan treatment (in days).

Time between HSCT-TMA diagnosis and start of nomacopan treatment (in days) will be derived as follows:

$$\begin{aligned} &Time\ between\ HSCT\text{-}TMA\ Diagnosis\ and\ Start\ of\ Nomacopan\ Treatment\ (days) \\ &\quad = Date\ of\ First\ Nomacopan\ Treatment - Date\ of\ HSCT\text{-}TMA\ Diagnosis + 1 \end{aligned}$$

A separate by-patient listing will be provided including patient number, date of ICF, patient age, time between HSCT and HSCT-TMA diagnosis and between HSCT-TMA diagnosis and start of nomacopan treatment.

5.3. Medical History

Medical history records will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0 or higher. The reported term, coded variables (system organ class [SOC] and preferred term [PT]) and start and end dates (or ongoing status) will be presented.

6. Treatments and Medications

6.1. Prior and Concomitant Medications

Although the dates of reported medications will be presented in the PPs as given in the database, imputation of partial dates will be applied in order to classify them as

- prior medication (prior to HSCT / on or post HSCT) or
- concomitant medication (taken during treatment with nomacopan).

Assuming HSCT date and nomacopan start date are always complete and never partial, the following imputation rules will be applied for incomplete medication start date:

- Day missing/unknown:
  - HSCT date and nomacopan start date are in different months
    - If medication month/year is prior to HSCT month/year, classify as “prior to HSCT”
    - If medication month/year is the same as or post HSCT month/year but prior to nomacopan start month/year, classify as “on or post HSCT”
    - If medication month/year is the same as or after nomacopan start month/year, classify as “concomitant”
  - HSCT date and nomacopan start date are in the same month
    - If medication month/year is prior to HSCT/nomacopan start month/year, classify as “prior to HSCT”
    - If medication month/year is the same as or post HSCT/nomacopan start month/year, classify as “concomitant”

- Day and month missing/unknown:
  - HSCT date and nomacopan start date are in different years
    - If medication year is prior to HSCT year, classify as “prior to HSCT”
    - If medication year is the same as HSCT year, classify as “on or post HSCT”
    - If medication year is the same as or after nomacopan start year, classify as “concomitant”
  - HSCT date and nomacopan start date are in the same year
    - If medication year is prior to HSCT/nomacopan start year, classify as “prior to HSCT”
    - If medication year is the same as or post HSCT/nomacopan start year, classify as “concomitant”.

PPs will be provided with all prior medications. Information will be presented identifying medications that started prior to HSCT and medications that started on the day of, or post, HSCT. The reported term, coded variables (PT and anatomic therapeutic chemical [ATC] Level 4) and start and end dates (or ongoing status) will be presented.

Additionally, all concomitant medications will be presented in a separate section of the PPs.

Medication records will be coded according to the World Health Organization drug dictionary (WHODRUG) March 2020, or higher.

6.2. Study Treatments

6.2.1. Extent of Exposure

The dosing regimen of each patient, with dose type (ablating or maintenance), expected and actual doses, as well as the reasons for every dose change will be provided in the PPs.

Additionally, the total duration of dosing will be presented, and calculated as follows:

$$Total\ Duration\ of\ Dosing\ (days) = Date\ of\ Last\ Nomacopan\ Treatment - Date\ of\ First\ Nomacopan\ Treatment + 1$$

A by-patient listing containing the following information will be provided: start date of study treatment, start ablating dose (mg/kg), maintenance dose (mg/kg), dose changes and respective reasons, end date of study treatment, total duration of dosing and percentage of drug adherence.

6.2.2. Drug Adherence

For each patient, a drug adherence measurement will be calculated based on the number of vials used and the number of vials expected to be used, as follows:

$$Drug\ Adherence\ (\%) = \frac{Number\ of\ Vials\ Actually\ Used}{Number\ of\ Vials\ Expected\ to\ be\ Used} * 100$$

The number of vials used will be present in the database and the number of vials expected to be used will be calculated according to the patient's cohort and weight (or weights in case the weight is re-assessed during the study for dosing purposes, see section 3.4), the total duration of dosing, the starting dose regimen (ablating and maintenance doses) and the regimen changes throughout the study (two possible dose increases, see protocol section 6.2).

An example of the calculation of the number of vials expected to be used is presented in Appendix 14.4.

7. Efficacy Analysis

7.1. Primary Efficacy Endpoint

The primary endpoint is comprised of two components:

- RBC transfusion independence for ≥ 28 days immediately prior to any scheduled visit up to Week 24

or

- UPCR ≤ 2 mg/mg for ≥ 28 days immediately prior to any scheduled visit up to Week 24

RBC transfusion independence is defined as no RBC 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.

UPCR will be assessed through urinalysis and the respective results provided by the local laboratory and recorded in the CRF.

Both these endpoint components will be assessed pre-dose during visits at Week 4, 8, 12, 16, 20 and 24 and if at any of these timepoints at least one of the endpoints is met, the patient will be considered as having met the primary endpoint.

