Swedish Orphan Biovitrum AB

An Open Label, Single Arm, Multi-Centre, Post-authorization Study to Describe the Safety and Efficacy of Emapalumab for the Treatment of Primary Hemophagocytic Lymphohistiocytosis in Treatment Experienced Chinese Patients

Sobi.EMAPALUMAB-104

Statistical Analysis Plan

Version: 4.0

Date: 06Aug2025

Sponsor Approval Page

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Company Name:

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Modification History

Version	Version Date	Author	Description
1.0	05DEC2022	[redacted]	FINAL
2.0	24OCTC2023	[redacted]	FINAL Definition of Overall Response updated with an addition of modified Overall Response as supplementary analysis (for details refer to Section 6.8.2 and Section 6.12).
3.0	24JUN2025	[redacted]	FINAL General statistical consideration updated to account for situation where non-numeric values are entered for quantitative measurements (for details refer to Section 6.1). Method of Overall Response analysis updated to clarify from which visit should observation be used (for details refer to Section 6.8.2). Overall survival added in Secondary Analysis Supporting Secondary Objectives (for details refer to Section 6.2.2 and 6.8.2) AE listings added in planned adverse event analysis (for details refer to Section 6.10.1).
4.0	06AUG2025	[redacted]	FINAL Method of Ability to Reduce Glucocorticoids analysis updated (for details refer to Section 6.8.2)

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Abbreviation

Abbreviation	Specification
AE	Adverse event
BP	Blood pressure
CRF	Case report form
CT	Computed tomography
DRM	Data review meeting
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
IV	Intravenous
HLGT	High level group term
HLH	Hemophagocytic lymphohistiocytosis
HLT	High level term
HSCT	Hematopoietic stem cell transplant
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
pHLH	Primary hemophagocytic lymphohistiocytosis
PO	Per os
PT	Preferred term
Q1	1st quartile
Q3	3rd quartile
sADR	Serious adverse drug reaction
SAE	Serious adverse event
SD	Study day
SOC	System organ class
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

This statistical analysis plan was drafted for the "*An Open Label, Single Arm, Multi-Centre, Post-authorization Study to Describe the Safety and Efficacy of Emapalumab for the Treatment of Primary Hemophagocytic Lymphohistiocytosis in Treatment Experienced Chinese Patients*" (protocol No.: Sobi.EMAPALUMAB-104) of *Swedish Orphan Biovitrum AB*. In this document, the contents and methods of statistical analysis will be described in detail.

This statistical analysis plan was based on protocol (version 2.0, 01Jun2022) and Case Report Form (CRF, version 1.0, 20Sep2022).

2. Study Design

This is an open-label, single-arm, multi-centre study to collect safety and efficacy data on emapalumab in treatment experienced male and female patients diagnosed with Primary hemophagocytic lymphohistiocytosis (pHLH). The study will be performed in China.

The study will recruit at least 10 patients, and up to 18 patients if enrolled within the recruitment period.

Patients should already have received conventional hemophagocytic lymphohistiocytosis (HLH) therapy (treatment experienced patients), without obtaining a satisfactory response according to the treating physician or having shown signs of intolerance to it.

Figure 1 summarizes the study design.

The study is divided into three parts: screening, treatment period, and follow-up. Patients will be admitted to the unit the day before the first administration of the study drug (study day minus one, SD-1).

Figure 1. Overview of the study design

<table>
<tr><th>SCREENING</th><th colspan="5">TREATMENT</th><th colspan="7">FOLLOW-UP</th></tr>
<tr><td rowspan="2">Day -14 to Visit 1</td><td>Visit 1 (SD 0)</td><td>Visit 2 (SD 3-4 and onwards) every 3-4 days</td><td>W8 Primary assessment timepoint if treatment continues</td><td>W9-onwards until start of conditioning for HSCT</td><td rowspan="2">EOT (3±1 day after last infusion) Primary assessment timepoint if treatment stopped before week 8</td><td>Pre-HSCT</td><td colspan="6">Post HSCT</td></tr>
<tr><td>Initial dose</td><td colspan="3">Subsequent doses</td><td>Pre-conditioning</td><td>W 1/2/3</td><td>D 30</td><td>D 60</td><td>D 100</td><td>M6</td><td>M 12 (EOS)</td></tr>
</table>

Abbreviations SD, study day; EOT, end of treatment; HSCT, hematopoietic stem cell transplant; W, week; D, day after HSCT; M, month; EOS, end of study

The patient will enter screening after informed consent is obtained and will undergo screening assessments to confirm eligibility. Duration of the screening period will be kept as short as possible and should not exceed 2 weeks.

First emapalumab infusion, at a dose of 1 mg/kg, marks the start of the treatment period. The treatment period is foreseen to continue until start of conditioning for HSCT, if deemed indicated for this patient. Infusions will take place twice weekly, at a dose determined by the Investigator for each infusion. Emapalumab will be administered on the background of dexamethasone, which can be tapered or increased as needed. No wash-out is required prior to conditioning for HSCT. Last visit of the treatment period is the end of treatment, which occurs 3 days after the last infusion of emapalumab. Assessment of efficacy objectives occurs at end of treatment. After the start of conditioning for HSCT (or treatment completion, if HSCT is not deemed indicated), the patient proceeds to follow-up period. Follow-up visits are planned in relation to the date of the HSCT, or last emapalumab infusion (if HSCT is not deemed indicated). Duration of the follow-up is one year after HSCT, or after the last emapalumab infusion. The end of study visit (EOS) for each patient will occur at the latest 18 months from first dose of emapalumab.

Patient will be considered screened after informed consent is obtained.

For further details on the schedule of events for treatment period and follow-up period, please refer to Table 3 and Table 4 in study protocol.

