PROTOCOL TITLE: An Open-label, Single Arm, Multicenter Study to Broaden Access to Emapalumab, an Anti Interferon Gamma (Anti-IFNγ) Monoclonal Antibody, and to Assess its Efficacy, Safety, Impact on Quality of Life, and Long-term Outcome in Pediatric Patients with Primary Hemophagocytic Lymphohistiocytosis

NCT Number: NCT03312751

| | |
|---|---|
| Sponsor | *Sobi AG* |
| Protocol Title: | *An Open-label, Single Arm, Multicenter Study to Broaden Access to Emapalumab, an Anti-Interferon Gamma (Anti-IFNγ) Monoclonal Antibody, and to Assess its Efficacy, Safety, Impact on Quality of Life, and Long-term Outcome in Pediatric Patients with Primary Hemophagocytic Lymphohistiocytosis* |
| Protocol Number: | *NI-0501-09* |
| Premier Research PCN: | *176784* |
| Document Version: | *Final Version 2.0* |
| Document Date: | *24Oct2022* |

## Approvals

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## Document History

| Version | Date | Reason for Amendment |
|---|---|---|
| 1.0 | 09-Apr-2021 | Not applicable. |
| 2.0 | 24-Oct-2022 | Section 5<br>Added the analysis set Evaluable Analysis Set Without Major Protocol Deviations so it is clear which analysis set is used in sensitivity analysis 5.<br>Section 6.1.5<br>Revision of analysis visit windows in order to clarify which visit should be used as the EOT/Week 8 visit.<br>Section 6.1.9.4/Section 9<br>Supplementary analysis included using an updated definition of overall response. The number of abnormalities at baseline is considered along with the number of abnormalities which worsen from baseline.<br>Section 6.1.9.4<br>Clarification of the response definition. |

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# List of Abbreviations

| Abbreviation | Definition |
|---|---|
| ADA | anti-drug antibody |
| AE | adverse event |
| ATC | anatomical therapeutic chemical |
| BAL | bronchoalveolar lavage |
| BASES | behavioral, affective and somatic experiences questionnaire |
| CBC | complete blood cell |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| COVID-19 | coronavirus disease 2019 |
| CSF | cerebrospinal fluid |
| CSR | clinical study report |
| iDMC | independent data monitoring committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EBV | Epstein-Barr virus |
| EMA | European Medicines Agency |
| EOT | end of treatment |
| FDA | food and drug administration |
| HLGT | high level group term |
| HLH | hemophagocytic lymphohistiocytosis |
| HLT | high level term |
| HSCT | hematopoietic stem cell transplantation |
| ICH | international council for harmonization |
| IFNγ | interferon gamma |
| IRR | infusion related reactions |
| IV | intravenous |
| LLOQ | lower limit of quantitation |
| MedDRA | medical dictionary for regulatory activities |
| n | number of patients |
| PD | pharmacodynamic |

| Abbreviation | Definition |
|---|---|
| PedsQL | Pediatric quality of life inventory |
| pHLH | primary hemophagocytic lymphohistiocytosis |
| PK | pharmacokinetic |
| PO | per os – by mouth in Latin |
| PT | preferred term |
| QOL | quality of life |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS® | a software system used for data analysis |
| SD | study day |
| SOC | system organ class |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| TLFs | tables, listings, and figures |
| ULOQ | upper limit of quantitation |
| US | United States of America |
| WHO-DD | world health organization drug dictionary |

# 1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Sobi protocol number NI-0501-09 (An Open-label, Single Arm, Multicenter Study to Broaden Access to Emapalumab, an Anti-Interferon Gamma [Anti-IFNγ] Monoclonal Antibody, and to Assess its Efficacy, Safety, Impact on Quality of Life, and Long-term Outcome in Pediatric Patients with Primary Hemophagocytic Lymphohistiocytosis), dated 31-Mar-2020 version 4.0.

Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents (e.g. case report forms, guidelines for completion of CRF, etc.). Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP meets the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[3] and the Royal Statistical Society[1], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to database lock of Sobi's study NI-0501-09.

# 2. Study Objectives and Endpoints

## 2.1. Study Objectives

- To gather additional safety and efficacy data on emapalumab (previously referred to as NI-0501) in primary hemophagocytic lymphohistiocytosis (pHLH) patients.
- To assess a starting dose of emapalumab of 3 mg/kg.
- To assess the impact of emapalumab on Quality of Life (QOL).
- To gather additional evidence on the long-term outcome of pHLH patients treated with emapalumab.
- To further evaluate the pharmacokinetic (PK) profile of emapalumab in pHLH patients.
- To further evaluate the pharmacodynamic (PD) effects (levels of circulating total IFNγ and biomarkers of its neutralization, namely CXCL9 and CXCL10).
- To assess the profile of other relevant HLH biomarkers, e.g., soluble IL-2 receptor

(sCD25) and other exploratory biomarkers.

- To monitor for potential occurrence of anti-drug antibodies (ADAs).

## 2.2. Study Endpoints

### 2.2.1. Efficacy Endpoints

#### 2.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is Overall Response, i.e., achievement of either Complete or Partial Response or HLH Improvement, at end of treatment (EOT) or Week 8 (whichever occurs earlier).

#### 2.2.1.2. Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints of this study include the following:

- Overall Survival, including survival to hematopoietic stem cell transplantation (HSCT) and survival after either HSCT or last emapalumab infusion (if HSCT is not performed).
- Event-free survival.
- Overall Response, i.e., achievement of either Complete or Partial Response or HLH Improvement, at start of conditioning (or at last emapalumab infusion if HSCT is not performed).
- Duration of Response, i.e., maintenance of the response achieved any time during the study (with censoring time at start of conditioning for patients with no event).
- Time to Response at any time during the study.
- Number of patients able to reduce glucocorticoids by 50% or more of the baseline dose at any time during emapalumab treatment.
- Number of patients able to proceed to HSCT, when deemed indicated.
- Quality of Life assessed through PedsQL™, Pediatric Quality of Life Inventory™.[4]
- Quality of Life assessed through BASES, The Behavioral, Affective and Somatic Experiences questionnaires.

### 2.2.2. Safety Endpoints

Safety and tolerability of emapalumab will be assessed as follows:

- Incidence, severity, causality and outcomes of adverse events (AEs) (serious and non-serious).

- Evolution of relevant laboratory parameters, e.g., complete blood cell (CBC) count, liver and renal function tests, and coagulation parameters.
- Number of patients who discontinued emapalumab treatment for safety reasons.

### 2.2.3. Pharmacokinetic/Pharmacodynamic Variable(s)

In the present SAP, the following PK/PD parameters are considered for the purpose of descriptive statistics only:

- Serum concentration of emapalumab.
- Levels of circulating total IFNγ (free + bound) at any time point.
- Markers of IFNγ neutralization, namely CXCL9 and CXCL10.
- Other relevant HLH biomarkers, e.g., sCD25 and other exploratory biomarkers.
- Level (if any) of circulating antibodies against emapalumab (ADAs).

Measurement of emapalumab concentrations and PD parameters in other matrices, e.g., cerebrospinal fluid (CSF), bronchoalveolar lavage (BAL), if clinically appropriate, will be used in an exploratory fashion.

## 3. Overall Study Design and Plan

### 3.1. Overall Design

This is an open-label, single arm, multicenter, interventional study conducted in Europe and North America.

The study enrols pediatric patients with confirmed or suspected pHLH who are treatment-naïve, have failed conventional HLH therapy, or have shown intolerance to it.

Patients will be in the treating unit the day before the first administration of emapalumab (study day minus 1, SD-1).

Patients are required to receive dexamethasone from SD-1. In treatment-naïve patients, a background therapy of 10 mg/m$^2$ dexamethasone will be required. In patients who failed previous HLH therapy, dexamethasone is to be administered at a dose of at least 5 mg/m$^2$ or at the dose administered prior to Screening if higher.

Lower dexamethasone doses are allowed in case of documented intolerance to glucocorticoids. During the study, dexamethasone can be tapered depending on the patient's condition, according to the judgment of the treating physician.

The study is divided into three parts:

- **Screening period.** Screening will be carried out within 2 weeks prior to first administration of emapalumab (SD0) to enable confirmation of patient eligibility and

following the signature of the Informed Consent Form.

- **Treatment period.** The duration of treatment is foreseen until the start of conditioning for HSCT but must not exceed 6 months. The minimum treatment duration is 4 weeks, if the patient's conditions and donor availability allow for HSCT. No washout period is required between the last administration of emapalumab and the start of conditioning.
- **Follow-up period.** After treatment completion or treatment discontinuation (for any reason), patients will continue in the study for long-term follow-up until 1 year after either HSCT or last emapalumab infusion (if HSCT is not performed). A patient who experiences HLH reactivation during the follow-up period, may be re-treated with emapalumab. Re-treated patients will follow the same schedule of assessments as applicable during the initial treatment and will enter follow-up period after completion of re-treatment.

The end of the study is defined as last patient last visit at 1 year after either HSCT or last emapalumab infusion (as applicable). In case of an ongoing serious adverse event (SAE) the patient will continue to be monitored until resolution or until the outcome of the event is known and stable, beyond the defined study end as necessary.

### 3.2. Sample Size and Power

The sample size calculation is based on the primary efficacy endpoint of Overall Response. Assuming an Overall Response Rate of 65%, a minimum of 34 treated patients is required to show a significant improvement above 40% with 85% power using an exact binomial test at a one-sided significance level of 2.5%. A drop-out rate of 20% may be expected, hence a total maximum of 41 patients may be enrolled. Due to the rarity of pHLH, recruitment is competitive across all European and North American sites in order to gather data in a reasonable timeframe.

### 3.3. Study Population

The study population comprises pHLH patients of both genders, from birth up to and including 18 years at diagnosis of HLH. Patients in this study can be naïve to HLH treatment or may have already received conventional HLH therapy without having obtained a satisfactory response according to the treating physician or shown signs of intolerance to HLH therapy.

### 3.4. Treatments Administered

This is an open-label, single-arm study and no randomization is being performed. Emapalumab will be administered by intravenous (IV) infusion over a period of 1 to 2 hours depending on the volume to infuse, at a dose of 3 mg/kg. Infusions will be performed twice weekly (not more than 4 days apart), except for the second infusion which must be administered on SD-3. The 3 mg/kg dose will be maintained unless the Investigator, guided by the clinical and laboratory response in each patient, deems that a dose increase is appropriate; at any time during the study, it will be possible to increase the emapalumab dose to 6 mg/kg. The dose of emapalumab may be further increased to 10 mg/kg per Investigator's decision based on the patient's clinical and laboratory response.

Upon achievement of Complete Response (i.e., normalization of all clinical and laboratory HLH parameters), the dose of emapalumab will be lowered to achieve 1 mg/kg twice a week and maintained until conditioning for transplant, as long as the patient's clinical conditions are satisfactory. Given the unpredictable course of the disease, in case of reactivation (e.g. triggered by intercurrent infections), subsequent dose increases to 3 mg/kg (and up to 6 or 10 mg/kg, as appropriate) may need to be considered and will be guided by the same clinical and laboratory parameters. Upon obtaining again a Complete Response, the dose of emapalumab will be lowered again to achieve 1 mg/kg twice a week. Should hematopoietic stem cell transplantation (HSCT) be scheduled beyond 12 weeks from emapalumab initiation for reasons unrelated to the administration of emapalumab (e.g., lack of donor availability) and provided Complete Response is maintained, the treatment with emapalumab may continue at the dose of 1 mg/kg once a week.

### 3.5. Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. Screening is carried out to enable confirmation of patient eligibility. Eligible patients are administered emapalumab.

### 3.6. Blinding and Unblinding

Not applicable.

### 3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1 and Table 2 of the protocol.

## 4. Statistical Analysis and Reporting

### 4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of patients (n) with non-missing values, mean, standard deviation, median, minimum, and maximum. The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Mean, standard deviation and median will be reported to 1 degree of precision more than the observed data.

Categorical (qualitative) variable summaries will include the frequency and percentage of patients who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of patients in the study population unless otherwise specified. Percentages will be rounded to 1 decimal place, unless otherwise

specified. Therefore, there may be cases where for instance the total of the percentages does not exactly equal 100%. In case confidence intervals are provided, they will be shown with 1 decimal place.

The number of missing values will be calculated as difference of the total number of subjects in the study population minus the number of non-missing values.

