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 DATE:	Final protocol, version 4.0 Global, dated 31 March 2020
NCT Number:	NCT03312751

Summary of changes for protocol versions prior to version 4.0

Final protocol, version 4.0 Global, dated 31 March 2020

Summary of changes for protocol versions prior to version 4.0

No samples for exploratory biomarkers were analyzed.

The following changes to the global protocol V1.0 (dated 19 September 2017) were included by amendments due to requests from the authorities:

The Protocol V1.1 for the EU (dated 12 December 2017) introduced the following changes:

- Inconsistencies between the body of the protocol, synopsis, and schedule of assessments were harmonized to ensure an optimal study conduct.
- The timing of chest X-ray assessment was moved to the Pre-conditioning visit to better reflect standard clinical practice.
- References to the new IB and updated information on ADA were added.

The protocol V2.0 for Germany (dated 24 May 2018) introduced the following changes:

- The study contact list was updated.
- It was added that the primary objective is to gather additional efficacy data on emapalumab in pHLH patients, and efficacy was removed from the first the secondary objective.
- The timeframe for the medical supervision of the infusions was extended from 1 hour to 2 hours, and it was added that active infections, as per patient's clinical presentation, have to be carefully followed over time.
- Viral load positivity, in particular for EBV, CMV and adenovirus, and evolution, was removed from the exceptions for AE recording requirements. Quantitative monitoring (e.g., viral loads, antigenemia, and antigenuria) as relevant according to the patient's clinical presentation, requiring EBV and CMV quantitative PCR at a minimum at screening, was added.
- It was added that any emergent safety concern will be timely assessed and appropriate measure will be taken for the patients, if relevant, by an iDMC.
- Another timepoint for vital signs measurement at 2 hours after the infusion was added.
- The estimate of the blood volume to be collected throughout the study was updated.

The Protocol V1.2 for the United Kingdom (dated 04 September 2018) introduced the following changes:

- In response to comments from the British authority, the protocol section on contraception was expanded.
- As an administrative change, contact details for 2 Sponsor team members were updated.

Protocol V2.0 for North America (dated 18 July 2018) introduced the following changes:

- The study contact list was updated.
- Vital signs assessments were made more frequently during each infusion when a dose increase was applied and during the subsequent infusions in any patient who had

experienced an IRR. The duration of monitoring after infusion was extended to up to 2 hours for all patients. Clinically appropriate windows were applied to these measurements.

- The required duration of TB search testing was added as a footnote to the schedule of assessments.
- In the rationale for dosing schema, simulations were updated to present the "worst-case" scenario in the dose escalation schema, based on the updated, larger dataset accumulated in emapalumab development program that was previously submitted to FDA.
- The considerations that could prompt the Investigator to increase the emapalumab dose were further clarified. A dedicated dose notification form was implemented to capture the specificities and reasoning around the Investigator decision.
- A higher flexibility around the possibility to add other HLH treatments in the first week of treatment, i.e., the use of etoposide (or other drugs), could be considered on SD6 in a patient in whom an HLH worsening or no initial response was observed after the first emapalumab dose increase on SD3. With regard to the addition of other HLH treatments later during the study, definition of "unsatisfactory HLH control" had replaced "unsatisfactory HLH improvement", in order to better reflect the clinical conditions in which the Investigator could decide so. For completeness in the guidance to the Investigator, a reference to section on decision to discontinue treatment was added.
- A window of 1 day was introduced in the circumstances of weekly emapalumab infusions, to decrease study burden for these patients who were expected to be clinically stable and likely outpatients.
- An iDMC was appointed in place of the safety management team to regularly assess the benefit/risk profile of emapalumab treatment.
- The requirement to particularly monitor signs of fluid retention and purpura was lifted, as these pathological elements were not judged to be specifically indicative of HLH. These signs and symptoms were collected in accordance with general principles of AE recording.
- To ensure correct questionnaire completion, the patient name field was removed from the questionnaire and replaced by patient ID.

The country-specific Protocols V3.0 for the USA/Canada and Germany and Protocols V2.0 for the United Kingdom and the EU (version for Italy, Spain, and Switzerland) (all versions dated 31 October 2019) introduced the following changes:

- The Sponsor name was changed from NovImmune to Swedish Orphan Biovitrum AG.

An Administrative Letter (dated 29 January 2019) provided the following clarification for the USA sites:

Following the approval of emapalumab in the USA and its commercialization as Gamifant® for the "treatment of adult and pediatric (newborn and older) patients with primary HLH with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy", the enrollment in USA was limited to those patients who were naïve to conventional HLH therapy.