3. Estimand

Objectives	Endpoints	Estimand
Primary Objective: To collect safety data on emapalumab in treatment-experienced Chinese pHLH patients	**Primary Endpoint:** Permanent discontinuation of study drug due to emapalumab-related adverse events as judged by the investigator	Estimand 1: Primary Estimand Target population: All patients received at least one infusion of IMP Treatment：Refer to Section 6.4 in study protocol Endpoints：Refer to the left column Strategies for addressing intercurrent events： The treatment policy strategy will be applied for the estimand Population-level summary: The number and percentage of patients who permanently discontinue study drug due to emapalumab-related adverse events
	Secondary Endpoint 1: Treatment-emergent adverse events (AEs)	Estimand 1.1 Target population: All patients received at least one infusion of IMP Treatment：Refer to Section 6.4 in study protocol Endpoints：Refer to the left column Strategies for addressing intercurrent events： The treatment policy strategy will be applied for the estimand Population-level summary: Incidence of treatment-emergent AEs
	Secondary Endpoint 2: Treatment-emergent serious adverse events (SAEs)	Estimand 1.2 Target population: All patients received at least one infusion of IMP Treatment：Refer to Section 6.4 in study protocol Endpoints：Refer to the left column Strategies for addressing intercurrent events： The treatment policy strategy will be applied for the estimand Population-level summary: Incidence of treatment-emergent SAEs (refer to Section 6.8)
	Secondary Endpoint 3:	Estimand 1.3

	Treatment-emergent laboratory abnormalities	Target population: All patients received at least one infusion of IMP Treatment：Refer to Section 6.4 in study protocol Endpoints：Refer to the left column Strategies for addressing intercurrent events： The treatment policy strategy will be applied for the estimand Population-level summary: Incidence of treatment-emergent laboratory abnormalities (refer to Section 6.8)
	Secondary Endpoint 4: Treatment-emergent vital sign abnormalities	Estimand 1.4 Target population: All patients received at least one infusion of IMP Treatment：Refer to Section 6.4 in study protocol Endpoints：Refer to the left column Strategies for addressing intercurrent events： The treatment policy strategy will be applied for the estimand Population-level summary: Incidence of treatment-emergent vital sign abnormalities (refer to Section 6.8)
Secondary Objective: To collect efficacy data on emapalumab in treatment-experienced Chinese pHLH patients	**Secondary Endpoint 1:** Overall Response, i.e., achievement of either Complete or Partial Response or HLH Improvement, at EOT or Week 8 (whichever occurs earlier)	Estimand 2.1 Target population: All patients received at least one infusion of IMP Treatment：Refer to Section 6.4 in study protocol Endpoints：Refer to the left column Strategies for addressing intercurrent events： The treatment policy strategy will be applied for the estimand Population-level summary: The number and percentage of patients achieving overall response and each component of overall response at EOT or week 8 (whichever occurs earlier)
	Secondary Endpoint 2: Time to first Overall Response, i.e., time from the date of first dose of	Estimand 2.2 Target population: All patients received at least one infusion of IMP

	emapalumab to the first achievement of response (Complete or Partial Response or HLH Improvement)	Treatment：Refer to Section 6.4 in study protocol Endpoints：Refer to the left column Strategies for addressing intercurrent events： The treatment policy strategy will be applied for the estimand Population-level summary: Time to first response prior to HSCT will be estimated using Kaplan-Meier method
	Secondary Endpoint 3: Cumulative duration of response, i.e., total time in response from the first achievement of an Overall Response until EOT	Estimand 2.3 Target population: All patients received at least one infusion of IMP excluding those who do not achieve response at least once between the date of first dose and EOT Treatment：Refer to Section 6.4 in study protocol Endpoints：Refer to the left column Strategies for addressing intercurrent events： The treatment policy strategy will be applied for the estimand Population-level summary: Duration of response will be estimated using descriptive statistics
	Secondary Endpoint 4: Ability to reduce glucocorticoids by 50% or more of the baseline dose during emapalumab treatment	Estimand 2.4 Target population: All patients received at least one infusion of IMP Treatment：Refer to Section 6.4 in study protocol Endpoints：Refer to the left column Strategies for addressing intercurrent events： The treatment policy strategy will be applied for the estimand Population-level summary: Number and percentage of patients able to reduce glucocorticoids by 50% or more of the baseline dose during emapalumab treatment
	Secondary Endpoint 5: Investigator assessed response	Estimand 2.5 Target population: All patients received at least one infusion of IMP

		Treatment：Refer to Section 6.4 in study protocol Endpoints：Refer to the left column Strategies for addressing intercurrent events： The treatment policy strategy will be applied for the estimand Population-level summary: Investigator's assessment of clinical response up to HSCT will be estimated using descriptive statistics
	Secondary Endpoint 6: Survival to start of HSCT conditioning, i.e., time from the date of first dose of Emapalumab to date of death, with censoring at conditioning for HSCT or at last date of contact for patients who did not undergo conditioning for HSCT	Estimand 2.6 Target population: All patients received at least one infusion of IMP Treatment：Refer to Section 6.4 in study protocol Endpoints：Refer to the left column Strategies for addressing intercurrent events： The treatment policy strategy will be applied for the estimand Population-level summary: Survival to start of HSCT conditioning will be estimated using Kaplan-Meier method
	Secondary Endpoint 7: Survival after HSCT, i.e., time from HSCT to death, with censoring time at last date of contact for patients with no event.	Estimand 2.7 Target population: All patients received at least one infusion of IMP and underwent HSCT Treatment：Refer to Section 6.4 in study protocol Endpoints：Refer to the left column Strategies for addressing intercurrent events： The treatment policy strategy will be applied for the estimand Population-level summary: Survival after HSCT will be estimated using Kaplan-Meier method

Secondary Objective: To collect efficacy data on emapalumab in treatment-experienced Chinese pHLH patients	[redacted]

4. Sample Size Consideration

Sample size is not based on statistical considerations but the data from up to 18 Chinese patients will add sufficient information to the safety and efficacy profile established during the global clinical development program for emapalumab in pHLH patients.

5. Analysis Sets

All screened analysis set

The All screened analysis set includes all patients who sign the informed consent/assent including screen failures. This population will be used only for the purpose of describing patient disposition and for protocol deviations (screen failures will be excluded in protocol deviation outputs).

All treated analysis set

All treated analysis set comprises all patients who received at least one infusion of IMP.

6. Statistical Methods

6.1. General Statistical Consideration

All subjects-related safety and efficacy data collected will be included. Annotated or illustrative description records will only be included in the listings. Suitable tabular and graphical summaries will be prepared for individual data and for appropriate summary statistics, and all data shall be listed. In this study, subject number will be used as the unique identification of subjects in data listings.

All safety and efficacy analyses will be based on the all treated analysis set unless specified otherwise. If applicable, all endpoints will be summarized using descriptive statistics. For continuous variables, the descriptive statistics will include the number of observations, mean, standard deviation, median, first and third quartiles (Q1, Q3), minimum and maximum. For categorical variables, the descriptive statistics will include the number of observations and percentage for each category. Two-sided 95% confidence interval may also be calculated for certain efficacy endpoints.

For continuous laboratory test measurements (including hematology, biochemistry, coagulation, sCD25, CSF analysis, and urinalysis), round to 1 decimal place for minimum and maximum statistics, 2 decimal places for mean, median, Q1 and Q3, and 3 decimal places for standard deviation. For other continuous measurements, the number of decimal places for minimum and maximum statistics will be kept consistent with source data; mean, median, Q1 and Q3 will be rounded to one more decimal place than source data; standard deviation will be rounded to two more decimal places than source data. For survival analysis, round to 1 decimal place for median survival time (and Q1, Q3) and survival rate, and 2 decimal places for standard deviation and confidence limits. For categorical measurements, the calculated percentage for each categories will be rounded to 1 decimal place, confidence limits will be round to 2 decimal places.