All p-values will be displayed to four decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a p-value less than 0.0001 occurs it will be shown in tables as <0.0001.

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

### 4.2. Interim Analysis and Data Monitoring

No interim analyses are planned.

An Independent Data Monitoring Committee (iDMC) has overall responsibility for safeguarding the interests of subjects by monitoring relevant data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted with the highest scientific and ethical standards.

## 5. Analysis Sets

The following analysis populations are planned for this study:

- **Enrolled Analysis Set:** The Enrolled Population Analysis Set includes all patients who sign the informed consent form including screen failures. This population will be used only for the purpose of describing patient disposition and for protocol deviations (note: screen failures will be excluded in protocol deviation outputs).
- **All Treated Analysis Set:** The All Treated Analysis Set includes all patients who receive any part of an infusion of study drug. The All Treated Analysis Set will be the primary population for efficacy endpoints, and will be used for safety and PK/PD endpoints.
- **Evaluable Analysis Set:** The Evaluable Analysis Set includes all patients in the All Treated Analysis Set who have
    - Received a minimum of 3 consecutive infusions of emapalumab, not more than 6 days between infusions,
    - Not had a diagnosis of secondary HLH subsequent to the initiation of emapalumab treatment.
- **Evaluable Analysis Set Without Major Protocol Deviations:** The Evaluable Analysis Set Without Major Protocol Deviations includes all patients in the Evaluable analysis set who do not have a major protocol deviation that is deemed to have an impact on the statistical analysis.

Inclusion in the analysis sets defined above will be determined at a data review meeting before database lock.

# 6. General Issues for Statistical Analysis

## 6.1. Statistical Definitions and Algorithms

### 6.1.1. Baseline

The last observation recorded prior to the first dose of emapalumab will be used as the baseline observation for all calculations of change from baseline.

### 6.1.2. Adjustments for Covariates

Not applicable.

### 6.1.3. Multiple Comparisons

Not applicable.

### 6.1.4. Handling of Dropouts or Missing Data

While all possible efforts will be made to ensure that patients stay in the study and all data is collected as scheduled, the occurrence of missing data cannot be completely eliminated.

Rules for handling missing or partial AEs or birth dates are described in Section 6.1.10

For defining the primary efficacy endpoint (Overall Response, see Section 6.1.9.4 for definition), values of some parameters may be missing, thus impacting the response assessment. Imputation rules for assessing disease response at EOT or Week 8 (whichever occurs earlier) and throughout the study have been pre-defined as follows. Note: Imputed values will be flagged in the listings for all endpoints where applicable.

Response at EOT or Week 8 (whichever occurs earlier):

- Missing data at EOT/Week 8 for the parameters relevant to assessment of Overall Response will be imputed by the closest available value from the EOT/Week 8 target day (as per Table 1 and Table 2) up to 8 days, provided upper window limit is before start of conditioning. For body temperature, in the event of repeated measures recorded on the same study day, the highest value will be selected.
- No imputation will be applied if no value is available within the time of the EOT/Week 8 target day up to 8 days. That parameter will be viewed as missing and complete response will not be assigned, even if all other parameters are normal.
- Values recorded at both scheduled and unscheduled visits will be considered.

- If all parameters are unable to be imputed then the overall response assessment will be recorded as missing.

Response throughout the study:

- For secondary time to event analyses (e.g., duration of response, time to response), both scheduled and unscheduled visits will be used for assessment of response.
- If a numerical parameter (i.e. Body Temperature, D-Dimer, Fibrinogen, Ferritin, Platelets, Neutrophils) needed for the response assessment is missing, the midpoint approach will be used to estimate the missing value – i.e., the last observed value before the missing period will be averaged with the first value available after the missing period. This rule will be applied to parameter values missing for a period of up to a maximum of 7 consecutive days.
  If a character parameter needed for the response assessment (i.e. Spleen Assessment, CNS) is missing, last observation carried forward method will be used to estimate the missing value – i.e., the last observed value within a maximum of 7 consecutive days before the missing period will be used.
  In case that, after imputation, data is still missing in any of the criteria considered for the definition of response, a Complete Response cannot be adjudicated.
- If the maintenance of response (of at least 4 days) cannot be confirmed due to missing data, the response will be assumed to be lost. In case of calculation of duration of response (i.e. durability of first response) the next response period will be considered. If none of the subject's responses could have been confirmed to last for at least 4 days or only one response was documented which could not have been confirmed to last for at least 4 days, the duration of response will be set to 1 day applying a conservative imputation strategy.
- Since data relevant to CNS assessment has been collected at irregular time-points (based on individual patient conditions), the investigators assessment of CNS status will be carried-forward until the time-points of relevance for response analysis

For descriptive statistics on the evolution over time of clinical signs characterizing HLH disease, the time windows listed in Table 1 and Table 2 will be applied in the case that a parameter is not available on the specified study day.

For any assessment, if there is more than one observation during the visit window, the closest value (within the visit window) to the target day will be chosen first. In the case that there are 2 equidistant values to the study day of interest, the observation that is after the study day in question will be selected.

### 6.1.5. Analysis Visit Windows

Statistical analyses will be based on the windowing displayed in Table 1 (patients with a

treatment duration less than 8 weeks, i.e. < 56 days) and Table 2 (patients with a treatment duration of 8 weeks or more, i.e. >= 56 days).

However, imputation of missing data will be applied as described in Section 6.1.4.

**Table 1: Treatment Visit Windows, treatment duration < 8 weeks**

| Visit Name | | Target day | Analysis visit window | |
|---|---|---|---|---|
| | | | From SD | To SD |
| Baseline | | | Last observation recorded prior to the first dose of emapalumab | |
| Study Day 0 (first infusion of emapalumab) | | 1 | 1 | 1 |
| Study Day 3 | | 4 | 2 | 5 |
| Study Day x | | Study Day x + 1 day | Target day – 1 day | Target day + 1 day |
| a) EOT visit available | Study Day n-1 | Study Day x +1 day | Target day – 1 day | Day of last infusion of emapalumab |
| | EOT / Week 8 | EOT visit | Day of last infusion of emapalumab +1 | EOT visit |
| | EOT | EOT visit | EOT visit | EOT visit |
| b) no EOT visit available | Study Day n-1 | Study Day x +1 day | Target day – 1 day | Day of last infusion of emapalumab – 1 day |
| | EOT / Week 8 | Start day of last infusion * | Start day of last infusion * | End day of last infusion * |
| | EOT | Start day of last infusion * | Start day of last infusion * | End day of last infusion * |

* Start and End date of infusion are in most of the cases the same date.

a) If an EOT visit was performed and treatment duration was < 8 weeks (i.e. < 56 days), the day of EOT visit will be assigned as EOT/Week 8 analysis visit and as EOT visit prior to start of conditioning.
b) If no EOT visit was performed and treatment duration was < 8 weeks (i.e. < 56 days), the day of last infusion will be assigned as EOT/Week 8 analysis visit and as EOT visit prior to start of conditioning.

**Table 2: Treatment Visit Windows, treatment duration >= 8 weeks**

| Visit Name | | Target day | Analysis visit window | |
|---|---|---|---|---|
| | | | From SD | To SD |
| Baseline | | | Last observation recorded prior to the first dose of emapalumab | |
| Study Day 0 (first infusion of emapalumab) | | 1 | 1 | 1 |
| Study Day 3 | | 4 | 2 | 5 |
| Study Day 6 | | 7 | 6 | 8 |
| Study Day 9 | | 10 | 9 | 11 |
| Study Day 12 | | 13 | 12 | 14 |
| Study Day 15 | | 16 | 15 | 17 |
| Study Day 18 | | 19 | 18 | 20 |
| Study Day 21 | | 22 | 21 | 23 |
| Study Day 24 | | 25 | 24 | 26 |
| Study Day 27 | | 28 | 27 | 29 |
| Study Day 30 | | 31 | 30 | 32 |
| Study Day 33 | | 34 | 33 | 35 |
| Study Day 36 | | 37 | 36 | 38 |
| Study Day 39 | | 40 | 39 | 41 |
| Study Day 42 | | 43 | 42 | 44 |
| Study Day 45 | | 46 | 45 | 47 |
| Study Day 48 | | 49 | 48 | 50 |
| Week 8 is the last week prior to EOT visit or last infusion | | | | |
| a) EOT visit available | Study Day 51 | 52 | 51 | Day of last infusion of emapalumab |
| | EOT / Week 8 | EOT visit | Day of last infusion of emapalumab + 1 day | EOT visit |
| | EOT | EOT visit | EOT visit | EOT visit |
| b) no EOT visit available | Study Day 51 | 52 | 51 | Day of last infusion of emapalumab - 1 day |
| | EOT / Week 8 | 57 | Day of last infusion of emapalumab | Day of last infusion of emapalumab + 6 days |
| | EOT | Start day of last infusion * | Start day of last infusion * | End day of last infusion * |

| Visit Name | | Target day | Analysis visit window | |
|---|---|---|---|---|
| | | | From SD | To SD |
| Week 8 is not the last week prior to EOT visit or last infusion (subsequent weeks (x to n)) | | | | |
| a) EOT visit available | Week x | Week (x*7) +1 | Target day – 3 days | EOT visit – 1 day |
| | EOT / Week 8 | 57 | 54 | 60 |
| | EOT | EOT visit | EOT visit | EOT visit |
| b) no EOT visit available | Week x | Week (x*7) +1 | Target day – 3 days | Day of last infusion of emapalumab – 1 day |
| | EOT / Week 8 | 57 | 54 | 60 |
| | EOT | Start day of last infusion * | Start day of last infusion * | End day of last infusion * |

* Start and End date of infusion are in most of the cases the same date.

If treatment duration was >= 8 weeks (i.e. >= 56 days) the visit within the analysis visit window of 54 and 60 days and closest to the target day will be assigned as EOT/Week 8 analysis visit.

a) If an EOT visit was performed the day of EOT visit will be assigned as EOT visit prior to start of conditioning.
b) If no EOT visit was performed the day of last infusion will be assigned as EOT visit prior to start of conditioning.

### 6.1.6. Treatment naïve / experienced patients

**Treatment naïve (First Line) patients:**

Patients who have not received any conventional treatment for pHLH. In treatment-naïve patients, an initial background therapy of 10 mg/m2 dexamethasone will be required. Dexamethasone not more than 7 days or Methylprednisolone pulses for less than 3 consecutive days until emapalumab treatment start (SD0).

**Treatment experienced (Second line) patients:**

Patients who have received conventional HLH therapy (as per site standard of care), e.g., any of the following alone or in combination (Etoposide, ATG, Alemtuzumab and Cyclosporine A) and Dexamethasone at 10 mg/m2 for more than 7 days or methylprednisolone pulses for 3 or more consecutive days before emapalumab treatment start (SD0).

The following derivation to identify second line patients will be done:

- Yes to Question: Was any HLH treatment administered at diagnosis [History of HLH treatments]

*and*

- Medication that:
  - Contains text 'HLH 2004'.

or

- Medication recorded in eCRF with a start date prior to emapalumab first infusion as follows: (priorities need to be followed as below list, check first condition first if not met then check second condition, if not met then the third and so on).

  o Etoposide [ATC04ID L01CB - Preferred code 00511901001], any dose, any duration
  o Antithymocyte immunoglobulin [ATC04ID L04AA - Preferred code 00575401001], any dose, any duration
  o Alemtuzumab [ATC04ID L04AA - Preferred code 01268601001], any dose, any duration
  o Cyclosporin A [ATC04ID L04AD - Preferred code 00549701001], any dose, any duration
  o Anakinra [ATC04ID L04AC - Preferred code 01345101001], any dose, any duration
  o Tocilizumab [ATC04ID L04AC - Preferred code 01759101001], any dose, any duration
  o Dexamethasone [ATC04ID H02AB - Preferred code 00016001001], dose ≥ 10mg/m$^2$ for at least 7 days

  o Methylprednisolone [ATC04ID H02AB - Preferred code 00049601001], with a verbatim indicating "pulses" or "high dose", or any dose for more than 7 days or 30 mg/kg for 3 consecutive days

*and any of the following*

- Having not achieved a satisfactory response (Unsatisfactory response)
- Having not responded or worsened (No response or worsening)
- Showing intolerance to previous conventional treatment of HLH.
- Having reactivated after satisfactory response based on investigator assessment at screening.