Blood transfusion details (date, number of units, indication and information on TMA relationship) will be provided separating between transfusions post HSCT and prior to nomacopan treatment and transfusions during nomacopan treatment. Imputation of partial dates for classification (between HSCT and start of nomacopan treatment, during nomacopan treatment) will be performed as described in section 6.1. All transfusions that were given starting from 30 days prior to enrollment will be included.

Additionally, the achievement or failure of the primary endpoint will be presented, explaining which component(s) were met or not met, and at which visit.

All UPCR results collected per scheduled timepoint will be presented.

7.2. Secondary Efficacy Endpoints

The following secondary endpoints will be assessed:

- Platelet transfusion independence ≥ 28 days immediately prior to any scheduled visit up to Week 24

Platelet transfusion independence is defined as no platelet transfusion attributable to, or required to manage, TMA. Transfusions required for causes other than TMA will not be considered within the evaluation of this secondary efficacy endpoint.

Platelet transfusion details (date, number of units, indication and information on TMA relationship) will be provided separating between transfusions post HSCT and prior to nomacopan treatment and transfusions during nomacopan treatment. Imputation of partial dates for classification (between HSCT and start of nomacopan treatment, during nomacopan treatment) will be performed as described in section 6.1. All transfusions that were given starting from 30 days prior to enrollment will be included.

This endpoint will be assessed pre-dose during visits at Week 4, 8, 12, 16, 20 and 24 and if at any of these timepoints the endpoint is met, the patient will be considered as having met this secondary endpoint.

- Serum sC5b-9 ≤ ULN

Serum sC5b-9 will be measured by the central laboratory and this endpoint assessed at the last efficacy assessment before nomacopan treatment is stopped, up to Week 24 visit.

All available sC5b-9 results will be presented in the PPs and values ≤ ULN will be flagged.

- LDH ≤ ULN

LDH will be measured by the local laboratory and recorded in the CRF. This endpoint will be assessed at the last efficacy assessment before nomacopan treatment is stopped, up to Week 24 visit.

All available LDH results will be presented in the PPs and values ≤ ULN will be flagged.

- Normalization of haptoglobin

Haptoglobin will be measured by the local laboratory and recorded in the CRF. For the subset of patients with an abnormal haptoglobin result at baseline, this endpoint will be assessed at the last efficacy assessment before nomacopan treatment is stopped, up to Week 24 visit.

All available haptoglobin results will be presented in the PPs along with the information if the result is still abnormal (no normalization) or normal (normalization), for the subset of patients described above.

The achievement or failure of each secondary endpoint will be presented in the PPs, along with details on which endpoint(s) were met at which visit.

7.3. Exploratory Efficacy Endpoints

Survival will be assessed at Week 24 and at 1 year and 2 years post HSCT for the patients who complete the respective period and for the patients who withdrew from the study earlier.

Patient's survival status, date of death (if applicable) and principal cause of death will be provided in the PPs.

The primary efficacy endpoint, secondary efficacy endpoints and overall survival endpoint will be presented as by-patient listings.

8. Safety Analysis

8.1. Adverse Events

All adverse events (AEs), serious AEs (SAEs) and AEs of special interest (AESIs) will be provided in the PPs.

Along with the reported term, coded variables, information on AE start and end dates (or ongoing status), outcome, severity measured by the Common Terminology Criteria for Adverse Events (CTCAE) criteria, action taken with study treatment, relationship to study treatment, seriousness and whether it caused study discontinuation will be presented.

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. The investigator will report in the CRF whether an SAE meets the criteria for being considered an AESI.

Adverse event records will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0 or higher.

8.1.1. Serious Adverse Events

A by-patient listing with all reported SAEs will also be provided, including the following information: reported term, coded variables (SOC and PT), start and end dates (or ongoing status), outcome, severity measured by the CTCAE criteria, action taken with study treatment, relationship to study treatment, whether it caused study discontinuation and reason for serious classification (e.g. hospitalization, life-threatening, death).

9. Pharmacokinetics

Nomacopan drug levels will be measured from plasma-EDTA by ELISA by the central laboratory and the results will be presented in the PPs.

All C5 samples will be sent to the central laboratory and the results will be provided in the PPs.

All urinary leukotriene B4 (LTB4) samples will be sent to the central laboratory and the results provided in the PPs.

10. Pharmacodynamics

TCA will be measured from serum by CH50 ELISA which measures formation of the terminal complement complex. CH50 will be measured by the central laboratory and the results provided in the PPs.

11. Interim Analysis

There is no interim analysis planned for Part A.

12. Changes in the Planned Analysis

Not applicable.

13. References

1. Cho BS, Yahng SA, Lee SE, Eom KS, Kim YJ, Kim HJ, Lee S, Min CK, Cho SG, Kim DW, Lee JW, Min WS, Park CW.
   Validation of recently proposed consensus criteria for thrombotic microangiopathy after allogeneic hematopoietic stem-cell transplantation.
   Transplantation 2010;90:918-26.