No formal statistical hypothesis testing will be performed for this study.

All statistical analyses will be performed with statistical analysis software (SAS) System (SAS Institute, Cary, NC) version 9.4 or later.

Baseline will be defined as the last available measurement or recording prior to the first study drug administration. For assessments performed only on screening visit prior to the first emapalumab infusion, the measurement or the recording of the screening visit will be used as baseline. For

assessments that are also performed pre-infusion on visit 1 in addition to screening visit, the measurement or recording pre-infusion on visit 1 will be used. If the measurement or recording pre-infusion on visit 1 is not available, then the measurement or recording of the screening visit will be used.

Unless otherwise noted, descriptive statistical summary will only include data from scheduled visits or time points. Data from unscheduled visits or time points will be presented in data listings.

For data of quantitative measurements but are collected with characters such as ">/≥" or "</≤", the numeric part of the value will be used in the descriptive analysis. For other cases where characters are entered for quantitative measurements, the result will not be used in the descriptive analysis but only included in data listing.

If deemed necessary, specific data points may be excluded from the analysis based on related discussion in the data review meeting (DRM). The decisions and reason(s) for exclusion will be documented separately in Resolution of Data Review Meeting in detail.

6.2. Data Handling

6.2.1. Premature Withdrawal and Missing Data

Missing data will not be imputed unless specified otherwise.

Determination of Treatment Emergent Adverse Event with Presence of Missing Data

The determination of treatment-emergent AE among records with missing data on starting date or time will be based on the non-missing components of their starting date and time. An AE with partial start date/time will be considered treatment-emergent in the following conditions:

- The start date of the event is completely missing;
- The start year of the event is equal to or later than the year of first infusion with the rest of the start date and time missing;
- The start year and month of the event are equal to or later than the year and month of first infusion with the rest of the start date and time missing;
- The start date of the event is equal to or later than the date of first infusion with the start time missing;
- The start date and hour of the event are equal to or later than the date and hour of first infusion with the minute of start time missing.

Correspondingly, an AE with partial start date/time will be considered as a pre-treatment event in the following conditions:

- The start year of the event is earlier than the year of first infusion with the rest of the start date and time missing;
- The start year and month of the event are earlier than the year and month of first infusion with the rest of the start date and time missing;
- The start date of the event is earlier than the date of first infusion with the start time missing;
- The start date and hour of the event are earlier than the date and hour of first infusion with the minute of start time missing.

Determination of Prior/Concomitant Medications or Non-Drug Therapies with Presence of Missing Data

The determination of whether a medication or non-drug therapy is considered prior or concomitant will be based on the end date of the medication/therapy. A medication/therapy with missing data on its end date will be considered concomitant in the following cases (otherwise it will be considered as a prior medication/therapy):

- The end date of the medication/therapy is completely missing;
- The end year of the medication/therapy is equal to or later than the year of first infusion with the rest of the end date missing;
- The end year and month of the medication/therapy are equal to or later than the month and year of first infusion with the end day missing.

For determination of pHLH conventional treatment history (prior pHLH conventional medication or non-drug therapy), similar rules will be applied by replacing end date as start date of the medication/non-drug therapy.

6.2.2. Derivation and Transformation on Data

Besides the calculation for certain endpoints (as listed below), which are based on data collected via CRF, no derivation or transformation will be applied. Outliers will be reported to data management function as a data issue to be resolved or confirmed before database lock. No special data handling will be done.

For the derivation of the achievement of Overall Response, refer to Section 6.8.2.

Age (in years) = (Date of informed consent/assent – birth date + 1)/365.25, rounding up to integer;

Time to first overall response (in days) = Date of the first achievement of response (Complete Response, Partial Response or HLH Improvement) – date of the first dose of emapalumab + 1, patients without a response will be censored at the date of EOT visit or last assessment;

Cumulative duration of response (in days) = Date of EOT visit – date of the first achievement of response + 1, for patients who achieve a response, lost that response, and then achieve any response subsequently, the total time in response will be calculated by adding together these separate periods in response;

Survival to start of HSCT conditioning (in days) = Date of death – date of first dose of emapalumab + 1, patients with no event will be censored at date of the start of conditioning for HSCT or last contact for patients who did not undergo HSCT;

Survival after HSCT (in days, calculated only for patients underwent HSCT) = Date of death – HSCT performed date+ 1, patients with no event will be censored at date of last contact;

Overall survival (in days) = Date of death – date of first dose of emapalumab + 1, patients with no event will be censored at date of last contact;

Dose administered (mg) = Prescribed dose [mg] × Approximate Proportion Administered [%];

Total duration of dosing (days) = Date of last infusion – date of first infusion + 1;

Average dosing frequency (times per day) = The total number of records of emapalumab infusion / total duration of dosing;

Prescribed dose change from first dosing (%) = (Prescribed dose at visit [mg] - prescribed dose at first dosing [mg])/ prescribed dose at first dosing [mg] × 100%.

6.3. Subject Disposition

The number of subjects will be calculated for all screened subjects. Subject will be considered screened after informed consent/assent is obtained.

Based on all screened subjects, the number and percentage of screen failures will be presented, as the main reason for screen failures will be tabulated. Screen failures will be listed.

Based on all screened subjects, the number and percentage of treated subjects who received the first dose of emapalumab will be presented.

Based on all treated subjects (subjects who received the first dose of emapalumab), the number and percentage of subjects who completed the treatment period prior to HSCT and those withdrawn from the treatment will be presented. The reason for withdrawal will be tabulated. Subjects withdrawn from the treatment period will also be listed.

Based on all subjects who completed the treatment period prior to HSCT, the number and percentage of subjects receiving HSCT and those who did not following the end of treatment will be presented. The reason for not receiving HSCT will also be tabulated.

Based on all subjects who completed the treatment period, the number and percentage of subjects who proceeded into the follow-up period and those who did not will be presented.

Based on all subjects who proceeded into the follow-up period, the number and percentage of subjects who completed the follow-up period and those who did not will be presented. The reason for withdrawal will also be tabulated. Subjects withdrawn from the follow-up period will also be listed.

Based on all screened subjects, the number and percentage of subjects included in the all treated analysis set will be calculated and summarized. A listing will be provided for subjects excluded from the analysis set with the reason of exclusion presented.

Based on all screened subjects excluding screen failures, important protocol deviation will be tabulated by protocol deviation category. Listings will be provided for all protocol deviations.