### 6.1.7. Subgroup Analyses

All data will be presented for the following subgroups, with the relevant analysis sets described in Table 3:

- **Treatment-naïve:** Patients in the All Treated Analysis Set who are naïve to HLH treatment (according to section 6.1.6).
- **Treatment-experienced:** Patients in the All Treated Analysis Set who have received conventional HLH therapy (as per site standard of care) without having obtained a satisfactory response according to the treating physician or having shown signs of intolerance to previous HLH therapy.

Conventional HLH therapy is defined as per site standard-of-care, e.g., any of the following, alone or in combination (etoposide, ATG, alemtuzumab and cyclosporine A) or glucocorticoids, namely dexamethasone at 10 mg/m$^2$ for at least 7 days or methylprednisolone pulses for 3 consecutive days.

**Table 3: Patient Populations for Each Analysis/Summary**

| Analyses | Patient Populations | | | | | | |
|---|---|---|---|---|---|---|---|
| | Enrolled Population Analysis Set | All Treated Analysis Set | | | Evaluable Analysis Set | | |
| | | Treatment naïve | Treatment experienced | Total | Treatment naïve | Treatment experienced | Total |
| Patient Disposition | X | X | X | X | X | X | X |
| Protocol Deviations | X* | | | | | | |
| Demographics, Baseline | | X | X | X | | | |
| Prior and Concomitant Therapies | | X | X | X | | | |
| Primary Efficacy Endpoint | | X | X | X | X | X | X |
| Secondary Efficacy Endpoints | | X | X | X | X | X | X |
| Sensitivity analysis 1: Overall Response at EOT or Week 8 (whichever occurs earlier) with deaths considered as non-responders | | X | X | X | | | |
| Sensitivity analysis 2: Overall Response at EOT or Week 8 (whichever occurs earlier) with early withdrawal considered as non-responders | | | | | X | X | X |
| Sensitivity analysis 3: Overall Response at EOT or Week 8 (whichever occurs earlier) with patients who receive concomitant administration of other HLH treatments considered as non-responders | | X | X | X | | | |

| Analyses | Patient Populations | | | | | | |
|---|---|---|---|---|---|---|---|
| | Enrolled Population Analysis Set | All Treated Analysis Set | | | Evaluable Analysis Set | | |
| | | Treatment naïve | Treatment experienced | Total | Treatment naïve | Treatment experienced | Total |
| Sensitivity analysis 4: Overall Response at EOT or Week 8 (whichever occurs earlier) with deaths, early withdrawals, and patients who receive concomitant administration of other HLH treatment considered as non-responders | | X | X | X | | | |
| Sensitivity analysis 5: Overall Response at EOT or Week 8 (whichever occurs earlier) with patients deemed as having a major protocol deviation impacting statistical analysis removed from the Analysis Set | | | | | X^ | X^ | X^ |
| Supplementary analysis: Overall Response at EOT or Week 8 (whichever occurs earlier) - Modified Definition | | X | X | X | | | |
| Exposure | | X | X | X | | | |
| Quality of life: PedsQL™, BASES | | X | X | X | | | |
| Safety: AEs, SAEs, Lab tests | | X | X | X | | | |
| Safety: Vital Signs, Physical Examination, ECG | | X | X | X | | | |

* Excluding Screening failures
^ Evaluable Analysis Set Without Major Protocol Deviations

### 6.1.8. Pooling of Sites

As relatively few patients are expected in the study, the centers will not be taken into account in the analyses.

### 6.1.9. Derived Variables

#### 6.1.9.1. General

- Sponsor defined study day = date of interest – date of first emapalumab infusion

  Note: This study day will be used in the analysis visit windowing and displayed on listings if required. Study Day 0 (SD0) is the day when first emapalumab infusion is performed.

- Change from baseline = value at current time point – value at baseline.

#### 6.1.9.2. Demography and Baseline Parameters

- Conversion factors: The following conversion factors will be used to convert days into months or years:
  - 1 month = 30.4375 days
  - 1 year = 365.25 days
- Age at diagnosis in years = date of diagnosis – date of birth +1.
- Age in days = date of informed consent – date of birth +1.
- Age in years = Age in days / 365.25.
- Age categories: The following groups will be used for categorizing age:

| Age Group | Definition |
|---|---|
| **Newborns (0-27 days)** | 0 ≤ (Date of informed consent – Date of Birth +1) ≤ 27 |
| **Infant and toddlers (28 days - 23 months)** | 28 ≤ (Date of informed consent – Date of Birth +1) and age in years = 1 |
| **Children (2-11 years)** | 2 <= age in years <= 11 |
| **Adolescents (12-18 years)** | 12 <= age in years <= 18 |

#### 6.1.9.3. Safety Parameters

**Table 4: Definition of Drug Administration Variables**

| Statistics for Exposure (dosing) | Derivation |
|---|---|
| Duration of exposure (days) | Date of last infusion of emapalumab – date of first infusion of emapalumab + 1 |
| Duration of exposure (weeks) | Duration of exposure (days)/7 |
| Maximum dose prescribed | Maximum of all doses prescribed (mg/kg) |
| Cumulative dose (mg/kg) | Sum of total actual dose per kg administered from first infusion date until last infusion date |
| Average dose frequency (days) | Duration of exposure (days)/ total number of infusions |
| Average dose of emapalumab per day (mg/kg) | Cumulative dose (mg/kg)/ duration of exposure (days) |
| Percentage of dose increases from baseline dose | (Number of dose increases from baseline dose / number of total doses) multiplied by 100. |
| Percentage of dose decreases from baseline dose | (Number of dose decreases from baseline dose / number of total doses) multiplied by 100. |

**Table 5: Definition of Adverse Events**

| Variable | Definition |
|---|---|
| Adverse Event (AE) | All recorded AEs (collection of AEs starts after ICF signature). |
| Treatment-Emergent Adverse Event (TEAE) | Any AE (serious and non-serious) with an onset date after the start of the first emapalumab infusion. |
| Pre-conditioning AE | Any AE (serious and non-serious) with start date before the start of conditioning for HSCT*. |

| Variable | Definition |
|---|---|
| Post-conditioning AE | Any AE (serious and non-serious) with start date after the start of conditioning for HSCT*. |
| TEAEs related to the study drug | Any AEs with an onset date after the start of the first emapalumab infusion with "Relationship to Study Drug" of "Related". |
| Serious TEAEs | Any AEs with an onset date after the start of the first emapalumab infusion with "Serious" of "Yes". |
| TEAEs leading to withdrawal of study drug | Any AEs with an onset date after the start of the first emapalumab infusion with "Action taken with study drug" of "Drug Withdrawn". |
| TEAEs resulting in death | Any AEs with an onset date after the start of the first emapalumab infusion with "Results in death" of "Yes". |
| TEAE with infections | Any AE with an onset date after the start of the first emapalumab infusion with system organ class (SOC) 'Infections and Infestations' or in the HLGT 'Microbiology and serology investigations'. |
| TEAE with infusion-related reactions (IRRs) | Any AE reported to have occurred within 24 hours after the start of infusion and reported as related to study treatment by the Investigator, excluding the following SOCs: "Infections and infestations," "Congenital familial and genetic disorders," "Neoplasms benign, malignant and unspecified (incl. cysts and polyps)," "Product issues," "Social circumstances," and "Surgical and medical procedures."<br><br>If the onset time of the AE or the start time of the infusion is missing, then an AE with an onset date equal to an infusion date or infusion date +1 will be considered for the assessment of IRRs, unless the available information clearly indicates the AE was not treatment-emergent. |

*Note: The start date of conditioning is captured in the HSCT module of the eCRF or CM module. For more information of HSCT medications see Appendix 16.2.

#### 6.1.9.4. Efficacy Parameters

- Overall Response at EOT or Week 8 = achievement (yes/no) of either Complete or Partial Response or HLH improvement at EOT or the Week 8 assessment, whichever occurs earlier.
- Overall Response at start of conditioning for HSCT = achievement (yes/no) of either Complete or Partial Response or HLH improvement at start of conditioning of HSCT (date of start of conditioning) or last emapalumab if HSCT is not performed.

The definition of the Overall Response for the primary endpoint is detailed in Table 6 along with additional clarifications.

The definition of the Overall Response used in the supplementary analysis is detailed in Table 7.

**Table 6: Definition of Response for the Primary Endpoint**

| Response for Primary Endpoint | Definition | Additional Clarifications |
|---|---|---|
| Complete Response | Complete Response is adjudicated if:<br>- No fever = body temperature < 37.5 °C<br>- Normal spleen size<br>- 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]<br>- No hyperferritinemia = serum ferritin level is < 2000 µg/L<br>- No evidence of coagulopathy, i.e., normal D-Dimer and/or normal (> 150 mg/dL) fibrinogen levels<br>- No neurological and CSF abnormalities attributed to HLH<br>- 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<br>- No AEs relating to organ failure<br>- All other parameters that were normal at baseline must still meet the definition of normalized<br>- 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<br>- Normal D-Dimer levels are <= 500 ug/L<br>- 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" (Appendix 15.3)<br>- No CSF abnormalities = no AE indicative of "CSF abnormalities" (Appendix 15.3) |

| Response for Primary Endpoint | Definition | Additional Clarifications |
|---|---|---|
| Partial Response | Partial Response is adjudicated if:<br>- At least 3 of the HLH clinical and laboratory abnormalities (including CNS abnormalities) meet the above mentioned criteria for "Complete Response"<br>- 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<br>- 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<br>- There is no progression of other aspects of HLH disease pathology | 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.<br><br>For all patients: no progression of other aspects of HLH disease pathology is assessed by absence of AEs indicating organ failure including no worsening of sCD25 levels. |

| Response for Primary Endpoint | Definition | Additional Clarifications |
|---|---|---|
| HLH Improvement | HLH Improvement is adjudicated if:<br>- Improvement (>50% change from baseline or normalization) of at least 3 HLH clinical and laboratory abnormalities (including CNS abnormalities).<br>- 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:<br>- Spleen size decreased by 50%, as recorded in cm from costal margin at physical examination.<br>- 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<br>- Ferritin decreased by 50%<br>- Fibrinogen increased by 50% or D-Dimer decreased by 50%<br>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" |
| 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 | | |

**Table 7: Definition of Response for Supplementary Analysis**

| Response for Supplementary Analysis | Definition | Additional Clarifications |
|---|---|---|
| Complete Response | Complete Response is adjudicated if:<br>- No fever = body temperature < 37.5 °C<br>- Normal spleen size<br>- 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]<br>- No hyperferritinemia = serum ferritin level is < 2000 µg/L<br>- No evidence of coagulopathy, i.e., normal D-Dimer and/or normal (> 150 mg/dL) fibrinogen levels<br>- No neurological and CSF abnormalities attributed to HLH<br>- 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<br>- No AEs relating to organ failure<br>- All other parameters that were normal at baseline must still meet the definition of normalized<br>- 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<br>- Normal D-Dimer levels are <= 500 ug/L<br>- 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" (Appendix 15.3)<br>- No CSF abnormalities = no AE indicative of "CSF abnormalities" (Appendix 15.3) |

| Response for Supplementary Analysis | Definition | Additional Clarifications |
|---|---|---|
| Partial Response | Partial Response is adjudicated if:<br>- 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)<br>- 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)<br>- 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 may be the same or worse as baseline (unless 2 or more parameters no longer meet the definition of normality)<br>- There is no progression of other aspects of HLH disease pathology | 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.<br><br>For all patients: no progression of other aspects of HLH disease pathology is assessed by absence of AEs indicating organ failure including no worsening of sCD25 levels. |

| Response for Supplementary Analysis | Definition | Additional Clarifications |
|---|---|---|
| HLH Improvement | - 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)<br>- 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. | Definition of 50% improvement from baseline:<br>- Spleen size decreased by 50%, as recorded in cm from costal margin at physical examination.<br>- 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<br>- Ferritin decreased by 50%<br>- Fibrinogen increased by 50% or D-Dimer decreased by 50%<br>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” |
| 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 | | |

- Overall Survival, defined as the time from the date of first dose to the date of death. Patients without an event will be censored at date of last contact. The analysis start and end dates and the censoring rules are described in the following scheme:

**Table 8: Overall Survival**

| Situation | Outcome (event or censored) | Analysis start date | Analysis end date |
|---|---|---|---|
| No assessments after first infusion | Censored | Start of treatment | Start of treatment + 1 |
| Death for any cause | Event | Start of treatment | Death |
| Alive at the end of the observation period* | Censored | Start of treatment | Last known alive |
| * end of study, or premature end of study for the patient (including withdrawal of consent) | | | |