14. Appendices

14.1. 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 -14 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	x	x[14]	x[14]	x[14]	x[14]		x	x	x	x	x
PK[6]		x	x	x	x	x	x	x	x	x	x[14]	x[14]	x[14]	x[14]		x	x	x	x	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.*
[7] *Serum sC5b-9 is mandatory before study entry and may be performed more frequently than shown at the investigator's discretion. Screening sample can be performed at a local laboratory.*
[8] *Liver function, Renal function including GFR Calculation & LDH.*
[9] *Including haptoglobin.*
[10] *Urinalysis: UPCR & Protein.*
[11] *For females of childbearing potential.*
[12] *Serum pregnancy test, where available.*
[13] *Urine pregnancy test.*
[14] *A dose increase CANNOT be given until Day 7 PK/PD results are available.*

14.2. 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**
	Predose	**Predose**	**Predose**	**Predose**	**Predose**	(± 5 days)				**Predose**
Medical History										
Demographics										
Physical Exam[1]	x	x	x	x	x	x	x	x	x	x
Coombs Test[2] & ECG										
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[14]				x	
Total C5[4]	x				x				x	
Antibodies[4]	x				x				x	
Urinary LTB4[4]	x				x				x	
sC5b-9[4,5]	x				x				x	
C3b[4]	x				x				x	
Chemistry[2,6]	x				x				x	
Haematology[2,7]	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.
[5] Serum sC5b-9 is mandatory before study entry and may be performed more frequently than shown at the investigator's discretion. Screening sample can be performed at a local laboratory.
[6] Liver function, Renal function including GFR 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 first diagnosis 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.

14.3. 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
	Predose	3 hrs	6 hrs	12 hrs Predose	Predose	6 hrs	12 hrs	Pre-dose	Predose	3 hrs	6 hrs	12 hrs Predose	
Eligibility & ICF													Scheduled visits will continue as scheduled. If a PKPD visit that is scheduled due to a dose increase coincides with a scheduled visit the visits will be combined.
Medical History													
Demographics													
Physical Exam[1]													
Coombs Test & ECG													
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 GFR 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.

14.4. Calculation of Number of Vials Expected to be Used (Example)

Patient is aged 4 years old, in cohort with ablating dose 1.3 mg/kg and with the following weight assessments: 17.2 kg at Day 1, 21.5 kg at Week 8 and 24.3 kg at Week 16.
Two dose increases are assumed for this patient: the first at Day 7 and the second at Day 14.
This patient is also assumed to end treatment at Week 24.

Please see sections 3.3 and 3.4 of this SAP and section 6.2 of the protocol for information on dose regimens and dose increases, respectively.

Dose in mg is calculated by multiplying the dose in mg/kg with the patient's weight in kg.

The number of vials needed according to the dose to be administered (in mg) is as follows:

Preparation of a dose that is	Number of vials needed
15 mg or less	1
16 – 30 mg	2
31 – 45 mg	3
46 – 60 mg	4
61 – 75 mg	5

The calculation of the number of vials expected to be used for the patient is presented below.

Day / Week	Morning Dose			Evening Dose		
	Dose (mg/kg)	**Dose (mg)**	**Number of vials**	**Dose (mg/kg)**	**Dose (mg)**	**Number of vials**
Day 1	1.3	22.36	2	1.3	22.36	2
Day 2	0.30	5.16	1	0.30	5.16	1
Day 3	0.30	5.16	1	0.30	5.16	1
Day 4	0.30	5.16	1	0.30	5.16	1
Day 5	0.30	5.16	1	0.30	5.16	1
Day 6	0.30	5.16	1	0.30	5.16	1
Day 7 (dose increase #1)	1.3	22.36	2	0.45	7.74	1
Day 8	0.45	7.74	1	0.45	7.74	1
Day 9	0.45	7.74	1	0.45	7.74	1
Day 10	0.45	7.74	1	0.45	7.74	1
Day 11	0.45	7.74	1	0.45	7.74	1
Day 12	0.45	7.74	1	0.45	7.74	1
Day 13	0.45	7.74	1	0.45	7.74	1
Day 14 (dose increase #2)	1.3	22.36	2	0.60	10.32	1
Week 3 to Week 7	0.60	10.32	35 (1 vial/dose, for 35 days)	0.60	10.32	35 (1 vial/dose, for 35 days)
Week 8 to Week 15 (weight re-assessed at Week 8)	0.60	12.90	56 (1 vial/dose, for 56 days)	0.60	12.90	56 (1 vial/dose, for 56 days)
Week 16 to Week 24 (weight re-assessed at Week 16)	0.60	14.58	56 (1 vial/dose, for 56 days)	0.60	14.58	56 (1 vial/dose, for 56 days)
Total			**164**			**162**

According to the table above, 164 vials would be needed for the morning doses and 162 for the evening doses which means that the total number of vials expected to be used is 326.