The global Protocol V4.0 (dated 31 March 2020) introduced the following changes:

- The study contact list was updated.
- Some clinical and laboratory parameters were defined broader in accordance with the observed median age at presentation and standard laboratory practices for routine tests.
- Suggestions from FDA for special circumstances in vital signs monitoring were implemented, blood pressure monitoring was homogenized across the countries using a conservative approach, and clinically appropriate windows were applied to the vital sign monitoring timepoints.
- Further changes were introduced to minimize the study burden on these severely ill and young patients and to simplify study conduct from logistical standpoint while still collecting sufficient data.
- Based on accumulated data, infection search was adapted to be more flexible and considerate of an individual patient while still being rigorous.
- To make the Schedule of Assessments a more complete tool for sites' convenience, a reminder about AE collection timelines was inserted, and an IRR was defined in the footnote. Definition of IRRs that required increased monitoring during subsequent infusions was expanded to include relatedness to ensure meaningful and risk-based monitoring.
- Additional measurements of height/length were introduced to accommodate calculation of creatinine clearance throughout the study duration.
- The approval of emapalumab in the USA was reflected, and updated information on other HLH treatment modalities and latest data accumulated in emapalumab development program were added.
- A provision for retreatment of patients who experience HLH reactivation in the follow-up period was made.
- The 2-year and 3-year survival data collection timepoints were removed from the body of the protocol, with the intention to collect those data in a separate study to provide a comprehensive long-term follow-up across the emapalumab development program. As per the note to file (dated 23 February 2023) to protocol version 4.0, an inconsistency within the protocol was addressed, as removal of collection of survival data at the 2-year and 3-year timepoints had been omitted in the synopsis. It was clarified that survival data collection would only be performed at 1 year after either HSCT or the last emapalumab infusion (as applicable).
- A separate section was added to list study committees to improve readability and easier search for this information.
- Clarifications on testing methods used for diagnosis of pHLH and assessment of eligibility criteria were made to reflect current global practices: NK-cell degranulation test was emerged as a more readily available alternative to NK-cell activity testing, and reference to sites' laboratories units for sCD25 was made.

- The wording on sexual abstinence was expanded based on suggestions from the British authority.
- Simulations were updated to present the “worst-case” scenario in the dose escalation schema, based on the updated, larger dataset accumulated in the emapalumab development program.
- The considerations that could prompt the Investigator to increase the emapalumab dose were further clarified. Also, additional instructions were included for lowering the dose of emapalumab to provide complete guidance to the Investigator.
- Language on the drug accountability was amended to include the reference to IRT.
- It was clarified that biologic drugs were not allowed for indications other than additional HLH treatments.
- Janus kinase inhibitors were added to the list of not allowed concomitant therapies due to their mechanism of action, possibly interfering with emapalumab efficacy and safety assessment.
- More explicit guidance was provided to the Investigator on introduction of additional HLH treatments in the beginning of the study. Also, “unsatisfactory HLH improvement” was replaced with “unsatisfactory HLH control”, a definition that better reflects the clinical conditions in which the Investigator could require additional HLH treatments.
- A window of 1 day was added to allow for more flexible scheduling of emapalumab infusions in the circumstances of weekly administration.
- The screening process was further detailed in the protocol. It was clarified that standard of care procedures performed before consent were accepted for screening.
  Two documents were made available and appended to the protocol in order to facilitate expeditious assessment of the patients (eligibility review form and pre-screening checklist).
- Blood sampling assessment was expanded in accordance with a German authority request.
- It was explicitly stated that race, ethnicity, and country of origin were only to be collected if allowed per local regulations.
- The safety monitoring section language was amended for clarity and to avoid any ambiguity.
- Specific references to signs of fluid retention and purpura were removed (since these data were already collected in physical examination).
- The risks and benefits considerations were updated with the latest available information, and the current IB version was referenced. References to the development risk management plan are removed.
- A minor rewording was performed in the stopping rules section to clarify the role of Sponsor in the process.
- A maximum number of dropouts was specified considering the ongoing pandemic.

- Regarding the disclosure of protocol and study results and publication policy, references to the Coordinating Investigator were removed. No Coordinating Investigator was appointed on the study-wide level.
- A serious GCP breach definition was provided for clarity, and the terminology was updated from violation to deviation.
- The PedsQL questionnaires were added to Appendix A.

An Addendum, V4.0 – V1.0 for Sweden, dated 26 August 2020, was generated to introduce measures to ensure patient safety and counteract potential study conduct disruption during a COVID-19 outbreak.

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Clinical Study Protocol

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

Study Number:	NI-0501-09
Protocol Number:	NI-0501-09
Version:	4.0 Global
Date:	31 March 2020
P-IND Number:	111015
EudraCT	2017-003114-10
Sponsor:	Swedish Orphan Biovitrum AG Corporate address: 12 Chemin des Aulx 1228 Plan-les-Ouates Switzerland Address for all study-related correspondence: 10 Messeplatz 4058 Basel Switzerland
Clinical Scientist	[redacted]

INVESTIGATOR AGREEMENT

Protocol Number: NI-0501-09

Protocol Date and Version: 31 March 2020 – Version 4.0 Global

Study Drug: Emapalumab

Study 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.