- Survival to HSCT, defined as the time from the date of first dose to the date of death. Patients who receive a HSCT will be censored at that date. Patients who did not receive HSCT will be censored at date of last contact. The analysis start and end dates and the censoring rules are described in the following scheme:

**Table 9: Survival to HSCT**

| Situation | Outcome (event or censored) | Analysis start date | Analysis end date |
|---|---|---|---|
| No assessments after first infusion | Censored | Start of treatment | Start of treatment + 1 |
| Death for any cause | Event | Start of treatment | Death |
| Alive at HSCT | Censored | Start of treatment | HSCT date |
| Alive without having received HSCT | Censored | Start of treatment | Last known alive date |

- Survival post HSCT, defined as the time from date of HSCT to the date of death. Patients without an event will be censored at date of last contact. Patients who do not proceed to HSCT will be excluded from this analysis. The analysis start and end dates and the censoring rules are described in the following scheme:

**Table 10: Survival post HSCT**

| Situation | Outcome (event or censored) | Analysis start date | Analysis end date |
|---|---|---|---|
| Death for any cause | Event | Date of HSCT | Death |
| Alive at the end of the observation period* | Censored | Date of HSCT | Last known alive date |
| * end of study, or any time during follow-up period (including withdrawal of consent) | | | |

- HLH Reactivation = any adverse event in the following preferred term (PT) (PT code):
  - Condition Aggravated (10010264)
- Graft failure = any adverse event in at least one of the following PTs (PT code):
  - Transplant failure (10060872)
  - Engraft failure (10068081)
  - Bone marrow transplant rejection (10048396)
  - Transplant rejection (10044439)
  - Complications of bone marrow transplant (10010162)
  - Graft loss (10048748)
- Event-free survival = time from HSCT to date of (whichever occurs first): death from any cause, graft failure, HLH reactivation. The analysis start and end dates and the censoring rules are described in the following scheme:

**Table 11: Event-Free Survival**

| Situation | Outcome (event or censored) | Analysis start date | Analysis end date |
|---|---|---|---|
| At least one event, i.e. graft failure, HLH reactivation, death for any cause | Event | Date of HSCT | Date of first event |
| None of the events at the end of the observation period* | Censored | Date of HSCT | Last known alive |
| * end of study, or any time during follow-up period (including withdrawal of consent) | | | |

- Duration of Response (i.e. maintenance of response achieved at any time during the study until EOT) is defined as the total elapsed time from achievement of first Overall Response to first loss of response, pending the duration of this response is at least 4 days. If the first observed response does not last for at least 4 days, then the next response period will be considered. Similarly, loss of response should persist for at least 4 days, otherwise the next loss of response period will be considered. Patients who are in response at EOT will be censored at that date. Patients who do not achieve at least HLH improvement once between the date of first dose and EOT will be excluded from the analysis.

  The analysis start and end dates and the censoring rules for calculation of duration of response are described in the following scheme:

**Table 12: Duration of Response**

| Situation | Outcome (event or censored) | Analysis start date | Analysis end date |
|---|---|---|---|
| Maintained loss of overall response | Event | Date of first response [2] | Date of loss of overall response [2] |
| Death for any cause | Event | Date of first response [2] | Date of death |
| In response at the end of the observation period[1] | Censored | Date of first response [2] | Last known response |

[1] end of treatment without conditioning, or start of conditioning for HSCT, or early termination (including withdrawal of consent);

[2] last for at least 4 days

- Cumulative Duration of Response = Total time in response from the first achievement of an Overall Response until HSCT conditioning (or EOT if the patient did not have HSCT performed). Considering 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. Patients who do not achieve response at least once between the date of first dose and the time of conditioning start are excluded from the analysis.
- Percent days in response = Cumulative response duration divided by number of days from first infusion until HSCT conditioning (or EOT if the patient did not have HSCT performed).
- Time to Response (i.e. time to first maintained response) is defined as elapse time from start of treatment to first achievement of a response maintained for at least 4 days prior to or at EOT. Patients with no post-baseline assessments (assessment after the first infusion) will be censored at the first dose date. The analysis start and end dates and the censoring rules are described in the following scheme:

**Table 13: Time to Response**

| Situation | Outcome (event or censored) | Analysis start date | Analysis end date |
|---|---|---|---|
| No assessments after first infusion | Censored | Start of treatment | Start of treatment + 1 |
| At least 1 event i.e. complete or partial response or HLH improvement | Censored | Start of treatment | Date of first response which lasted for at least 4 days |
| Death for any cause | Censored | Start of treatment | Death |
| Alive at the end of the observation period* | Censored | Start of treatment | Last known alive |
| * end of study, or premature end of study for the patient (including withdrawal of consent) | | | |

### Medication Parameters

The definition of treatment naïve and treatment experienced patients are described in detail in section 6.1.6.

**Table 14: Derivations for Medications**

| Dexamethasone daily dose |
|---|
| The dose of dexamethasone is to be expressed as mg/m$^2$/day in order to give homogeneous metrics across patients.<br>The 'Systemic Steroids Administration' module of the eCRF also collects other glucocorticoids that need to be converted to dexamethasone equivalent using the following assumptions:<br>• The equivalent dose will include only glucocorticoids administered IV or per os (PO)<br>• IV and PO route of administration are equivalent, which means 1 mg of IV dexamethasone is equivalent to 1 mg of PO dexamethasone, and 1 mg of IV methylprednisolone is equivalent to 1 mg of PO methylprednisolone.<br>• Conversion factor:<br>o 1 for dexamethasone<br>o 1/5.3 for methylprednisolone<br>o 1/6.7 for prednisolone<br>o 1/6.7 for prednisone<br>o 1/5.3 for triamcinolone<br>o 1/26.6 for hydrocortisone<br>o 1/33.3 for cortisone<br>• Dose unit: If the dose unit is not mg, then the following conversion will be done:<br>o 1 g = 1000 mg<br>o 1 mcg = 0.001 mg<br>Given the possibility of having dexamethasone doses recorded differently in the eCRF or conversions from other glucocorticoids required the following calculation will be performed:<br>• Daily dose = Conversion factor* Dose of dexamethasone in mg<br>* number of administrations per day<br>• BSA Surface Area (BSA) [VS]<br>• Equivalent dose (mg/m$^2$/day) = Daily dose / BSA |

**Glucocorticoid tapering**

For the reduction of glucocorticoid dose by 50% or more of baseline dose, the use of glucocorticoid for systemic use during the study period will be obtained by the CM (ATC04ID H02AB) or medications captured on the SSA module of the eCRF. Drug names on the SSA page are standardized (Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone), not coded. The calculation of reduction of glucocorticoid dose by 50% or more of baseline dose will take into consideration the following:

- Dexamethasone (H02AB - PREFERRED CODE 00016001001) dose expressed as mg/m2/day at
  - Baseline = SD-1 or closest day to SD0
  - The lowest dose received during the study and the corresponding SD,
  - The dose received at EOT

provided that:

- No other glucocorticoids have been received by oral or IV route on the SD of interest with reference to:
  - Methylprednisolone (CM page: H02AB - PREFERRED CODE 00049601001)
  - Prednisolone (CM page: H02AB - PREFERRED CODE 00016201001)
  - Prednisone (CM page: H02AB - PREFERRED CODE 00044701001)
  - Hydrocortisone (CM page: H02AB – PREFERRED CODE 00028601001, 00028603001,00028602001)
  - Triamcinolone (CM page: H02AB – PREFERRED CODE 00031901001 if single ingredient medication; in case of multiple ingredients medications or salt derivates every entry need to be checked manually for Triamcinolone)
  - Cortisone (CM page: H02AB – PREFERRED CODE 00014601001 if single ingredient medication; in case of multiple ingredients medications or salt derivates every entry need to be checked manually for Cortisone)

In that case, the dose of the other glucocorticoids has to be summed up, taking into consideration glucocorticoid conversion.

- Glucocorticoids reduction until EOT

  A patient will achieve a glucocorticoids reduction by 50% or more of the baseline dose if the equivalent dose of dexamethasone at any post-baseline time until EOT is less than or equal to (≤) ½ the equivalent dose of dexamethasone at baseline. This reduction has to be maintained for at least one week.

- Patients proceeding to HSCT = patient with HSCT (date of HSCT non missing in the HSCT module of the eCRF).

**Quality of Life Parameters**

- The Pediatric Quality of Life Inventory (PedsQL) is a brief measure of health-related quality of life in children and adults. PedsQL™ 4.0 generic core scales (ages 2 to over 26) and PedsQL™ infant scales (ages 1 to 24 months) are used in the study. The PedsQL™ 4.0 generic core scales can be completed by parents (Parent Proxy-Report from 2 years old) as well as children and adults (Child/Adult Self-Report from 5 years old). The PedsQL generic core scales are composed of four scales grouped together in one questionnaire:
    - Physical functioning
    - Emotional functioning
    - Social functioning
    - School functioning

  The PedsQL Infant Scales, specific for healthy and ill infants ages 1-24 months, are completed by parents and composed of five scales grouped together in one questionnaire:
    - Physical functioning
    - Physical symptoms
    - Emotional functioning
    - Social functioning
    - Cognitive functioning

  Scales are estimated using the following 2-step process as described in the 'Scaling and Scoring of the Pediatric Quality of Life Inventory PedsQL' version 17, dated May 2017 and available online https://www.pedsql.org/PedsQL-Scoring.pdf .

  1) Calculate reversed scored items transforming the 0-4 scale item to 0-100 as follows:

| Response Choices | Never | Almost Never | Sometimes | Often | Almost Always |
|---|---|---|---|---|---|
| Raw scores | 0 | 1 | 2 | 3 | 4 |
| Reversed score | 100 | 75 | 50 | 25 | 0 |

Notes:
- Higher scale scores indicate better HRQOL (Health-Related Quality of Life).
- 3-point scales: 0 (Not at all), 2 (Sometimes) and 4 (A lot) applicable for the young child (ages 5-7) self-report.

2) Calculate the average as sum of the items divided by the number of items answered. If more than 50% of the items in the scale are missing, the Scale Score should not be computed.

- Functioning scale scores as average of the transformed functioning scale items
  - Physical Functioning Scale Score = average of transformed physical functioning scale items; up to 6 items for infants (1-12 months), 9 items for infants (13-24 months), and 8 items for toddlers, young children, children, teens, and young adults.
  - Physical Symptoms Scale Score = average of transformed physical symptoms scale items; up to 10 items for infants (1-12 months) and infants (13-24 months). This scale score is not available for toddlers, young children, children, teens, and young adults.
  - Emotional Functioning Scale Score = average of the transformed emotional functioning scale items; up to 12 items for infants (1-12 months) and infants (13-24 months) and 5 items for toddlers, young children, children, teens, and young adults.
  - Social Functioning Scale Score = average of the transformed social functioning scale items; up to 4 items for infants (1-12 months) and 5 items for infants (13-24 months), toddlers, young children, children, teens, and young adults.
  - Work/Study Functioning Scale Score = average of the transformed school functioning scale items; up to 3 items for toddler and 5 items for young children, children, teens, and young adults. This scale was not collected for infants (1-12 months) or infants (13-24 months).
  - Cognitive Functioning Scale Score = average of the transformed cognitive functioning scale items; up to 4 items for infants (1-12 months) and 9 items for infants (13-24 months). This scale score is not available for toddlers, young children, children, teens, and young adults.
- Health summary scores
  - Physical Health Summary Score = Physical Functioning Scale Score for toddlers, young children, children, teens, and young adults. For infants (1-12 months) and infants (13-24 months), it is the sum of transformed items over the number of items answered in physical functioning and physical symptoms scales.
  - Psychosocial Health Summary Score = sum of transformed items over the number of items answered in Emotional, Social, and Work/Study Functioning Scales for toddlers, young children, children, teens, and young adults. It is the sum of transformed items over the number of items answered in Emotional, Social, and Cognitive Functioning Scales for infants (1-12 months) and infants (13-24 months).

- Total Scale Score = sum of all the transformed items over the number of items answered on all the scales. (i.e. average as sum of the items divided by the number of items answered).