6.4. Demographics and Background Characteristics

Subject demographics including sex, birth date, race, and whether the subject has child-bearing potential will be collected in CRF. Information on HLH history including pHLH diagnosis, genetic test result (molecular diagnosis), NK-cell functional test result, family history, and conventional treatment received will be collected in details via CRF. Medical history including name of the medical condition or event, start and end date, and ongoing status will be collected in CRF. Medical history data will be coded using the latest updated English version of Medical Dictionary for Regulatory Activities (MedDRA).

Analysis on demographic data and background characteristics will be based on all treated subjects. Subjects' demographic and background characteristics will be summarized using descriptive statistics. And data listings will be provided. For conventional treatment record, pHLH conventional treatment history including medication and non-drug therapy will be

presented. Prior pHLH conventional medication will be tabulated by anatomical main group and therapeutic subgroup, and prior pHLH conventional non-drug therapy will be tabulated by therapy name. A medication/non-drug therapy will be considered pHLH conventional medication/non-drug therapy if the indication is conventional pHLH treatment (ongoing or discontinued at screening) as reflected in the CRF. A pHLH conventional medication/therapy will be considered treatment history if the start date is earlier than the date of first infusion. For records with its start date completely or partially missing, similar method as described in Section 6.2.1 will be applied (replacing end date by start date in the specified rules). For medical history data, concurrent disease and condition will be tabulated separately from medical history record and historic event. A medical history record with its ongoing status specified as yes will be considered concurrent (and otherwise historic event). Medical history and concurrent disease will be tabulated at subject level grouping by System Organ Classes (SOCs) and Preferred Terms (PTs).

Analysis of safety assessments at screening visit will be based on all treated subjects, for other details please refer to Section 6.10.

6.5. Exposure and Compliance

IMP administration including level of dose prescribed, prescribed dose, date, time and duration of dose administration, and information on dose increase and dose interruption will be collected in the CRF.

The total prescribed dose, total dose administered, total duration of dosing (in days), and average dose frequency (times per day) will be summarized using descriptive statistics. The dose administered will be calculated based on prescribed dose and approximate proportion administered (refer to Section 6.2.2). The total duration of dosing will be calculated based on the date of last infusion and the date of first infusion (refer to Section 6.2.2). The average dosing frequency will be calculated based on the total duration of dosing and the total number of records of emapalumab infusion (refer to Section 6.2.2).

The emapalumab dose change from the first dosing will be summarized showing the number and percentage of patients with a dose increase or a dose decrease at each visit. Moreover, the percentage of dose increases and decreases from the first dose for each patient will be summarized using a descriptive table. Percentage of dose increase or decrease from first dose will be calculated based on prescribed dose at first dosing and prescribed dose at each visit (refer to Section 6.2.2).

Data listing containing all information collected for IMP administration will be provided. In addition, IMP administration will be listed at patient level including all dose adjustments over time and summarized in terms of the number of doses administered, maximum dose, equivalent dose of dexamethasone, duration of exposure from the first dose to the last dose of treatment, cumulative dose, average dose frequency and average dose per day.

6.6. Prior/Concomitant Medication and Non-Drug Therapy

Medication name, dosage, frequency, route, start and end date, indication and ongoing status will be collected for prior/concomitant medication in the CRF. For non-drug therapy, information including therapy name, start and end date, indication and ongoing status will be collected.

Prior and concomitant medications will be coded using the latest updated global version of World Health Organization Drug Dictionary (WHO-DD) B3 format. A medication/therapy will be considered concomitant if the end date is equal to or later than the date of first infusion, and will be considered as prior medication/therapy otherwise. For records with its end date completely or partially missing, please refer to Section 6.2.1.

The frequency and percentage of prior and concomitant medications will be tabulated at subject level grouping by anatomical main group, therapeutic subgroup, chemical subgroup and generic name. The frequency and percentage of prior and concomitant non-drug therapy will be tabulated at subject level grouping by therapy name.

In addition, concomitant pHLH conventional medication will be tabulated by anatomical main group and therapeutic subgroup, and concomitant pHLH conventional non-drug therapy will be tabulated by therapy name.

6.7. Primary Analysis

Primary analysis on permanent discontinuation of study drug due to emapalumab-related adverse events will be based on all treated analysis set.

6.7.1. Primary Estimand Analysis

Permanent Discontinuation of Study Drug Due to Emapalumab-Related AEs

The treatment policy strategy will be applied for estimating the primary endpoint. Permanent discontinuation of study drug due to emapalumab-related adverse events will be estimated as described below regardless of any potential intercurrent events.

The number and percentage of subjects who permanently discontinue study drug due to emapalumab-related AEs will be presented.

6.8. Secondary Analysis

All secondary analyses will be based on all treated analysis set unless specified otherwise.

6.8.1. Secondary Analysis Supporting Primary Objective

For the definition and determination of treatment-emergent AEs/SAEs, refer to Section 6.10.2.

Treatment-Emergent AEs

The treatment policy strategy will be applied for estimating the incidence of treatment-emergent AEs. AEs recorded since receiving the first dose of investigational medication until EOS will be presented regardless of any potential intercurrent events.

The overall incidence of treatment-emergent AEs will be summarized at event level and subject level by SOCs and PTs.

Treatment-Emergent SAEs

The treatment policy strategy will be applied for estimating the incidence of treatment-emergent SAEs. SAEs recorded since receiving the first dose of investigational medication until EOS will be presented regardless of any potential intercurrent events.

The overall incidence of treatment-emergent SAEs will be summarized at event level and subject level by SOCs and PTs.

Treatment-Emergent Laboratory Abnormalities

The treatment policy strategy will be applied for estimating the incidence of treatment-emergent laboratory abnormalities. Laboratory abnormalities recorded since receiving the first dose of investigational medication until EOS will be presented regardless of any potential intercurrent events. Laboratory abnormalities that are absent at baseline will be considered treatment-emergent.

The overall incidence of treatment-emergent laboratory abnormalities will be summarized at event level and subject level by test name (e.g. hematology, biochemistry, coagulation, sCD25, urinalysis, or cerebrospinal fluid analysis if applicable) and test item.

Treatment-Emergent Vital Sign Abnormalities

The treatment policy strategy will be applied for estimating the incidence of treatment-emergent vital sign abnormalities. Vital sign abnormalities recorded since receiving the first dose of investigational medication until EOS will be presented regardless of any potential intercurrent events. Vital sign abnormalities that are absent at baseline will be considered treatment-emergent.

The overall incidence of treatment-emergent vital sign abnormalities will be summarized at event level and subject level by test item.