Investigator Endorsement:

I, the undersigned, am responsible for the conduct of this study at this site and agree to conduct the study according to the protocol and any approved protocol amendments, ICH GCP and all applicable regulatory authority requirements.

I will not deviate from the protocol without prior permission from Swedish Orphan Biovitrum AG and prior review and written approval from the Institutional Review Board/Independent Ethics Committee, and where applicable, from Competent Health Authorities, except where necessary to prevent any immediate danger to a patient.

I have read and understand fully the Investigator Brochure for emapalumab and I am familiar with the investigational product and its use according to this protocol.

_____ _____

Site Investigator's Signature Date

_____

Site Investigator's Name

CONTACT LIST

Study Location:	Multicenter
Sponsor:	Swedish Orphan Biovitrum AG Corporate address: 12 Chemin des Aulx 1228 Plan les Ouates Switzerland Phone: +41 22 839 71 41 Fax: +41 22 839 71 42 Address for all study-related correspondence: 10 Messeplatz 4058 Basel Switzerland
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Clinical Scientist:	[redacted] Phone: [redacted] Mobile phone: [redacted] Email: [redacted]
Drug Safety Physician:	[redacted] Phone: [redacted] Mobile phone: [redacted] Email: [redacted]
Clinical Operations Manager:	[redacted] Phone : [redacted] Mobile phone: [redacted] Email: [redacted]
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NI-0501-09 SYNOPSIS

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
Sponsor:	Swedish Orphan Biovitrum AG, Switzerland
Study Type and Design:	Study NI-0501-09 is an open-label, single arm, multicenter, interventional study performed both in North America and in Europe. The study is open to enrolment to pediatric patients with confirmed or suspected primary HLH (pHLH) who are either treatment-naïve, or failed conventional HLH therapy or showed intolerance to it. The study is divided into three parts: screening, treatment period, and follow-up. Patients will be in the treating unit the day before the first administration of emapalumab (Study Day minus one, SD-1).
Study Objectives:	- To gather additional safety and efficacy data on emapalumab in 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 pharmacokinetics (PK) profile of emapalumab in pHLH patients - To further evaluate the pharmacodynamic (PD) effects (levels of circulating total Interferon Gamma (IFNγ) and biomarkers of its neutralization, namely CXCL9 and CXCL10) - To assess the profile of other relevant HLH biomarkers, e.g., sCD25 and other exploratory biomarkers - To monitor for potential occurrence of anti-drug antibodies (ADAs).
Study Population:	Male and female pHLH patients, from birth up to and including 18 years at diagnosis of HLH. Patients can be naïve to HLH treatment or may have received conventional HLH therapy without having obtained a satisfactory response according to the treating physician, or having shown signs of intolerance to previous HLH therapy.
Inclusion Criteria:	1. Of note, the enrolment of patients will continue until emapalumab is commercially available for a given indication, or until sample size is reached, whichever comes first; thus, US enrolment will be limited to treatment-naïve patients.Male and female pHLH

patients, from birth up to and including 18 years at diagnosis of HLH.

2. A molecular diagnosis or familial history consistent with pHLH or fulfilment of HLH-2004 diagnostic criteria, i.e., five of the eight criteria below:
    - Fever
    - Splenomegaly
    - Cytopenias affecting 2 of 3 lineages in the peripheral blood (hemoglobin <90 g/L; platelets <100 x 10^9/L; neutrophils <1 x 10^9/L)
    - Hypertriglyceridemia (fasting triglycerides ≥3 mmol/L or ≥265 mg/dL) and/or hypofibrinogenemia (≤1.5 g/L)
    - Hemophagocytosis in bone marrow, spleen or lymph nodes, with no evidence of malignancy
    - Low or absent natural killer (NK)-cell activity
    - Ferritin ≥500 µg/L
    - Soluble CD25 (sCD25, i.e., soluble IL-2 receptor) ≥2400 U/mL
3. Presence of active HLH disease as assessed by the treating physician.
4. Patients having already received conventional HLH therapy must fulfil one of the following criteria as assessed by the treating physician:
    - Having not responded
    - Having not achieved a satisfactory response or worsened
    - Having reactivated
    - Showing intolerance to previous conventional treatment of HLH.

    At the time of enrolment, eligible patients might still be receiving treatment (induction or maintenance) or might have already discontinued it.
5. Informed consent signed by the patient (as required by local law), or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as applicable.
6. Having received guidance on contraception for both male and female patients sexually active and having reached puberty.

    Females of child-bearing potential require use of highly effective contraceptive measures (failure rate of less than 1% per year) from Screening until 6 months after receiving last dose of the study drug.