- The BASES questionnaire is a validated 38 item questionnaire. In this study a reduced non-validated 22 item version is used in an exploratory nature for the secondary endpoint. BASES subscale scores will be calculated using a 5-point Likert scale from 1 to 5 for all items and they will be weighted equally to calculate subscale scores. for the following domains:
    - Physical Discomfort, items 1 to 5 (5 items – where 1 is considered best response for all items)
    - Cooperation/Compliance, items 6 to 10 (5 items – where 1 is considered best response for all items)
    - Mood/Behavior, items 11 to 17 (7 items – where 5 is considered best response for all items)
    - Quality of Interactions, items 18 to 20 (3 items – where 1 is considered best response for all items)
    - Activity/Sleep, items 21 to 22 (2 items – where 5 is considered best response for patient's activity level and 1 is considered best response for patient's sleeping)

### 6.1.10. Data Adjustments/Handling/Conventions

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 (or later) thesaurus.

Medications will be coded using World Health Organization Drug Dictionary (WHO-DD) B2 Enhanced v. March 2018 (or later).

Tables describing AEs will show SOCs by descending number of patients and preferred terms within SOC also by descending number of patients. Tables describing prior and concomitant medication will show Anatomical Therapeutic Chemical (ATC) level 1 by descending number of patients and ATC level 2 term also by descending number of patients.

A treatment-related AE is any AE with a relationship to the study drug of 'related'. If a particular event is missing the relationship, the strongest possible relationship will be assumed for analysis (relationship = related).

Adverse events will also be described by intensity (mild, moderate, severe). If a particular event is missing the intensity, the strongest possible intensity will be assumed for analysis (intensity=severe).

Partially missing dates for AEs will be imputed as follows. Note, imputation of missing/partial AE date will be performed only to identify treatment emergent AEs.

AE onset dates

- Partially missing onset dates will be imputed as follows:
    - When only day is missing:
        - If month and year of the onset date are the same as month and year of the first infusion date, the imputed onset date will be imputed as the minimum of the first infusion date and the AE resolution date (imputed if needed).
        - Otherwise, the missing day will be replaced as the first day of the month.
    - When day and month are missing:
        - If year of the onset date is the same as year of the first infusion date, the imputed onset date will be imputed as the minimum of the first infusion date and the AE end date (imputed if needed).
        - Otherwise, the missing day and month will be replaced by "01JAN".
- Complete missing onset dates for AEs will be imputed by the first infusion date and the AE will be considered as treatment emergent unless, the end date of the AE (imputed if needed) or the end year of the AE (if day and month are missing) is entered and is before the first infusion date.

AE end dates (for non-ongoing events)

- If only day is missing, incomplete end dates will be replaced by the last day of the month, if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete end date.
- If day and month are missing, day and month will be replaced by "31DEC", if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete end date.
- In all other cases the incomplete end date will not be imputed.

Medication dates

Partially or missing dates for medications will be imputed as follows. Note, imputation of missing/partial medication dates will be performed for differentiating between prior vs

concomitant medications and used in the derivation of equivalent daily dose of dexamethasone.

- If the start date of the medication is unknown (i.e., complete missing date) and there is no end date or any evidence to suggest the medication is ongoing, the worst-case scenario will be assumed. The medication will be considered as both a prior and concomitant medication.

- If the month and the day of the start date of the medication are missing, the month and day will be imputed as "01JAN" of the year specified.

- If the day of the start date of the medication is missing and there is no end date, the day will be imputed as the first day of the month specified.

- If the month and the day of the end date of the medication are missing, the month and day will be imputed as "31DEC" of the year specified, unless there is evidence that the medication is not ongoing in the NI-0501-09 study (although complete end date is unknown). In such circumstances the medication will be considered as prior to enrolment.

- If the day of the end of the medication is missing, the day will be imputed to the last day of the month specified, unless there is evidence that the medication is not ongoing in the NI-0501-09 study (although complete end date is unknown). In such circumstances the medication will be considered as prior to enrolment.

No other dates will be imputed, unless otherwise specified. In data listings, the original incomplete, missing or partial dates (not the imputed dates) will be presented.

Laboratory parameters

For laboratory results, as well as pharmacokinetic and pharmacodynamic results, with values below the lower limit of quantitation (i.e. < LLOQ), values will be imputed to zeros when summarizing for descriptive statistics and presented as "Below LLOQ" in listings. Values above the upper limit of quantitation (i.e. > ULOQ) for individual values will be imputed to ULOQ values when summarizing for descriptive statistics and presented as "Above ULOQ" in listings.

Pharmacokinetic/Pharmacodynamic/Immunogenicity parameters

For PK, PD and ADA the primary samples should be used in analyses, unless there is a reason (e.g., sample mishandling or bioanalytical reason) for the primary data to be considered invalid, in which case the back-up sample will be utilized. All results will be listed.

### 6.1.11. COVID-19

A Coronavirus Disease 2019 (COVID-19) Continuity Plan will be written to mitigate the negative effects of the COVID-19 pandemic on the conduct of this clinical trial.

The impact of COVID-19 on this clinical trial and trial participants will be extensively described both in the tables, listings, figures (TLFs) and in the CSR.

The following aspects will be summarized when due to COVID-19:

- Changes to treatment dispensation
- Changes to treatment administration
- Changes to visit windows to accommodate delays for some assessments
- Protocol deviations
- Missing efficacy endpoints
- Missing visits

The situation is rapidly evolving and further updates to the COVID-19 Continuity Plan and to this SAP are possible and likely.

# 7. Study Patients/Subjects and Demographics

## 7.1. Disposition of Patients/Subjects and Withdrawals

The number of patients for each of the following categories will be presented in a table:

- Patients screened (i.e. Enrolled Population Analysis Set)
- Patients as screen failures and reason for screen failures
- Treated patients
    - Treatment naïve patients
    - Treatment experienced patients
- All Treated Analysis Set
- Evaluable Analysis Set
- Patients who completed the study
- Patients who stopped treatment and reason for stopping treatment
- Patients who prematurely terminated the study and primary reason for early study termination

Percentages will be calculated using the number of patients in the All Treated Analysis Set as the denominator unless otherwise specified.

A separate tabulation of re-treated patients will be provided, outlining the number of re-treated patients and number of re-treated periods per patient.

## 7.2. Protocol Violations and Deviations

Protocol deviations will be identified and classified as important/non-important during the study in line with ICH guidelines after a medical review.

**Important protocol deviations:** are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data, or that may significantly affect a subject's rights, safety or well-being.

**Major protocol deviations:** are defined as protocol deviations that have an impact on efficacy.

Classification of important and major protocol deviations will be assessed at ongoing PD review meetings and the blinded data review meeting prior to data base lock.

Any major deviations will lead to an individual being excluded from the Evaluable Analysis Set Without Major Protocol Deviations in a sensitivity analysis as outlined in Section 8.1.

Important deviations will be summarized by category and relationship to COVID-19 in a table considering at minimum the following categories:

- Eligibility: patients entering the study who do not meet all eligibility criteria
- Co-medication: non-adherence to protocol with regard to administration of concomitant medications
    - Patients are required to receive dexamethasone from not later than SD-1. Treatment-naïve patients: 10 mg/m2 of dexamethasone will be required. In patients who failed previous HLH therapy (second line patients): At least 5 mg/m2, or at the dose administered prior to Screening if higher. Lower dexamethasone doses at study entry are allowed in case of documented intolerance to glucocorticoids
    - Biologic drugs (for other indications than HLH) during emapalumab administration. The following are allowed: Granulocyte-colony-stimulating factor (G-CSF), in case of prolonged neutropenia and Rituximab, in case of documented EBV infection.
    - Cyclosporin A (CsA) can be continued, if already administered prior to Screening. CsA is not to be introduced (or re-introduced) during the course of the study once emapalumab administration has started.
    - Janus kinase (JAK) inhibitors used concomitantly with emapalumab
    - IVIG at doses expected to produce immunomodulatory effect (IVIG is only allowed as replacement therapy)
- Study drug:
    - Patients receiving less than 3 consecutive infusions (i.e. an infusion will be considered as missed If infusions are given more than 6 days apart) of emapalumab and major deviations to treatment dose assessed as impacting efficacy by the study team.

- Assessments: deviations re. schedule of assessments (e.g., missing examinations assessed as impacting the efficacy evaluation)
- Other protocol deviations impacting on patient evaluability (e.g. GCP incompliance)

Important protocol deviations by category, statistical major and minor classification and those due to COVID-19 will be listed by patient.

An assessment of the potential impact on study data analysis and subject's well-being (e.g. major, minor) will also be included.

### 7.3. Demographics and Other Baseline Characteristics

Demographics and baseline data will be summarized as outlined in Table 3.

- **Summary of patient demographics**

  Summary statistics for age at informed consent (as continuous and categorical variables), body weight (kg), height (cm), body surface area ($m^2$), gender (including childbearing potential), race, ethnicity, and country of origin will be presented.

  Patients reporting more than 1 race will be counted in a 'More than one race' category for purposes of tabulating summary statistics race.

- **Summary of HLH disease characteristics at diagnosis**

  The following will be summarized:

  - Age at HLH diagnosis (years)
  - Number of patients meeting each HLH criteria
  - Number of patients with genetic mutations identified and which mutations

- **Summary of medical history other than HLH disease**

  The number and percentage of patients reporting various medical histories, grouped by MedDRA system organ class and preferred term will be tabulated.

- **Summary of HLH disease characteristics at Screening and Baseline**

  - Number of patients meeting each HLH criteria at screening and baseline
  - Number of patients presenting with CNS involvement at screening and baseline (as defined in Appendix 15.4)

- **Summary of steroid use prior to first emapalumab infusion**

- **Summary of previous HLH treatments**

  - Number of patients who received HLH treatment including type of drug will be tabulated grouped by ATC level 1 and level 2.

All demographic and baseline characteristic data will be presented in patient listings.

## 7.4. Exposure and Compliance

Investigational product 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.

The emapalumab dose change from the baseline dose will be summarized showing the number of patients with a dose increase or a dose decrease at each visit. Moreover, the percentage of dose increases and decreases for each patient will be summarized using a descriptive table.

A listing outlining dose increases along with dose level increased to and reasons for the increase, as well as dose decreases over the study will be provided.

This analysis will be conducted as outlined in Table 3.

# 8. Efficacy Analysis

The evolution of clinical signs (fever, liver and spleen size) characterizing HLH disease, will be presented per visit using descriptive statistics.

All efficacy data will be presented in patient listings.

## 8.1. Primary Efficacy Analysis

The primary efficacy endpoint is Overall Response at EOT or Week 8 (whichever occurs earlier) (Section 6.1.9.4) with imputation of missing values. The primary efficacy endpoint and its components (Complete Response, Partial Response, and HLH Improvement) will be summarized using descriptive statistics. The analysis of the primary endpoint will utilize an exact binomial test to evaluate the following hypotheses:

$$H_0: R \leq 40\%$$

$$H_1: R > 40\%$$

where R is the percentage of the number of patients that achieved Overall Response in the All Treated Analysis Set divided by the total number of patients in the All Treated Analysis Set. The test will be undertaken at the one-sided 0.025 level. The 2-sided exact 95% confidence interval will be provided as well as the 95% confidence interval calculated via the Wilson score method as supportive.

This evaluation will be presented as described in Table 3.

The components of the primary efficacy endpoint (Complete Response, Partial Response, HLH Improvement and No response) will be summarized using counts and percentages at Week 8 or EOT (whichever occurs first).

Sensitivity analyses will be performed on the primary efficacy endpoint using the same test, and displayed as outlined in Table 3:

Sensitivity analysis 1: Overall Response at EOT or Week 8 (whichever occurs earlier) with deaths considered as non-responders.

Sensitivity analysis 2: Overall Response at EOT or Week 8 (whichever occurs earlier) with early withdrawal considered as non-responders.

Sensitivity analysis 3: Overall Response at EOT or Week 8 (whichever occurs earlier) with patients who receive concomitant administration of other HLH treatments considered as non-responders.

Sensitivity analysis 4: Overall Response at EOT or Week 8 (whichever occurs earlier) with deaths, early withdrawals, and patients who receive concomitant administration of other HLH treatment considered as non-responders.

Sensitivity analysis 5: Overall Response at EOT or Week 8 (whichever occurs earlier) with patients deemed as having a major protocol deviation impacting statistical analysis removed from the Evaluable Analysis Set.