6.8.2. Secondary Analysis Supporting Secondary Objectives

Overall Response

Achievement of response will be assessed after the database lock via a programmed algorithm. The derivation of the Overall Response is detailed below.

Overall Response

Response	Definition	Additional Clarifications
Complete Response	Complete Response is adjudicated if: - No fever = body temperature <37.5°C - Normal spleen size - No cytopenia = Absolute Neutrophil Counts ≥1.0x10^9/L and platelet count ≥100x10^9/L [absence of G-CSF and transfusion support must be documented for at least 4 days to report no cytopenia] - No hyperferritinemia = serum ferritin level is <2000 µ g/L - No evidence of coagulopathy, i.e., normal D-Dimer and/or normal (>150 mg/dL) fibrinogen levels - No neurological and CSF abnormalities attributed to HLH - No sustained worsening of sCD25 (as indicated by at least two consecutive measurements that are > 2-fold higher than baseline)	- All HLH parameters that were abnormal at baseline must be normalized - No AEs relating to organ failure[1] - All other parameters that were normal at baseline must still meet the definition of normalized - Normal spleen size confirmed by abdominal ultrasound (US) whenever possible based on the splenomegaly not present; if US not performed physical examination will be used - Normal D-Dimer levels are <= 500 ug/L - No neurological abnormalities attributed to HLH = "normal" neurological assessment by investigator in the neurological examination page (without findings in brain imaging (Brain MRI/Brain CT/cranial ultrasound) or AEs indicative of "CNS involvement"[2] - No CSF abnormalities = no AE indicative of "CSF abnormalities"[2]
Partial Response	Partial Response is adjudicated if: - At least 3 of the HLH clinical and laboratory abnormalities (including CNS abnormalities) meet	If a patient is not considered as "reactivated" or a patient is considered "reactivated" with 4 or more abnormal HLH features upon entry to the study and

	the above mentioned criteria for "Complete Response" - In the case of "reactivated patients" who enter the study with 3 abnormal HLH features, Partial Response is adjudicated if at least 2 parameters normalize - In case of reactivated patients who enter the study with 2 abnormal HLH clinical and laboratory parameters only, Partial Response is adjudicated if one of the 2 parameters normalizes - There is no progression of other aspects of HLH disease pathology	at least 3 of the HLH clinical and laboratory abnormalities (including CNS abnormalities) meet the above-mentioned criteria for "Complete Response" Partial Response is adjudicated. For all patients: no progression of other aspects of HLH disease pathology is assessed by absence of AEs indicating organ failure[1] including no worsening of sCD25 levels.
HLH improvement	HLH Improvement is adjudicated if: - Improvement (>50% change from baseline or normalization) of at least 3 HLH clinical and laboratory abnormalities (including CNS abnormalities). - In the case of "reactivated patients" who enter the study with only 2 abnormal HLH features, a change from baseline greater than 50% for both will define HLH as improved.	Definition of 50% improvement from baseline: - Spleen size decreased by 50%, as recorded in cm from costal margin at physical examination. - Absolute Neutrophil Count increased by 50%, if G-CSF has not been administered in the previous 4 days andPlatelet count increased by 50%, if no platelet transfusion has been administered in the previous 4 days - Ferritin decreased by 50% - Fibrinogen increased by 50% or D-Dimer decreased by 50% Normalization of CNS abnormalities = normal neurological assessment by investigator without findings in brain imaging (Brain MRI/Brain CT/cranial ultrasound), CSF analysis or AEs indicative of "CNS involvement" or "CSF abnormalities"[2]
No Response	If a subject does not meet the criteria for at least HLH improvement, response is categorized as "No Response"	
Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; G-CSF, granulocyte-colony-stimulating factor; HLH, hemophagocytic lymphohistiocytosis		

[1] AE indicating organ failures will be pre-specified according to Appendix 1.

[2] AE indicative of CNS involvement/CSF abnormalities will be pre-specified according to Appendix 2.

The treatment policy strategy will be applied. The achievement of response based on the above definition at EOT or week 8 will be estimated as described below regardless of any potential intercurrent events.

Subjects who failed to meet the definition for above categories (Complete Response, Partial Response or HLH Improvement) will be considered as No Response. The number and percentage of patients achieving Overall Response at EOT or week 8 (whichever occurs earlier), i.e., Complete Response or Partial Response or HLH improvement, as well as No Response will be provided. In addition, 95% confidence interval will be estimated using Clopper-Pearson exact method for the percentages of subjects achieving each Overall Response category. Subjects' response status and assessments corresponding to each response criterion will be listed.

For subjects that did not withdraw treatment before week 8, observed data from the visit closest to 56 days (8 weeks) after first infusion will be used in the analysis. If there are more than one visits that are the same distance from 56 days after first infusion, data from the earlier/earliest visit will be used.

Time to First Overall Response

The treatment policy strategy will be applied. The time to overall response (based on the above definition) prior to HSCT will be estimated as described below regardless of any potential intercurrent events.

Time to first Overall Response is defined as time from the date of first dose of emapalumab to the first achievement of response (refer to Section 6.2.2). Patients with no response will be censored at the date of EOT visit or last assessment. Time to first response prior to HSCT will be presented by Kaplan-Meier curve with median calculated if available. Associated two-sided 95% confidence intervals will be calculated for the median.

Cumulative Duration of Response

The treatment policy strategy will be applied. The cumulative duration of response will be estimated as described below regardless of any potential intercurrent events.

Cumulative duration of response is defined as total time in response from the first achievement of an Overall Response until EOT (refer to Section 6.2.2). For patients who achieve a response, lost that response, and then achieve it subsequently, the total time in response will be calculated by adding together these separate periods in response. The cumulative duration of response will be calculated under the hypothetical assumption that a patient's response achieved at any visit will maintain up until the next visit. Patients who do not achieve response at least once between the date of first dose and EOT will be excluded from the analysis. Cumulative duration of response will be summarized using descriptive statistics.

Ability to Reduce Glucocorticoids

The ability to reduce glucocorticoids by 50% will be defined as reduction in the equivalent dose from baseline by at least 50% and maintained for at least 7 days.

Baseline will be defined as the equivalent dose on the day before first infusion (SD-1). If the equivalent dose on the day before first infusion (SD-1) is not available, then the equivalent dose before first infusion that is closest to SD0 will be used.

The equivalent dose will be calculated as follows:

The equivalent dose will include only glucocorticoids administered orally (PO) or intravenously (IV) (route of "Oral", "Intravenous injection", or "Intravenous injection drip" as collected in the CRF). IV and PO routes of administration are considered dose-equivalent in the analysis.