    Highly effective contraceptive measures include:

    - Sexual abstinence
    - Hormonal contraceptives: combination or progesterone only
    - Intrauterine methods: intrauterine devices or systems

	○ Bilateral tubal occlusion ○ Vasectomised partner. Males with partner(s) of child-bearing potential must agree to take appropriate precautions (such as sexual abstinence, barrier contraception, vasectomy) to avoid fathering a child from Screening until 6 months after receiving last dose of study drug.
Exclusion Criteria:	1. Diagnosis of secondary HLH consequent to a proven rheumatic, metabolic or neoplastic disease. 2. Active mycobacteria, *Histoplasma capsulatum, Shigella, Salmonella, Campylobacter* or *Leishmania* infections. 3. Evidence of latent tuberculosis. 4. Presence of malignancy. 5. Patients who have another concomitant disease or malformation severely affecting cardiovascular, pulmonary, central nervous system (CNS), liver, or renal function that in the opinion of the Investigator may significantly affect the likelihood to respond to treatment and/or the assessment of emapalumab safety and/or efficacy. 6. History of hypersensitivity or allergy to any component of the study regimen (e.g., polysorbate). 7. Receipt of a bacille Calmette-Guerin (BCG) vaccine within 12 weeks prior to Screening. 8. Receipt of a live or attenuated live (other than BCG) vaccine within 6 weeks prior to Screening. 9. Pregnant or lactating female patients.
Study Drug:	Emapalumab (previously referred to as NI-0501) is a fully human high affinity anti-IFNγ monoclonal antibody that binds to and neutralizes human IFNγ.
Dosing Regimen & Frequency of Administration:	Emapalumab will be administered by 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 Study Day 3 (SD3). 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 (see parameters to be satisfied for dose increase in Section 5.3). 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 (as per Section 5.3). Upon achievement of Complete Response (i.e., normalization of all clinical and laboratory HLH parameters), the dose of emapalumab should 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. Decrease of emapalumab dose will occur in a stepwise fashion (e.g. if patient was on 6 mg/kg, emapalumab will be administered in 3 mg/kg for at least one infusion before achieving 1 mg/kg). 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 described in Section 5.3. Upon regaining 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.
Treatment Duration:	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 condition and donor availability allow the performance of HSCT. No wash-out period is required between the last administration of emapalumab and the start of conditioning. 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 (in case HSCT is not performed). This will represent the last visit in the study. A patient who experiences HLH reactivation during the follow-up period, may be re-treated with emapalumab upon discussion with Sponsor. Re-treated patients will follow the same schedule of assessments as applicable during initial treatment (i.e., starting from Visit 1), and will enter the follow-up period after completion of re-treatment. Attempts to gather additional information on survival only will be made at 2 and 3 years after either HSCT or last emapalumab infusion (as applicable) to extend the assessment of long-term survival.
Background Therapy & Concomitant Medication:	Emapalumab will be administered initially on a background of dexamethasone. Patients are required to receive dexamethasone from not later than SD-1. In treatment-naïve patients, an initial 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 at study entry 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. Prophylaxis for *Herpes Zoster* virus infection has to be in place from the day before initiation of emapalumab treatment until serum levels of emapalumab are no longer detectable. Patients will receive any required prophylactic antimicrobial treatments according to local recommendations for the management of pHLH. Cyclosporin A (CsA) can be continued if already being administered to the patient prior to Screening. CsA can be withdrawn at any time, upon judgment of the Investigator. CsA is not to be introduced (or re-introduced) during the course of the study once emapalumab administration has started. If the patient is receiving intrathecal (IT) therapy (e.g., methotrexate and glucocorticoids) at the time of emapalumab treatment initiation, this therapy will be continued until clinically indicated. The introduction of IT therapy during emapalumab treatment is allowed should CNS signs and symptoms occur. IV immunoglobulins are only allowed as replacement treatment. Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, IV parenteral nutrition, inotropic support, antibiotics, anti-fungal and anti-viral treatment, hemofiltration or hemodialysis, as well as general supportive care are allowed. Vaccination with a live or attenuated (including BCG) vaccine must be avoided until serum levels of emapalumab are no longer detectable. The administration of additional HLH treatments will be allowed in a patient in whom an HLH worsening or no initial response has been observed after an increase of emapalumab dose to 6 mg/kg on SD3, as well as later during the course of emapalumab treatment in case of unsatisfactory HLH control, provided that emapalumab has been administered at a dose of 6 mg/kg (or 10 mg/kg, if the Investigator decided to do so) for at least 2 infusions. Unsatisfactory HLH control is defined as follows: - patients who have not achieved or maintained a disease control and general conditions that would allow to proceed to transplant - patients who present a clinically relevant HLH worsening. If an additional HLH treatment is needed, etoposide is the drug of choice, unless there is evidence indicating that an alternative agent should be selected.
Sample Size:	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 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.
Number of Sites:	It is estimated that approximately 13 sites in North America and approximately 15 sites in Europe will participate in this study.
Study Duration and Study End Definition:	After treatment completion or treatment discontinuation (for any reason), patients will continue in the study for a long-term follow-up. End of the study is defined as last patient last visit at 1 year after either HSCT or last emapalumab infusion (as applicable). Survival data obtained at 2 year and 3 year follow-up will be analyzed separately.
Study Surveillance, Safety Reporting and Stopping Rules:	Infusions should be performed under medical supervision and monitored as per local standard of care based on patient's conditions, with a minimum requirement of monitoring blood pressure, body temperature, heart rate and oxygen saturation during the administration of emapalumab, and up to 2 hours after the end of the infusion. Adverse events (AEs) will be recorded from the date of the informed consent form (ICF) signature until serum levels of emapalumab are no longer detectable, except for the following: - Common HLH signs and symptoms (e.g. anemia, neutropenia, thrombocytopenia, hepatosplenomegaly) will not be reported as separate events unless clearly attributed to a cause different from HLH; however, reactivation or worsening of HLH from start of treatment with emapalumab will be reported as AE; - fever will only be reported when not linked to an identified cause (fever of unknown origin). If fever is considered as a sign of a confirmed infection or of HLH worsening or reactivation, it will not be reported as `fever`, but the cause will be reported as an AE; - viral load positivity, in particular for Epstein-Barr virus (EBV), cytomegalovirus (CMV) and adenovirus, and evolution will be collected on a dedicated electronic Case Report Form (eCRF) module. - Active infections will be reported as AEs, indicating whether constituting a primary infection or a reactivation (whenever possible). Pathogen positivity and evolution will be collected in a dedicated eCRF module. - expected effects of conditioning (i.e., pancytopenia during conditioning and until engraftment) will not be reported as AEs Any serious adverse event (SAE) that occurs during the course of the study, and regardless of causality to the study drug, must be notified by