## 8.2. Secondary Efficacy Analysis

All secondary efficacy endpoints are viewed as supportive for the primary endpoint and therefore no formal hierarchy of endpoint will be declared.

The evaluations will be performed as outlined in Table 3.

The secondary efficacy endpoints of this study are included in the following sections.

### 8.2.1. Overall Survival

Overall Survival, Survival to HSCT and Survival post HSCT (Section 6.1.9.4) will be analysed using a descriptive time-to-event approach including Kaplan-Meier curves.

Summaries will include the number and rates of patients experiencing the event and the number of censored observations; the median and 95% confidence interval, and lower quartile and upper quartile estimates of time-to-event; survival estimates at specified timepoints; and the median, minimum and maximum follow-up time in months.

### 8.2.2. Event-free Survival

Event-free survival (Section 6.1.9.4) will be analysed using the same methods described in Section 8.2.1.

### 8.2.3. Overall Response at Start of Conditioning

Overall Response (Section 6.1.9.4) at the start of conditioning will be analysed using the same methods described for the primary efficacy endpoint in Section.

### 8.2.4. Duration of Response

The Duration of Response (Section 6.1.9.4) will be calculated only for patients showing confirmed overall response and will be analysed using the same methods described in Section 8.2.1. The Cumulative Duration of Response will be analysed in absolute days and percent days in response using descriptive summaries.

Swimmer plots will be presented to show response progression and duration of response by patient.

### 8.2.5. Time to Response

The Time to Response will be analysed using comparable methods described in Section 8.2.1. However, the survival function will be plotted based on the complement of the Kaplan-Meier estimates (1-KM) to provide an estimate of the cumulative incidence of response over time.

### 8.2.6. Clinical Response

Assessment of Clinical Response using the response categories seen in Table 6, will be described using counts and percentages at each visit.

### 8.2.7. Glucocorticoids Reduction

Number of patients able to reduce glucocorticoids by 50% or more of the baseline dose during emapalumab treatment (Section 6.1.9.4) will be described using counts and percentages.

### 8.2.8. Number of Patients Proceeding to HSCT

The number of patients proceeding to HSCT (Section 6.1.9.4) will be described using counts and percentages.

### 8.2.9. Quality of Life Assessed Through PedsQL™, Pediatric Quality of Life Inventory

Descriptive summaries of absolute score and change from baseline will be calculated for the PedsQL total scale score, the health summary scores, and the functioning scale scores (Section 6.1.9.4) for all visits where the questionnaire was completed (Baseline, Visit 3 post-infusion, EOT and follow-up visits D+30, D+100, 6 months and 1 year). PedsQL parent and child/adult reports as well as parent report for infants will be presented separately as outlined in Table 3.

PedsQL subject-data, including derived scores, will be listed.

### 8.2.10. Quality of Life Assessed Through BASES Questionnaires

The BASES questionnaire scores for the 6 domains (note: activity and sleep subscales will be split into two separate domains due to differing best responses and exploratory nature of questionnaire) at the EOT and follow-up visits D+30, D+100, 6 months and 1 year will be

described using descriptive summaries of absolute values. BASES nurse and parent reports will be presented separately. Only patients with HSCT planned and/or performed will be analysed. Note: HSCT planned is defined as patients captured on the HSCT module of the eCRF with a start of conditioning date or on the CM module with HSCT conditioning medications as indicated in Appendix 15.3.

## 9. Supplementary Analysis

A supplementary analysis for Overall Response at EOT or Week 8 (whichever occurs earlier) using the definition of Overall Response in Table 7 will be performed. This will be evaluated using an exact binomial test as outlined in Section 8.1 and with the components of the overall response (Complete Response, Partial Response, HLH Improvement and No response) summarized using counts and percentages at Week 8 or EOT (whichever occurs first).

## 10. Safety and Tolerability Analysis

All safety analyses will be performed as specified in Table 3. All data relating to safety will be listed and summarized using descriptive statistics. No inferential statistical tests will be performed.

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each patient:

- Adverse events, treatment-emergent AEs (TEAEs), non-TEAEs, serious AEs (SAEs) and non-serious TEAEs
- Clinical laboratory parameters
- Vital signs

Where applicable, analyses will be performed separately for the pre and post-conditioning time periods and by treatment naïve/experienced (unless otherwise specified).

Data of patients who have not undergone HSCT will be analyzed in the pre-conditioning period.

### 10.1. Adverse Events

All AEs, non-TEAEs, TEAEs, and SAEs will be coded using the MedDRA v. 21.0 (or later). For definitions of AEs see Table 5.

A summary table will present:

- All AEs
- Non-TEAEs
- TEAEs

- TEAEs related to study drug
- Mild TEAEs
- Moderate TEAEs
- Severe TEAEs
- TEAEs leading to withdrawal of study drug
- TEAEs resulting in death
- Serious TEAEs
- Treatment emergent SAEs related to study drug
- TEAEs with IRRs
- TEAEs with Infections
- Mild infections
- Moderate infections
- Severe infections

For summary tables the incidence of the safety event of interest (i.e. AE, TEAE, non-SAE) and the number of patients with at least one safety event of interest will be given. A patient with more than one occurrence of the same safety event of interest will be counted only once in the total of those experiencing this safety event.

Information grouped by severity (mild, moderate, severe) will be presented by the worst severity per patient. Any AEs with a missing severity will be reported in the "missing" category grade.

The following safety events of interest will be provided in summary tables grouped by MedDRA system organ class and preferred term (coded using MedDRA v. 21.0 or later):

- AEs
  - overall
  - by severity
- TEAEs
  - overall
  - by severity
  - by relationship to the study drug
- Non-TEAEs
  - overall
- Non-SAEs
  - overall
- pre-conditioning TEAEs
  - overall
  - by severity
  - by relationship to the study drug
- post-conditioning TEAEs

- overall
- by severity
- by relationship to the study drug

In the AE data listings, all AEs will be displayed. AEs that are treatment-emergent will be flagged. Additional listings for pre-conditioning and post-conditioning AE will be displayed.

#### 10.1.1. Adverse Events Leading to Study Drug Withdrawal

A summary of incidence rates (percentages) of TEAEs leading to study drug withdrawal and preferred term will be displayed as specified in Table 3.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

#### 10.1.2. Deaths and Serious Adverse Events

TEAEs resulting in death will be listed and tabulated by preferred term.

Serious TEAEs will be tabulated by system organ class and preferred term separately for overall, by pre-conditioning and post-conditioning.

#### 10.1.3. Treatment-Emergent Adverse Events with Infections

The number and percentage of patients reporting infections, by SOC and preferred term, and by severity will be tabulated separately for pre-conditioning and post-conditioning infections.

#### 10.1.4. Infusion-related reactions

Infusion-related reactions will be tabulated by system organ class and preferred term.

### 10.2. Clinical Laboratory Evaluations

#### 10.2.1. Hematology, Coagulation and Clinical Chemistry

The number of patients with clinical laboratory values below, within, or above the normal range by visit and in relation to baseline will be tabulated for each clinical laboratory analyte (shift table). Denominator of the percentages will be the number of patients in the All Treated Analysis Set. Clinical chemistry, hematology, and coagulation results will be presented in separate tables.

Box and whisker plots for each parameter under clinical chemistry, hematology and coagulation will be produced to display absolute values over time.

All laboratory data will be provided in data listings. Laboratory data will be listed by patient

number and visit, and flagged according to pre/post-conditioning. Laboratory values that are outside the normal range will be flagged in the data listings.

### 10.2.2. Urinalysis

Urinalysis results will be listed only.

### 10.2.3. Cerebrospinal Fluid Data

The following information has been collected during the study with regard to CSF analysis:

- Protein
- RBC
- WBC
- Neopterin

All CSF data will be provided in data listings including comments on the results and reasons if not performed.

## 10.3. Vital Signs

Vital signs results will be presented in listings by patient number and visit. Values outside the normal range (+/-10%) and body temperature >= 37.5 Celsius will be flagged.

## 10.4. Physical examination

A by-patient listing will be provided for physical examination results by patient number and visit.

## 10.5. Electrocardiograms

ECG results will be presented in listings.

## 10.6. Imaging Test Results

A by-patient listing will be provided separately for abdominal ultrasound, chest examinations (including x-ray and CT) and brain examinations (including MRI and CT).

## 10.7. Systematic Search for Infections

Abnormal results of TB search as well as adenovirus, CMV, EBV and other specific infections assessed as medically relevant were to be recorded as AEs and will be presented in AE tables.

A by-patient listing will be provided with results from each infection search.

## 10.8. Hematopoietic Stem Cell Transplantation (HSCT)

A by-patient listing will be provided including patients undergoing HSCT with regards to:

- Date of start of conditioning / HSCT
- Stem cell source
- Graft manipulation
- Donor type.

## 10.9. Concomitant Medications and Procedures

Prior medication/therapy is defined as any medication/therapy with an end date prior to the first emapalumab infusion date or recorded with ongoing = 'No', if the end date is unknown. A concomitant medication is defined as a medication taken on or after the first dose of study drug (start date/time is on or after the first dose of study medication, end date/time is after the first dose of study drug), or recorded with ongoing = 'Yes', if the end date is unknown. If a medication starts prior to the date of first dose and continues after the date of first dose it will be considered both prior and concomitant.

Prior and concomitant medications will be summarized descriptively using counts and percentages as specified in Table 3. Summary tables of concomitant steroid use and concomitant HLH treatment (from the time of the first emapalumab infusion) will be provided.

Prior medications will be presented separately from concomitant medications. Prior medications will be split by previous HLH treatment and previous medications other than HLH treatment. Concomitant medications will be split by concomitant medications for HLH treatment and concomitant medications other than HLH treatment.

The frequency and percentage of medications will be summarized by ATC level 2 within level 1 by treatment groups, unless otherwise specified.

Prior and concomitant medications will be presented in listings. Prior and concomitant procedures will be listed separately and defined similarly as specified for prior and concomitant medications.

# 11. Changes from Planned Analysis

A summary of the changes with respect to analyses described in the study protocol is given below:

- Protocol Violations and Deviations – terminology of major protocol deviations is used in the protocol. Due to an update in regulations ICH E3 Q&A R1 and ICH GCP E6 R2 terminology of important and non-important will be used when referring to protocol deviation classification from a study conduct perspective.
- Pharmacokinetic endpoints- population PK analysis will not be conducted as part of this

study. However, data from this study might be used in combination with data from other studies to refine existing population PK models.

- Pharmacodynamic endpoints- Population PK/PD analysis using non-linear mixed effects modelling will not be conducted as part of this study. However, data from this study might be used in combination with data from other studies to refine existing population PK/PD models. As part of the SAP, only PD parameters (i.e., concentrations) will be reported descriptively.
- Secondary efficacy endpoint: cumulative duration of response has been added to protocol specified endpoints.
- 'Evaluable Analysis Set Without Major Protocol Deviations' added which contains patients in the Evaluable analysis set who do not have a major protocol deviation that is deemed to have an impact on the statistical analysis.
- Sensitivity analysis 5 added where the overall response at EOT or Week 8 (whichever occurs earlier) is displayed based on patients in the 'Evaluable Analysis Set Without Major Protocol Deviations'.
- 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.

# 12. Other Planned Analysis

## 12.1. Pharmacokinetic/Pharmacodynamic/Immunogenicity Analysis

Descriptive summaries per timepoint of the serum concentration of emapalumab, PD parameters and ADAs (if any), as well as corresponding listings including CSF analysis or other matrices as applicable, will be provided in TLFs of this SAP.

Descriptive summaries of the following results will be presented in appropriate graphical analysis and tables for the All Treated Analysis Set:

- Levels of circulating total IFNγ (free IFNγ + bound to emapalumab) after initiation of emapalumab treatment.
- Levels of the main IFNγ-induced chemokines (CXCL9, CXCL10).
- Levels of other potential disease biomarkers.
- Level (if any) of circulating antibodies against emapalumab (ADAs).
- Serum concentration of emapalumab.
- Levels of serum sCD25

# 13. References

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179,

pages 49583-49598. September 16, 1998.

2. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm
3. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014.
4. Varni, J.W., Seid, M., Rode, C.A (1999). The PedsQL™: Measurement Model for the Pediatric Quality of Life Inventory. Medical Care, 37(2), 126-139.
5. Phipps, S., Hinds, P. S., Channell, S., & Bell, G. L. (1994). Measurement of Behavioral, Affective, and Somatic Responses to Pediatric Bone Marrow Transplantation: Development of the BASES Scale. Journal of Pediatric Oncology Nursing, 11(3), 109–117.
6. Phipps, S., Dunavant, M., Lensing, S., Rai, S.N. (2002). Acute health-related quality of life in children undergoing stem cell transplant: II. Medical and demographic determinants. Bone Marrow Transplantation, 29 (5) 435-442.

## 14. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

### 14.1. Planned Table Descriptions

The following are planned summary tables for protocol number NI-0501-09. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

## Table 15: Planned Tables

| Table Number | Table Title / Summary | Population(s) | Supporting listing |
|---|---|---|---|
| **14.1 Demographic Data** | | | |
| 14.1.1.1 | Summary of Patient Enrollment and Disposition | Enrolled Pop | 16.2.1.1, 16.2.1.2 |
| 14.1.1.2 | Summary of Re-Treated Patients | All Treated Pop | 16.2.1.1, 16.2.5.1 |
| 14.1.2 | Summary of Protocol Deviations | Enrolled Pop Excluding Screen Failures | 16.2.2.1 |
| 14.1.3.1 | Demographic Characteristics | All Treated Pop | 16.2.4.1 |
| 14.1.3.2 | Baseline Characteristics | All Treated Pop | 16.2.4.1 |
| 14.1.4.1 | HLH Disease Characteristics at Diagnosis | All Treated Pop | 16.2.4.4, 16.2.4.5 |
| 14.1.4.2 | Medical History Other Than HLH Disease by System Organ Class and Preferred Term | All Treated Pop | 16.2.4.2 |
| 14.1.4.3 | HLH Disease Characteristics at Screening/Baseline | All Treated Pop | 16.2.4.11, 16.2.4.12 |
| 14.1.5 | Summary of Previous HLH Treatment by ATC Level 1 and Level 2 | All Treated Pop | 16.2.4.3 |
| 14.1.6 | Summary of Systemic Steroid Use Prior to First Emapalumab Infusion | All Treated Pop | 16.2.4.3 |
| 14.1. | Summary of Prior Medications Other Than HLH Treatment by ATC Level 1 and Level 2 | All Treated Pop | 16.2.4.6 |
| **14.2 Efficacy Data** | | | |
| 14.2.1.1.1 | Statistical Analysis of the Overall Response | All Treated Pop, Evaluable Pop | 16.2.6.3 |
| 14.2.1.1.2 | Sensitivity Analysis 1: Overall Response at EOT or Week 8 (Whichever Occurs Earlier) With Deaths Considered as Non-Responders | All Treated Pop | 16.2.6.3 |
| 14.2.1.1.3 | Sensitivity Analysis 2: Overall Response at EOT or Week 8 (Whichever Occurs Earlier) With Early Withdrawal Considered as Non-Responders | All Treated Pop | 16.2.6.3 |

| Table Number | Table Title / Summary | Population(s) | Supporting listing |
|---|---|---|---|
| 14.2.1.1.4 | Sensitivity Analysis 3: Overall Response at EOT or Week 8 (Whichever Occurs Earlier) With Patients Who Receive Concomitant Administration of Other HLH Treatments Considered as Non-Responders | All Treated Pop | 16.2.6.3 |
| 14.2.1.1.5 | Sensitivity Analysis 4: Overall Response at EOT or Week 8 (Whichever Occurs Earlier) With Deaths, Early Withdrawals, and Patients Who Receive Concomitant Administration of Other HLH Treatment Considered as Non-Responders | All Treated Pop | 16.2.6.3 |
| 14.2.1.1.6 | Sensitivity analysis 5: Overall Response at EOT or Week 8 (whichever occurs earlier) with patients deemed as having a protocol deviation impacting statistical analysis removed | Evaluable Pop Without Major PDs | 16.2.6.3 |
| 14.2.1.1.7 | Supplementary Analysis: Overall Response at EOT or Week 8 (whichever occurs earlier) – Modified Definition | All Treated Pop | 16.2.6.3 |
| 14.2.1.2 | Overall Response Components: Complete Response, Partial Response, HLH Improvement, No Response | All Treated Pop, Evaluable Pop | 16.2.6.3 |
| 14.2.1.3.1 | Evolution of Clinical Signs Characterizing HLH Disease - Part 1 | All Treated Pop, Evaluable Pop | 16.2.6.1.1, 16.2.9.3. |
| 14.2.1.3.2 | Evolution of Clinical Signs Characterizing HLH Disease - Part 2 | All Treated Pop, Evaluable Pop | 16.2.9.4 |
| 14.2.2.1 | Overall Survival | All Treated Pop, Evaluable Pop | 16.2.6.2 |
| 14.2.2.2 | Survival to HSCT | All Treated Pop, Evaluable Pop | 16.2.6.2 |
| 14.2.2.3 | Survival post HSCT | All Treated Pop, Evaluable Pop | 16.2.6.2 |
| 14.2.3 | Event-free Survival post HSCT | All Treated Pop, Evaluable Pop | 16.2.6.2 |
| 14.2.4.1 | Duration of Response | All Treated Pop, Evaluable Pop | 16.2.6.2 |
| 14.2.4.2 | Cumulative Duration of Response for Patients Achieving Overall Response | All Treated Pop, Evaluable Pop | 16.2.6.1.1, 16.2.6.1.2, 16.2.6.1.3, 16.2.6.1.4. |

| Table Number | Table Title / Summary | Population(s) | Supporting listing |
|---|---|---|---|
| 14.2.5 | Time-to-Response | All Treated Pop, Evaluable Pop | 16.2.6.2 |
| 14.2.6 | Investigator Assessment of Clinical Response | All Treated Pop, Evaluable Pop | 16.2.6.4 |
| 14.2.7.1 | Summary of Dexamethasone Daily Dose (mg/m^2) Over Time | All Treated Pop, Evaluable Pop | 16.2.5.3 |
| 14.2.7.2 | Glucocorticoids Reduction | All Treated Pop, Evaluable Pop | 16.2.6.3 |
| 14.2.7.3 | Patients Proceeding to HSCT | All Treated Pop, Evaluable Pop | 16.2.6.3 |
| 14.2.8.1 | Summary of PedsQL Total Scale Score (Parent Reports) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.8 |
| 14.2.8.2 | Summary of PedsQL Physical Health Summary Score (Parent Reports) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.8 |
| 14.2.8.3 | Summary of PedsQL Psychosocial Health Summary Score (Parent Reports) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.8 |
| 14.2.8.4 | Summary of PedsQL Physical Functioning Scale Score (Parent Reports) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.8 |
| 14.2.8.5 | Summary of PedsQL Emotional Functioning Scale Score (Parent Reports) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.8 |
| 14.2.8.6 | Summary of PedsQL Social Functioning Scale Score (Parent Reports) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.8 |
| 14.2.8.7 | Summary of PedsQL Work/Study Functioning Scale Score (Parent Reports for Child >24 months) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.8 |
| 14.2.8.8 | Summary of PedsQL Physical Symptoms Scale Score (Parent Reports for Infants 1-24 months) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.8 |
| 14.2.8.9 | Summary of PedsQL Cognitive Functioning Scale Score (Parent Reports for Infants 1-24 months) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.8 |
| 14.2.9.1 | Summary of PedsQL Total Scale Score (Child Reports) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.9 |

| Table Number | Table Title / Summary | Population(s) | Supporting listing |
|---|---|---|---|
| 14.2.9.2 | Summary of PedsQL Physical Health Summary Score (Child Reports) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.9 |
| 14.2.9.3 | Summary of PedsQL Psychosocial Health Summary Score (Child Reports) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.9 |
| 14.2.9.4 | Summary of PedsQL Physical Functioning Scale Score (Child Reports) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.9 |
| 14.2.9.5 | Summary of PedsQL Emotional Functioning Scale Score (Child Reports) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.9 |
| 14.2.9.6 | Summary of PedsQL Social Functioning Scale Score (Child Reports) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.9 |
| 14.2.9.7 | Summary of PedsQL Work/Study Functioning Scale Score (Child Reports 5-25 years) and Change from Baseline by Questionnaire Age Group | All Treated Pop, Evaluable Pop | 16.2.6.9 |
| 14.2.10.1 | Summary of BASES Questionnaire (Parent Reports) | All Treated Pop, Evaluable Pop | 16.2.6.10 |
| 14.2.10.2 | Summary of BASES Questionnaire (Nurse Reports) | All Treated Pop, Evaluable Pop | 16.2.6.11 |
| **14.3 Safety Data** | | | |
| 14.3.1.1.1 | Summary of all Adverse Events | All Treated Pop | 16.2.7.1.1 |
| 14.3.1.1.2 | Summary of Adverse Events occurring prior to HSCT conditioning | All Treated Pop | 16.2.7.1.2 |
| 14.3.1.1.3 | Summary of Adverse Events occurring post HSCT conditioning | All Treated Pop | 16.2.7.1.3 |
| 14.3.1.2.1 | Summary of Adverse Events by System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.1 |
| 14.3.1.2.2 | Summary of non-SAEs by System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.1 |
| 14.3.1.3 | Summary of Adverse Events by Maximum Severity, System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.1 |
| 14.3.1.4.1 | Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.1 |
| 14.3.1.4.2 | Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.1 |
| 14.3.1.4.3 | Summary of Treatment-Emergent Adverse Events by Relationship to Study Drug, System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.1 |

| Table Number | Table Title / Summary | Population(s) | Supporting listing |
|---|---|---|---|
| 14.3.1.5.1 | Summary of Treatment-Emergent Adverse Events occurring prior to HSCT conditioning by System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.2 |
| 14.3.1.5.2 | Summary of Treatment-Emergent Adverse Events occurring prior to HSCT conditioning by Maximum Severity, System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.2 |
| 14.3.1.5.3 | Summary of Treatment-Emergent Adverse Events occurring prior to HSCT conditioning by Relationship to Study Drug, System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.2 |
| 14.3.1.6.1 | Summary of Treatment-Emergent Adverse Events occurring post HSCT conditioning by System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.3 |
| 14.3.1.6.2 | Summary of Treatment-Emergent Adverse Events occurring post HSCT conditioning by Maximum Severity, System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.3 |
| 14.3.1.6.3 | Summary of Treatment-Emergent Adverse Events occurring post to HSCT conditioning by Relationship to Study Drug, System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.3 |
| 14.3.2.1 | Summary of Treatment-Emergent Adverse Events Leading to Study Drug Withdrawal by Preferred Term | All Treated Pop | 16.2.7.3 |
| 14.3.2.2 | Summary of Treatment-Emergent Adverse Events Resulting in Death by Preferred Term | All Treated Pop | 16.2.7.4 |
| 14.3.2.3.1 | Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term | All Treated Pop | 16.2.7.2 |
| 14.3.2.3.2 | Summary of Serious Treatment-Emergent Adverse Events occurring prior to HSCT conditioning by System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.2<br>16.2.7.2 |
| 14.3.2.3.3 | Summary of Serious Treatment-Emergent Adverse Events occurring post HSCT conditioning by System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.3<br>16.2.7.2 |
| 14.3.2.4 | Summary of Treatment-Emergent Adverse Events with Infusion-related Reactions by System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.1 |
| 14.3.2.5.1 | Summary of Treatment-Emergent Adverse Events with Infections occurring prior to HSCT conditioning by Severity, System Organ Class and Preferred Term | All Treated Pop | 16.2.7.1.2 |
| 14.3.2.5.2 | Summary of Treatment-Emergent Adverse Events with Infections occurring post to HSCT conditioning by Severity, System Organ Class and Preferred Term | All Treated Pop (only patients with start date of conditioning for HSCT) | 16.2.7.1.3 |
| 14.3.5.1.1 | Shift Table of Clinical Chemistry Results | All Treated Pop | 16.2.8.1 |
| 14.3.5.1.2 | Shift Table of Clinical Chemistry Results by Treatment Type | All Treated Pop | 16.2.8.1 |

| Table Number | Table Title / Summary | Population(s) | Supporting listing |
|---|---|---|---|
| 14.3.5.2.1 | Shift Table of Hematology Results | All Treated Pop | 16.2.8.2 |
| 14.3.5.2.2 | Shift Table of Hematology Results by Treatment Type | All Treated Pop | 16.2.8.2 |
| 14.3.5.3.1 | Shift Table of Coagulation Results | All Treated Pop | 16.2.8.3 |
| 14.3.5.3.2 | Shift Table of Coagulation Results by Treatment Type | All Treated Pop | 16.2.8.3 |
| 14.3.6.1 | Concomitant Medications for HLH Treatment by ATC Level 1 and Standardized Medication Term | All Treated Pop, Evaluable Pop | 16.2.4.8 |
| 14.3.6.2 | Concomitant Medications other than HLH Treatment by ATC Level 1 and Level 2 | All Treated Pop, Evaluable Pop | 16.2.4.9 |
| 14.3.6.3.1 | Summary of Exposure to Emapalumab | All Treated Pop, Evaluable Pop | 16.2.5.1<br>16.2.5.2 |
| 14.3.6.3.2 | Percentage of Emapalumab Dose Changes from the Baseline Dose | All Treated Pop, Evaluable Pop | 16.2.5.1<br>16.2.5.2 |
| 14.3.6.4 | Summary of Serum Concentration of Emapalumab Levels | All Treated Pop | 16.2.9.8.2 |
| 14.3.6.5 | Summary of Pharmacodynamic Parameters | All Treated Pop | 16.2.9.8.3 |
| 14.3.6.6 | Summary of ADA Parameters | All Treated Pop | 16.2.9.8.4 |

## 14.2. Planned Listing Descriptions

The following are planned data and patient data listings for protocol number NI-0501-09.