- Daily dose = Conversion factor × Dose of glucocorticoids in mg × number of administrations per day *
  * If two or more different glucocorticoids were administered in one day then the total daily dose would equal the sum of daily doses for each glucocorticoid.
- BSA Surface Area (BSA) = Height (cm) × Weight (kg)/3600
- Equivalent dose ($mg/m^2/day$) = Daily dose / BSA

The conversion factors for glucocorticoids are listed as below:

Glucocorticoids	Conversion factor
Dexamethasone	1
Methylprednisolone	1/5.3
Prednisolone	1/6.7
Prednisone	1/6.7
Triamcinolone	1/5.3
Hydrocortisone	1/26.6
Cortisone	1/33.3

The number of administrations per day will be assigned based on dose frequency collected in the CRF:

Dose frequency	Number of administrations per day
Once a day	1
Twice a day	2
Thrice a day	3
Once every two days	0.5
Single administration	1
As needed	1
Unknown	1
Other	1

The treatment policy strategy will be applied. The ability to reduce glucocorticoids will be estimated as described below regardless of any potential intercurrent events.

The number and percentage of subjects able to reduce glucocorticoids by 50% or more of the baseline dose during emapalumab treatment will be provided.

Investigator Assessed Response

The treatment policy strategy will be applied. The investigator assessed response will be estimated as described below regardless of any potential intercurrent events.

In addition to Overall Response assessed by programmed algorithm, achievement of response assessed by investigator (Complete Response, Partial Response, or No Response) will also be collected in the CRF during the treatment period. The number and percentage of subjects achieved each category of investigator assessed response by visit will be presented.

Survival to Start of HSCT Conditioning

The treatment policy strategy will be applied. Survival to start of HSCT will be estimated as described below regardless of any potential intercurrent events.

Survival to start of HSCT conditioning is defined as time from first dose of emapalumab to date of death from any cause, with censoring time at date of the start of conditioning for HSCT (or last contact, if patient did not undergo HSCT) for patients with no event (refer to Section 6.2.2).

Survival to start of HSCT conditioning will be estimated applying Kaplan-Meier methodology. Median survival time, 75th and 25th percentiles will be calculated where available with associated

two-sided 95% confidence intervals. Survival rates and associated two-sided 95% confidence intervals will be calculated at day 7 (1 week), day 14 (2 week), day 21 (3 week), day 30, day 60, day 100, day 180 (6 month) and day 360 (12 month).

Survival after HSCT

The treatment policy strategy will be applied. Survival after HSCT will be estimated as described below regardless of any potential intercurrent events.

Survival after HSCT is defined as time from HSCT to date of death from any cause, with censoring time at last date of contact for patients with no event (refer to Section 6.2.2). Only patients undergoing HSCT will be included in the analysis.

Survival after HSCT will be estimated applying Kaplan-Meier methodology. Median survival time, 75th and 25th percentiles will be calculated where available with associated two-sided 95% confidence intervals. Survival rates and associated two-sided 95% confidence intervals will be calculated at day 7 (1 week), day 14 (2 week), day 21 (3 week), day 30, day 60, day 100, day 180 (6 month) and day 360 (12 month).

Overall Survival

The treatment policy strategy will be applied. Overall survival will be estimated as described below regardless of any potential intercurrent events.

Overall survival is defined as time from first dose of emapalumab to date of death from any cause, with censoring time at last date of contact for patients with no event (refer to Section 6.2.2).

Overall survival will be estimated applying Kaplan-Meier methodology. Median survival time, 75th and 25th percentiles will be calculated where available with associated two-sided 95% confidence intervals. Survival rates and associated two-sided 95% confidence intervals will be calculated at day 7 (1 week), day 14 (2 week), day 21 (3 week), day 30, day 60, day 100, day 180 (6 month) and day 360 (12 month).

6.9. Exploratory Analysis

6.10. Safety Analysis

All safety analyses will be based on all treated analysis set.

6.10.1. Adverse Events

Detailed information on AEs occurring after the first dose of investigational medication until EOS including adverse event term, start data and time, end date and time, outcome, maximum severity, relationship to IMP and potential causative factors, whether the AE caused study discontinuation, answer indicating whether the event is a SAE, and criteria met for SAE will be collected in the CRF. All AE records collected will be included in the analysis. Adverse event terms will be standardized using the latest updated English version of MedDRA.

An adverse event will be considered treatment-emergent if the start date and time of the event are equal to or later than the date and time of first infusion (otherwise pre-treatment event). For determination of treatment-emergent AEs with presence of missing data, please refer to Section 6.2.1.

Besides secondary analyses described in Section 6.8.1, the overall incidence of TEAEs related to study drug (non-serious related AEs) and serious TEAEs related to study drug will be summarized at event level and subject level by SOCs and PTs.

In addition, the incidence of treatment-emergent AEs and treatment-emergent SAEs will be tabulated by SOCs and PTs based on maximum severity.

The overall incidence of all AEs, treatment-emergent AEs, treatment-emergent SAEs, severe treatment-emergent AEs, infusion-related AEs, infection-related AEs, treatment-emergent AEs related to study drug, severe treatment-emergent AEs related to study drug, all SAEs, treatment-emergent SAEs, serious treatment-emergent AEs related to study drug, infusion-related SAEs, infection-related SAEs, AE leading to treatment temporarily interrupted related to study drug, AEs leading to treatment permanently discontinued related to study drug, AEs leading to study withdrawal and AEs leading to death at event level and subject level will be tabulated in a summary table. In addition, AEs occurred prior to HSCT and after HSCT will be similarly tabulated.

For all treatment-emergent SAEs, the incidence will be tabulated at event level and subject level by criteria met in a summary table.

Listings will be provided for all AEs, SAEs, AEs resulting in study discontinuation, AEs resulting in death, infusion-related AEs, infection-related AEs, and AEs leading to treatment temporarily interrupted/treatment permanently discontinued related to study drug.

6.10.2. Laboratory Test Results

Data on the test item(s), result, clinical significance, unit, normal range limits, and additional comments for hematology, biochemistry, coagulation, sCD25, urinalysis, and cerebrospinal fluid (CSF) analysis (if clinically indicated) will be documented in the CRF. Laboratory test data will be collected at all scheduled visits for the treatment period and the follow-up period.

The numeric findings of laboratory test result (including hematology, biochemistry, coagulation, sCD25, CSF analysis, and urinalysis) will be summarized for screening visit and following visits using descriptive statistics. Actual values and actual changes from baseline will be presented. Qualitative clinical evaluation (normal, not clinically significant, clinically significant, or not done) will be tabulated for screening visit and presented using shift table for following visits. CSF analysis will only be tabulated for subjects with available baseline CSF analysis results and available CSF results for at least one post-treatment visit.

Listings will be provided for all laboratory data collected for scheduled and unscheduled visits. In addition, all abnormal laboratory findings of subjects with normal result at baseline will be listed.