	the Investigator to Swedish Orphan Biovitrum AG, by fax or electronic transmission, within 24 hours of awareness, with the exception of: - elective hospitalizations for surgical procedures that are a result of patient's pre-existing condition(s) which have not worsened during the study; - hospitalizations required for emapalumab infusion and study visits (including a possible hospital stay overnight, if due to logistic convenience); - hospitalizations post-HSCT lasting less than 72 hours and not leading to a new diagnosis, but triggered by a sign which will be reported as an AE. If a new diagnosis is found, it will be reported as an SAE. After elimination of emapalumab only SAEs will be reported. There are no predefined rules for permanent study drug discontinuation based on the current safety profile of the drug. An independent Data Monitoring Committee (iDMC) will be formed to ensure that any emergent safety concern will be timely assessed and appropriate measure taken for the patients, if relevant. Moreover, iDMC will be specifically tasked with regular assessment of extent of benefit and fatal events prior to transplant in treatment-naïve subgroup of patients. A patient, his/her representative or the Investigator can decide at any time to prematurely discontinue treatment or to withdraw a patient from the study. This decision will have no impact on the patient's care. A patient who prematurely discontinues treatment will receive alternative HLH therapy, according to the standard of care at the site.
Efficacy Endpoints:	Primary efficacy endpoint: • 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). Secondary efficacy endpoints: • Overall Survival, including survival to 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 response achieved any time during the study (with censoring time at start of conditioning for patients with no events) • Time to Response at any time during the study • Number of patients able to reduce glucocorticoids by 50% or more of baseline dose during emapalumab treatment

	• Number of patients able to proceed to HSCT, when deemed indicated • QOL indices.
Safety Endpoints:	• Incidence, severity, causality and outcomes of AEs (serious and non-serious). • Evolutions 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.
PK/PD Endpoints:	• Serum concentrations of emapalumab to further evaluate emapalumab PK profile. • Determination of PD parameters (levels of circulating total IFNγ and markers of its neutralization, namely CXCL9 and CXCL10). • Determination of other relevant disease biomarkers, e.g., sCD25 and other exploratory biomarkers. • Measurement of emapalumab concentrations and PD parameters in other matrices, e.g., cerebrospinal fluid (CSF), bronchoalveolar lavage (BAL), if clinically appropriate (exploratory). • Level (if any) of circulating antibodies against emapalumab (ADAs).
Statistical Analysis:	The primary endpoint Overall Response Rate will be evaluated using the exact binomial test at the one-sided 0.025 level. Time to Response, Duration of Response, and Survival time will be presented using Kaplan-Meier curves with medians calculated where available. Associated two-sided 95% confidence intervals will be calculated for the median for each of these endpoints. Additional endpoints based on binary outcomes including number of patients who reduce glucocorticoids by 50% or more and number of patients able to proceed to HSCT will be converted to proportions and associated 95% confidence intervals calculated. Statistical significance in terms of p-values will only be obtained for the primary endpoint. All other endpoints will be viewed as supportive for the primary endpoint and as a consequence no formal hierarchy of endpoints will be declared.