In general, one listing will be produced per CRF domain. All listings will be sorted by treatment, site, and patient number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each patient. Within a data listing, if an item appears line after line (e.g., repetition of patient number), then only the first occurrence will be displayed.

In data listings, the information for one patient will be kept on one page if at all possible, rather than splitting a patient's information across pages.

## Table 16: Planned Listings

| Listing Number | Listing Title / Summary | Population(s) |
|---|---|---|
| 16.2.1.1 | Study Completion Status and Assignment to Analysis Populations | All Treated Pop |
| 16.2.1.2 | List of Reasons for Screening Failure | Screen Failures |
| 16.2.2.1 | Protocol Deviations | Enrolled Pop Excluding Screen Failure |
| 16.2.3.1 | Analysis Populations | All Treated Pop |
| 16.2.4.1 | Demographic Data | All Treated Pop |
| 16.2.4.2 | Medical History | All Treated Pop |
| 16.2.4.3 | History of HLH Treatments | All Treated Pop |
| 16.2.4.4 | Primary HLH Diagnosis Part 1 | All Treated Pop |
| 16.2.4.5 | Primary HLH Diagnosis Part 2 | All Treated Pop |
| 16.2.4.6 | Prior Medications Other Than HLH Treatments | All Treated Pop |
| 16.2.4.7 | Prior Procedures | All Treated Pop |
| 16.2.4.8 | Concomitant Medications for HLH Treatment | All Treated Pop |
| 16.2.4.9 | Concomitant Medications Other Than HLH Treatment | All Treated Pop |
| 16.2.4.10 | Concomitant Procedures | All Treated Pop |
| 16.2.4.11 | HLH Disease Characteristics at Screening / Baseline - Part 1 | All Treated Pop |
| 16.2.4.12 | HLH Disease Characteristics at Screening / Baseline - Part 2 | All Treated Pop |
| 16.2.5.1 | Study Drug Administration | All Treated Pop |
| 16.2.5.2 | Study Drug Exposure | All Treated Pop |
| 16.2.5.3 | Systemic Glucocorticoids Administration | All Treated Pop |
| 16.2.6.1.1 | Response Criteria and Response Status by Visit – Part 1 | All Treated Pop |
| 16.2.6.1.2 | Response Criteria and Response Status by Visit – Part 2 | All Treated Pop |
| 16.2.6.1.3 | Response Criteria and Response Status by Visit – Part 3 | All Treated Pop |

| Listing Number | Listing Title / Summary | Population(s) |
|---|---|---|
| 16.2.6.1.4 | Response Criteria and Response Status by Visit – Part 4 | All Treated Pop |
| 16.2.6.2 | Time-to-Event Efficacy Endpoints | All Treated Pop |
| 16.2.6.3 | Overall Response, Glucocorticoids Reduction, and Ability to Proceed to HSCT | All Treated Pop |
| 16.2.6.4 | Investigator Assessment of Clinical Response | All Treated Pop |
| 16.2.6.5 | HSCT | All Treated Pop |
| 16.2.6.6 | Post-HSCT Outcome | All Treated Pop |
| 16.2.6.7 | Survival Assessment | All Treated Pop |
| 16.2.6.8 | PedsQL Parent Reports | All Treated Pop |
| 16.2.6.9 | PedsQL Child Reports | All Treated Pop |
| 16.2.6.10 | BASES Parent Reports | All Treated Pop |
| 16.2.6.11 | BASES Nurse Reports | All Treated Pop |
| 16.2.7.1.1 | Adverse Events | All Treated Pop |
| 16.2.7.1.2 | Adverse Events occurring prior to HSCT conditioning | All Treated Pop |
| 16.2.7.1.3 | Adverse Events occurring post HSCT conditioning | All Treated Pop |
| 16.2.7.2 | Serious Adverse Events | All Treated Pop |
| 16.2.7.3 | Adverse Events Leading to Withdrawal of Study Drug | All Treated Pop |
| 16.2.7.4 | Deaths | All Treated Pop |
| 16.2.7.5 | Tuberculosis | All Treated Pop |
| 16.2.7.6 | Adenovirus, Epstein-Barr Virus, Cytomegalovirus | All Treated Pop |
| 16.2.7.7 | Other Specific Infections | All Treated Pop |
| 16.2.8.1 | Clinical Chemistry Results | All Treated Pop |
| 16.2.8.2 | Hematology Results | All Treated Pop |
| 16.2.8.3 | Coagulation Results | All Treated Pop |

| Listing Number | Listing Title / Summary | Population(s) |
|---|---|---|
| 16.2.8.4 | Urinalysis Results | All Treated Pop |
| 16.2.8.5 | Pregnancy Test Results | All Treated Pop |
| 16.2.9.1 | Vital Signs | All Treated Pop |
| 16.2.9.2 | ECG Results | All Treated Pop |
| 16.2.9.3 | Physical Examination Results | All Treated Pop |
| 16.2.9.4 | Neurological Examination Results | All Treated Pop |
| 16.2.9.5 | Hospitalization | All Treated Pop |
| 16.2.9.6 | Abdominal Ultrasound | All Treated Pop |
| 16.2.9.7.1 | Chest Examinations | All Treated Pop |
| 16.2.9.7.2 | Brain and Cranial Examinations | All Treated Pop |
| 16.2.9.8.1 | CSF Analysis Results | All Treated Pop |
| 16.2.9.8.2 | Serum Concentration of Emapalumab | All Treated Pop |
| 16.2.9.8.3 | Pharmacodynamic Measurements | All Treated Pop |
| 16.2.9.8.4 | ADA Findings | All Treated Pop |
| 16.2.9.9 | Transfusion | All Treated Pop |
| 16.2.9.10 | List of Patients Who Were Affected by COVID-19 | All Treated Pop |

## 14.3. Planned Figure Descriptions

The following are planned summary figures for protocol number NI-0501-09. The figure numbers and page numbers are placeholders only and will be determined when the figures are produced.

## Table 17: Planned Figures

| Figure Number | Figure Title/Summary | Population |
|---|---|---|
| 14.4.1.1 | Kaplan-Meier Graph of Overall Survival | All Treated Pop |
| 14.4.1.2 | Kaplan-Meier Graph of Survival to HSCT | All Treated Pop |
| 14.4.1.3 | Kaplan-Meier Graph of Survival post HSCT | All Treated Pop |
| 14.4.2 | Kaplan-Meier Graph of Event-free Survival | All Treated Pop |
| 14.4.3 | Cumulative Incidence Graph of Time to Response | All Treated Pop |
| 14.4.4 | Kaplan-Meier Graph of Duration of Response | All Treated Pop |
| 14.4.5.1 | Box and Whisker Plots of Clinical Biochemistry Results | All Treated Pop |
| 14.4.5.2 | Box and Whisker Plots of Hematology Results | All Treated Pop |
| 14.4.5.3 | Box and Whisker Plots of Coagulation Results | All Treated Pop |

# 15. Tables, Listings, and Listing Shells

## 15.1. Standard Layout for all Tables, Listings, and Figures

The following standard layout will be applied to all Tables, Listings, and Figures in support of this study. Note that programming notes may be added if appropriate after each TLF shell.

**Figure 1: Standardized Layout**

Sobi AG
Protocol: NI-0501-09

Page xx of xx
Version xxx

Table, Listing, Figure xx.x.x
<Title of Table Listing or Figure>
<Study Population and if applicable subgroup Description>

---

Body of Table, Listing or Figure

---

Abbreviations: XXXXX
Note: XXXXX
Source: XXXXX

Footnote: Program path and name
Footnote: Executed on DDMMMYYY at HH:MM on data from DDMMMYYYY

## 15.2. Planned TFL Shells

Table and listing shells are provided as a separate document. Descriptions are provided for figures.

# 16. APPENDICES

## 16.1. Calculation of Dexamethasone daily dose

Dexamethasone daily dose will be calculated based on the recorded dose frequency as follows:

**Table 18: Dexamethasone Daily Dose**

| Dose frequency | Total daily dose = CMDOSE*factor |
|---|---|
| QD (once a day) | CMDOSE |
| BID (twice a day) | CMDOSE*2 |
| TID (three times a day) | CMDOSE*3 |
| QID (four times a day) | CMDOSE*4 |
| PRN (as needed) | 0 per day (not included) |
| QHS (at bedtime) | CMDOSE*1 |
| ONCE (once for the reporting period) | CMDOSE/(end date – start date + 1) per day |
| WEEKLY | CMDOSE/7 per day |
| OTHER – Q6HR/Q6HRS | CMDOSE*4 |
| OTHER – Q8HR/Q8HRS | CMDOSE*3 |
| OTHER – EVERY OTHER DAY | CMDOSE/2 |
| OTHER – DAILY CUMULATIVE DOSE | CMDOSE |

## 16.2. Concomitant Medications for HSCT Conditioning

**Table 19: Concomitant HSCT Conditioning Medication Preferred Terms**

| ATC Level 4 | Preferred Code | Preferred Text |
|---|---|---|
| L01AA | 00021101001 | CYCLOPHOSPHAMIDE |
| | 00006401001 | MELPHALAN |
| L01AB | 00036801001 | BUSULFAN |
| | 00418901001 | TREOSULFAN |
| L01AC | 00053501001 | THIOTEPA |
| L01BB | 02122001001 | CLOFARABINE |
| | 01004601001 | FLUDARABINE |
| | 01004602001 | FLUDARABINE PHOSPHATE |
| L01BC | 00146201001 | CYTARABINE |
| L01BC | 00511901001 | ETOPOSIDE |
| | 00511902001 | ETOPOSIDE PHOSPHATE |
| L01XC | 01402501001 | RITUXIMAB |
| L04AA | 01268601001 | ALEMTUZUMAB |
| | 00575401001 | ANTITHYMOCYTE IMMUNOGLOBULIN |
| | 00575402001 | ANTITHYMOCYTE IMMUNOGLOBULIN (RABBIT) |
| | 02082701001 | ANTILYMPHOCYTE IMMUNOGLOBULIN |

### 16.3. Disease Indicating Central Nervous System (CNS) Involvement / CSF abnormalities by Medical History/AE Preferred Term and Code

**Table 20: Medical History/AE Preferred Terms for 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 |

The overall response criterion ‘No neurological and CSF abnormalities attributed to HLH’ is not fulfilled during the time period in which any of the above listed AEs is present or the assessment on neurological examination CRF is ‘abnormal’ with comment ‘CNS involvement’.

## 16.4. Adverse Events Indicating Organ Failure by MedDRA Preferred Term and Code

**Table 21: AE Preferred Terms for Organ Failure**

| Preferred Term Code | Preferred Term |
|---|---|
| 10007554 | Cardiac failure |
| 10007556 | Cardiac failure acute |
| 10060953 | Ventricular failure |
| 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 |

Progression of other aspects of HLH disease pathology (i.e. worsening of disease, as assessed by absence of AEs indicating organ failure) is fulfilled during the time period in which any of the above listed AEs is present and partial response cannot be adjudicated even if other criteria were fulfilled.