6.10.3. 12-Lead Electrocardiogram

Clinical evaluation of 12-lead ECG (normal, not clinically significant, or clinically significant) will be collected at screening, week 8, and EOT visit during treatment period.

Clinical evaluation will be tabulated for screening visit and presented using shift table for each applicable scheduled visit. Listings will be provided for all ECG data collected for scheduled and

unscheduled visits. In addition, all abnormal ECG findings of subjects with normal result at baseline will be listed.

6.10.4. Other Safety Results

Vital signs

Numeric result and clinical evaluation (normal, not clinically significant, or clinically significant) of body temperature, heart rate, blood pressure (BP), and oxygen saturation will be collected in the CRF for all visits. Body temperature will be measured pre-infusion, at the end of the infusion, 1 hour and 2 hours after the end of each infusion. Oxygen saturation will be measured every 30 minutes during the infusion, at the end of infusion and 1 and 2 hours post-infusion. For the first infusion, oxygen saturation will be measured continuously during the infusion and up to 2 hour post-infusion. For the first infusion (or the first infusion after an increased dose) BP and heart rate will be measured every 15 minutes during the infusion, at the end of infusion and 1 and 2 hours post-infusion. For EOT and subsequent follow-up visits, if no infusion-related reactions have occurred, BP and heart rate will be measured every 30 minutes, at the end of infusion and 1 and 2 hours post-infusion.

Body temperature, heart rate, BP measurements, and oxygen saturation will be summarized for screening visit and each planned time point for the following scheduled visits using descriptive statistics. Actual values and actual changes from baseline will be presented. Clinical evaluation will be tabulated for screening visit and presented using shift table for following scheduled visits.

Listings will be provided for all vital signs data from scheduled and unscheduled visits. In addition, all abnormal vital signs findings of subjects with normal result at baseline will be listed.

Physical Examination

Clinical evaluation (normal, not clinically significant, clinically significant, or not done) of a complete physical examination (including spleen size, liver size, general appearance of the skin, neurological status, head, ears, eyes, nose and throat, lungs, cardiac, abdomen, musculoskeletal system and other) will be collected for the screening visit in the CRF. For all other scheduled visits, results of a brief examination (including spleen size, liver size, general appearance of the skin, neurological status and other) will be collected in the CRF.

Clinical evaluation will be tabulated for screening visit and presented using shift table for following scheduled visits.

Listings will be provided for all physical examination data from scheduled and unscheduled visits. In addition, all abnormal physical examination findings of subjects with normal result at baseline will be listed.

Imaging

The result of abdominal ultrasound, chest x-ray or chest CT (computed tomography), and brain MRI (Magnetic resonance imaging) or brain CT or cranial ultrasound if clinically indicated will be collected at the screening visit. Abdominal ultrasound will be performed every two weeks during the treatment period, and at the pre-conditioning visit, D+100 visit and the EOS visit of the follow-up period. For the treatment period and the follow-up period, chest and brain imaging (chest x-ray or chest CT, and brain MRI or brain CT or cranial ultrasound) will be performed if clinically indicated.

Longitudinal length of the spleen measured from abdominal ultrasound will be summarized using descriptive statistics for screening visit and all scheduled visits. Actual values and actual changes from baseline will be presented. Clinical evaluation of available imaging results (normal, not clinically significant, or clinically significant) will be tabulated for screening visit and presented using shift table for applicable scheduled visits. Chest imaging will only be tabulated for subjects with available chest X-ray or chest CT result from at least one post-treatment visit. Brain imaging will only be tabulated for subjects with available baseline brain MRI or brain CT or cranial ultrasound result and available brain imaging result from at least one post-treatment visit.

Data listing will be provided for all imaging data from scheduled and unscheduled visits. In addition, all abnormal imaging findings of subjects with normal result at baseline will be listed.

Search for Infections

Specimen type, test name, numeric test result and unit, normal range limits, clinical evaluation (normal, not clinically significant, or clinically significant), and confirmation of infection will be collected for the pre-specified pathogenic infections (including tuberculosis, Adenovirus, Epstein-Barr virus, Cytomegalovirus, atypical mycobacteria, Histoplasma capsulatum, Salmonella, Leishmania, Brucella if clinically indicated, and other infections) at screening visit. For the treatment period and the follow-up period, testing will be performed if clinically indicated.

Results of the infection assessments will be tabulated at screening visit and each applicable scheduled visit.

Listings will be provided for all pathogenic infection data from scheduled and unscheduled visits. In addition, all records of confirmed infection confirmed post-treatment which were absent at baseline will be listed.

Weight and Height

Measured date and time, and subjects' weight will be collected at all scheduled visits during treatment period, and EOS visit of the follow-up period. Subjects' height will be collected at screening, week 8, EOT visit of the treatment period, and EOS visit of the follow-up period (for subjects older than 18 years old, height will only be collect at screening visit).

Weight and height will be summarized for screening visit and each applicable scheduled visit using descriptive statistics. Actual values and actual changes from baseline will be presented.

Listings will be provided for all height and weight measurements from scheduled and unscheduled visits.

Pregnancy Test

The result of pregnancy test (negative or positive) and type of specimen tested (serum or urine) will be collected for female subjects of childbearing potential. Female subjects of childbearing potential will have a serum pregnancy test taken at screening, visit 1 and EOT visit, and local pregnancy test (urine or blood) will be taken monthly (week 4, 8, 12, etc.) during the treatment period and at day 30, 60, 100 and 6 months after HCST.

A data listing will be provided for pregnancy test results from all scheduled and unscheduled visits.

Allergy History

Subjects' allergy history will be collected at screening visit.

The number and percentage of subjects with allergy history will be tabulated by name of the allergen. A data listing will also be provided.

6.11. Subgroup Analysis

Not applicable.

6.12. Supplementary Analysis

Overall Response, Modified Definition

Overall response by modified definition will be tabulated similarly to overall response (refer to Section 6.8.2). The modified definitions of Partial Response and HLH Improvement are detailed below.