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
BAL	Bronchoalveolar lavage
BCG	Bacillus Calmette-Guérin
BLA	Biologics license application
CBC	Complete blood cell (count)
CDC	Complement dependent cytotoxicity
CFR	Code of Federal Regulation
CMV	Cytomegalovirus
CNS	Central nervous system
CRA	Clinical Research Associate
CRF	Case report form
CRP	C-reactive protein
CRO	Contract Research Organization
CsA	Cyclosporin A
CSF	Cerebrospinal fluid
CT	Computerized tomography
CU	Compassionate use
CYP	Cytochrome P450 enzyme
eCRF	Electronic case report form
EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiogram
EMA	European Medicines Agency
EOT	End of treatment
FDA	Food and Drug Administration
γGT	Gamma glutamyl transferase
G-CSF	Granulocyte-colony-stimulating factor
HGB	Hemoglobin

HLH	Hemophagocytic lymphohistiocytosis
HSCT	Hematopoietic stem cell transplantation
HZ[V]	Herpes zoster [virus]
HZV	Herpes zoster virus
ICF	Informed consent form
ICMJE	International Committee of Medical Journal Editors
iDMC	Independent Data Monitoring Committee
IFNγ	Interferon gamma
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IgG1	Immunoglobulin G1
IGRA	Interferon gamma release assays
IL	Interleukin
IMP	Investigational medicinal product
IND	Investigational New Drug
Inf	Infusion
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRT	Interactive response technology
IT	Intrathecal
IV	Intravenous
IVIG	IV immunoglobulin
JAK	Janus kinase
LCMV	Lymphocytic choriomeningitis virus
LDH	Lactate dehydrogenase
LPLV	Last patient last visit
LUC	Large unstained cells
MAA	Market authorization application
MAS	Macrophage activating syndrome
MRI	Magnetic resonance imaging
NA	North America
NEU	Neutrophils
NaCl	Sodium chloride
NK	Natural killer
ORR	Overall response rate
PCR	Polymerase chain reaction
PD	Pharmacodynamic
pHLH	Primary hemophagocytic lymphohistiocytosis

PLT	Platelets
PK	Pharmacokinetic
PPD	Purified protein derivative
PT	Prothrombin time
QOL	Quality of life
REB	Research ethics boards
ROC	Receiver operating characteristic
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical analysis plan
sCD25	Soluble CD25 (i.e., soluble IL-2 receptor)
SD	Study day
SD(n)	Study day number (e.g., Study day 1 = SD1)
sHLH	Secondary hemophagocytic lymphohistiocytosis
sJIA	Systemic juvenile idiopathic arthritis
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	treatment-emergent adverse event
TG	Triglycerides
TLR9	Toll-like receptor-9
TMF	Trial master file
TP-DI	Therapeutic protein-drug interactions
US	Ultrasound
USA	United States of America
Wk	Week

Table 1: Schedule of Assessments – Screening and Treatment Period

Assessments		Screening Visit (up to 2 Weeks prior to Visit 1)	Week 1		Week 2 →	Week 8 Assessment Visit [b]	EOT (3±1 days after last inf.)	UV [c]
			Visit 1 / SD0	Visit 2 / SD3	Visit 3 onwards	Visit X [a]	Visit X [b]	
Dexamethasone [d]		X						
Anti-viral Prophylaxis [d]		X						
Informed Consent/Assent		X						
Infusion [e]			X	X	X	X		
Patient Information [f]		X						
Clinical Assessments	Vital Signs [g]	X	X (Pre/post-inf.)	X (Pre/post-inf.)	X (Pre/post-inf.)	X (Pre/post-inf.)	X	
	Physical Examination [h]	X	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X	
	QOL - PedsQL™, Pediatric Quality of Life Inventory™	X			X [o]	X	X	
	QOL – BASES [p]						X	
Procedure	ECG	X					X	
Search for Infections	TB [i]	X	X (every 4 weeks)					
	Infection search & monitoring	X (at minimum EBV & CMV viral loads)	n case of suspicion of infection or if there is an active infection at screening/baseline to monitor evolution of viral load and positivity for an identified pathogen					
	Atypical mycobacteria, *Histoplasma capsulatum*, *Shigella*, *Salmonella, Campylobacter*, *Leishmania*	X	In case of suspicion of infection					
Laboratory	CBC [t]	X	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X	
	Coagulation [t]	X	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X	
	Biochemistry [t]	X	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X	
	Pregnancy Test (if applicable)	X					X	
	Urinalysis [j]		X				X	
Imaging	Abdominal Ultrasound [k,t]	X	X (every 2 weeks)			X	X	
	Chest X-ray [u,t]	X	If clinically indicated (e.g. in case of clinical suspicion of pulmonary infection or to follow-up a pre-existing infection at screening/baseline)					
	Brain MRI [l,t]	X [l]	If clinically indicated (to monitor evolution or to confirm occurrence of new CNS symptoms)					
Histopathology	CSF Analysis (if coagulation allows) [m]	X	If clinically indicated (to monitor evolution of CSF abnormalities or in case of occurrence of new CNS symptoms)					