Overall Response		
Response	Definition	Additional Clarifications
Complete Response	Complete Response is adjudicated if: - No fever = body temperature <37.5°C - Normal spleen size - No cytopenia = Absolute Neutrophil Counts ≥1.0x10^9/L and platelet count ≥100x10^9/L [absence of G-CSF and transfusion support must be documented for at least 4 days to report no cytopenia] - No hyperferritinemia = serum ferritin level is <2000 µ g/L - No evidence of coagulopathy, i.e., normal D-Dimer and/or normal (>150 mg/dL) fibrinogen levels - No neurological and CSF abnormalities attributed to HLH - No sustained worsening of sCD25 (as indicated by at least two consecutive measurements that are > 2-fold higher than baseline)	- All HLH parameters that were abnormal at baseline must be normalized - No AEs relating to organ failure[1] - All other parameters that were normal at baseline must still meet the definition of normalized - Normal spleen size confirmed by abdominal ultrasound (US) whenever possible based on the splenomegaly not present; if US not performed physical examination will be used - Normal D-Dimer levels are <= 500 ug/L - No neurological abnormalities attributed to HLH = "normal" neurological assessment by investigator in the neurological examination page (without findings in brain imaging (Brain MRI/Brain CT/cranial ultrasound) or AEs indicative of "CNS involvement"[2] - No CSF abnormalities = no AE indicative of "CSF abnormalities"[2]
Partial Response	Partial Response is adjudicated if: - A patient has more than 3 abnormal HLH features at baseline and at least 3 parameters normalize. The remaining may be the same or worse as baseline (unless 2 or more parameters no longer meet the definition of normality). - In the case where a patient has only 3 abnormal HLH features at baseline, Partial Response is adjudicated if at least 2 parameters normalize. The remaining may be the same or worse as baseline (unless 2 or more parameters no longer meet the definition of normality) - In the case where a patient has only 2 abnormal HLH features at baseline, Partial Response is adjudicated if one of the 2 parameters normalizes. The remaining	If a patient is not considered as "reactivated" or a patient is considered "reactivated" with 4 or more abnormal HLH features upon entry to the study and at least 3 of the HLH clinical and laboratory abnormalities (including CNS abnormalities) meet the above-mentioned criteria for "Complete Response" Partial Response is adjudicated. For all patients: no progression of other aspects of HLH disease pathology is assessed by absence of AEs indicating organ failure[1] including no worsening of sCD25 levels.

	may be the same or worse as baseline (unless 2 or more parameters no longer meet the definition of normality) - There is no progression of other aspects of HLH disease pathology	
HLH improvement	HLH Improvement is adjudicated if: - At least 3 of the HLH parameters that were abnormal at baseline must be normalized or improved (i.e., ⩾ 50% change from baseline). The remaining may be the same or worse as baseline (unless 2 or more parameters no longer meet the definition of normality). - In the case where a patient has only 2 abnormal HLH features at baseline, a change from baseline greater than 50% for both will define HLH as improved. The remaining may be the same or worse as baseline (unless 2 or more parameters no longer meet the definition of normality).	Definition of 50% improvement from baseline: - Spleen size decreased by 50%, as recorded in cm from costal margin at physical examination. - Absolute Neutrophil Count increased by 50%, if G-CSF has not been administered in the previous 4 days and - Platelet count increased by 50%, if no platelet transfusion has been administered in the previous 4 days - Ferritin decreased by 50% - Fibrinogen increased by 50% or D-Dimer decreased by 50% Normalization of CNS abnormalities = normal neurological assessment by investigator without findings in brain imaging (Brain MRI/Brain CT/cranial ultrasound), CSF analysis or AEs indicative of "CNS involvement" or "CSF abnormalities"[2]
No Response	If a subject does not meet the criteria for at least HLH improvement, response is categorized as "No Response"	
Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; G-CSF, granulocyte-colony-stimulating factor; HLH, hemophagocytic lymphohistiocytosis		

[1] AE indicating organ failures will be pre-specified according to Appendix 1.

[2] AE indicative of CNS involvement/CSF abnormalities will be pre-specified according to Appendix 2.

Post-HSCT Outcome

Post-HSCT outcome including date of engraftment, specimen type, specimen collection date, and chimerism of donor chimerism test performed will be collected for subjects received HSCT during the follow-up period post-HSCT.

The number and percentage of patients received engraftment, and the number and percentage of subjects developed graft versus host disease will be presented, as donor chimerism achieved will be summarized using descriptive statistics for subjects received HSCT if available. Listings will be provided.

Reactivation

Reactivation of pHLH during the follow-up period including date of reactivation and criteria met for reactivation will be collected for subjects proceeded to the follow-up period.

The number and percentage of patients reactivated by reactivation criteria will be presented. And a listing will also be provided.

6.13. Baseline Data Summary

Subject demographics and other baseline characteristics including HLH history, medical history and weight and height at screening will be summarized as described in Section 6.4 prior to final analysis for publication purposes after data from the screening visit are collected for all subjects.

7. Multiplicity

Not applicable since no formal statistical hypothesis testing will be performed.

8. Interim Analyses

No formal interim analysis is planned for this study.

9. Change from the Analysis Plan in Protocol

Supplementary analysis added where the overall response at EOT or Week 8 (whichever occurs earlier) is derived checking the number of abnormalities at baseline and the number of HLH criteria which worsen from baseline. For more details, please refer to Section 6.12.
Overall survival added in secondary analyses. Please refer to Section 6.8.2 for details.

10. Reference

(1) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. E9 Statistical Principles for Clinical Trials.

11. TFL Shell and Dataset Specification

11.1. TFL Shell

Please refer to *TFL Mock Shells.*

11.2. Dataset Specification

Please refer to *SDTM Specifications* and *ADaM Programming Specifications.*

Appendix 1.
Listing of MedDRA Terms for AE Indicating Organ Failures

Preferred Term Code	Preferred Term
10007554	Cardiac failure
10007556	Cardiac failure acute
10024119	Left ventricular failure
10063081	Acute left ventricular failure
10039163	Right ventricular failure
10063082	Acute right ventricular failure
10051093	Cardiopulmonary failure
10038695	Respiratory failure
10001053	Acute respiratory failure
10019663	Hepatic failure
10000804	Acute hepatic failure
10077305	Acute on chronic liver failure
10019845	Hepatorenal failure
10038435	Renal failure
10077361	Multiple organ dysfunction syndrome
10053159	Organ failure
10010264	Condition aggravated

Appendix 2. Listing of MedDRA Terms for AE Indicative of CNS Involvement/CSF Abnormalities

Preferred Term Code	Preferred Term
10029818	Nuclear magnetic resonance imaging brain abnormal
10059703	CSF test abnormal
10053805	CSF white blood cell count increased
10011522	CSF cell count increased
10035551	Pleocytosis
10012559	Developmental delay
10056832	Neurological examination abnormal
10047641	VIth nerve paralysis
10020745	Hyperreflexia
10041962	Status epilepticus
10039906	Seizure
10021118	Hypotonia
10002948	Aphasia
10029202	Nervous system disorder
10017577	Gait disturbance
10048334	Mobility decreased
10008096	Cerebral atrophy
10015037	Epilepsy
10071066	Posterior reversible encephalopathy syndrome
10022840	Intraventricular haemorrhage