Assessments	Screening Visit (up to 2 Weeks prior to Visit 1)	Week 1		Week 2 →	Week 8 Assessment Visit [b]	EOT (3±1 days after last inf.)	UV [c]
		Visit 1 / SD0	Visit 2 / SD3	Visit 3 onwards	Visit X [a]	Visit X [b]	
Assessment of clinical response		X (every 2 weeks)			X	X	
AE Recording[s]		X	X	X	X	X	X
IMP Handling (Preparation, Dispensing, Accountability)		X	X	X	X		
PK (Emapalumab Concentration)		X (Pre - post inf.)	X (Pre - post inf.)	X (Pre - post inf.) [n]	X (Pre - post inf.)	X	
PD (CXCL9, CXCL10, sCD25), total IFNγ, and other exploratory biomarkers		X (Pre - inf)	X (Pre-inf.)	X (Pre-inf.) [n]	X (Pre-inf.)	X	
Immunogenicity (ADAs)		X		X[q]	X	X	

Abbreviations: ADAs, anti-drug antibodies; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine transaminase, aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CBC, complete blood count; CMV, cytomegalovirus; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; ECG, electrocardiogram; EOT, end of treatment; γGT, gamma glutamyl transferase; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; ICF, informed consent form; IGRA, interferon-gamma release assays; IFNγ, interferon gamma; IMP, investigational medicinal product; inf, infusion; INR, International normalized ratio; IRR, infusion related reaction; LDH, lactate dehydrogenase; LUC, large unstained cells; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PD, pharmacodynamic; PK, pharmacokinetic; PPD, purified protein derivative; PT, prothrombin time; QOL, quality of life; SD, study day; TB, tuberculosis; US, ultrasound

CBC: complete blood count (white blood cells and differential, red blood cells , hemoglobin, hematocrit, platelets, LUC (if performed as routine). **Coagulation:** aPTT (time and/or ratio), PT and/or INR, d-Dimers, fibrinogen. **Biochemistry:** glucose, CRP, ferritin, triglycerides, liver (AST, ALT, γGT, LDH, ALP, bilirubin) and renal function (albumin, creatinine and urea)

[a] **Visit X:** sequential visit number to be attributed

[b] **Week 8 Assessment Visit:** indicates a full patient assessment performed 3 days after the last emapalumab infusion performed during week 8. If emapalumab treatment continues and the visit is performed on the same day of next infusion, all indicated assessments are to be performed pre- or post- infusion, as appropriate. If treatment with emapalumab is completed before Week 8, only an EOT visit will be performed 3 (±1) days after the last infusion. **EOT**: indicates a full patient assessment performed 3 days after last emapalumab infusion

[c] **UV:** assessments to be performed as clinically indicated

[d] **Dexamethasone and anti-viralprophylaxis:** starting from SD-1 (at latest). A prophylaxis for herpes zoster virus infection has to be in place from the day before initiation of emapalumab treatment until serum levels of emapalumab are no longer detectable. Patients will receive any required prophylactic antimicrobial treatment according to local recommendations in pHLH

[e] **Infusion:** to be performed over a period of 1 to 2 hours, twice weekly, not more than 4 days apart, except for the second infusion which must be administered on SD3

[f] **Patient Information:** Includes demographic and medical history, medications at Screening, HLH induction treatment received when applicable, date of HLH diagnosis, molecular diagnosis and relevant functional tests performed for the diagnosis of HLH if available, date and assessment of eligibility criteria

[g] **Vital Signs:** include body temperature, heart rate, blood pressure, oxygen saturation. Temperature is to be measured pre-infusion, at the end of the infusion, 1 hour and 2 hours after the end of each infusion. For the first infusion for each patient (SD0), for the first infusion at an increased dose and/or for any infusions in a patient who has experienced an IRR (defined as signs or symptoms with a temporal relationship to the administration of an infusion and assessed as related, occurring typically soon following the start of the infusion, although symptoms may be delayed for up to 24h; they might be limited (skin reaction), or systemic), blood pressure, heart rate and oxygen saturation are to be collected every 15 minutes during and until the end of the infusion, 1 hour and 2 hours after the end of the infusion. After the first infusion in all other cases, blood pressure, heart rate and oxygen saturation can be collected pre-infusion, at 30 minutes after the beginning of the infusion, at the end of the infusion, 1 hour and 2 hours after the end of the infusion

[h] **Physical Examination** includes as a minimum: weight, height/length (at screening only), spleen and liver size (by abdominal palpation), neurological examination

[i] **TB:** search for tuberculosis mycobacteria: at screening: IGRA/PPD and PCR; after screening by PCR.

[j] **Urinalysis:** glucose, blood, protein and/or albumin, leukocytes, ketones, pH, gravity

[k] **Abdominal ultrasound:** must include longitudinal measure of spleen. At SD0 only if 2 weeks elapsed between the screening visit and SD0.

[l] **Brain MRI:** to be performed in case of CNS disease and/or onset of neurological signs and/or symptoms. Brain CT or cranial ultrasound will be accepted as a replacement of brain MRI.

[m] **CSF analysis:** if lumbar puncture is performed at the site for monitoring/therapy of CNS disease, spare sample (if any) may be analyzed for emapalumab and biomarkers levels

[n] **PK & PD samplings:** from Visit 3 onwards, every other infusion

[o] **QOL, PedsQL**: to be performed post-infusion at Visit 3

[p] **QOL, BASES**: if HSCT is planned

[q] **Immunogenicity (ADAs)**: only at Week 4, to be collected together with a PK sample

[s] **AE recording**: all AEs are collected after signing of ICF up to Study Completion or until serum levels of emapalumab are no longer detectable (whichever occurs first)

[t] **CBC, coagulation, biochemistry and imaging assessments**: If cannot be performed on the day of the scheduled visit, assessments within ±1 day window from scheduled visit date will be accepted.

[u] **Chest X-ray**: Chest CT will be accepted as a replacement for Chest X-ray.

Table 2: Schedule of Assessments - Follow-up Period

Assessments		Follow-up pre-HSCT [a]		Follow-up post-HSCT (or after last emapalumab infusion, as applicable)						UV [f]
		EOT [b]	Pre Conditioning visit [c]	Weekly visits wk 1 – 2 – 3 [d]	D+30 visit [d]	D+60 visit [d]	D+100 visit [d]	6 month visit [d]	1 year visit [d]/ WD [e]	
Clinical Assessments	Vital signs	As indicated in Table 1	X	X	X	X	X	X	X	
	Physical Examination [g]		X	X	X	X	X	X	X	
	Post-HSCT outcome [h]			X	X	X	X	X	X	
	QOL - PedsQL™, Pediatric Quality of Life Inventory™				X		X	X	X	
	QOL – BASES (if HSCT done)				X		X	X	X	
	Survival		X	X	X	X	X	X	X	
Laboratory	CBC		X	X	X	X	X	X	X	
	Coagulation		X	X	X	X	X	X	X	
	Biochemistry		X	X	X	X	X	X	X	
	Urinalysis		X	X	X	X	X	X	X	
Search for infections	TB[m]				X	X	X	X	X	
	Infection search & monitoring		In case of suspicion of infection - according to the patient's clinical presentation							
Imaging	Chest X ray [i]		X [i]	In case of suspicion of infection						
	Abdominal US [j]		X				X		X	
AE recording[n]			X	X	X	X	X	X	X	X
PK/PD (emapalumab concentrations / total IFNγ and other biomarkers)			X	X [k]	X	X [l]	X [l]	X [l]	X [l]	
Immunogenicity (ADAs)							X		X	

Abbreviations: ADAs, anti-drug antibodies; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine transaminase, aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CBC, complete blood count; cm, centimeter; CMV, cytomegalovirus; CRP, C-reactive protein; D, day; EBV, Epstein-Barr virus; EOT, end of treatment; γGT, gamma glutamyl transferase; HSCT, hematopoietic stem cell transplantation; ICF, informed consent form; IFNγ, interferon gamma; INR, International normalized ratio; LDH, lactate dehydrogenase; LUC, large unstained cells; mo, month; PD, pharmacodynamic; PK, pharmacokinetic; PT, prothrombin time; QOL, quality of life; SAE, serious adverse event; TB, tuberculosis; US, ultrasound; UV, unscheduled visit; WD, withdrawal visit; wk, week; yr, year
CBC: white blood cells and differential, red blood cells, hemoglobin, hematocrit, platelets, LUC (as available). **Coagulation:** aPTT (time and/or ratio), PT and/or INR, d-Dimers, fibrinogen. **Biochemistry:** glucose, CRP, ferritin, triglycerides, liver (AST, ALT, γGT, LDH, ALP, bilirubin) and renal function (albumin, creatinine and urea). **Urinalysis:** glucose, blood, protein and/or albumin, leukocytes, ketones, pH, gravity

[a] **Follow-up pre-HSCT:** if HSCT is not planned, patient will directly follow the Schedule of Assessment indicated for Follow-up after last emapalumab infusion

[b] **EOT:** indicated as reference only, refer to Table 1

[c] **Pre Conditioning visit:** may be combined with EOT visit (if not more than 2 days apart). The EOT schedule of assessments has to be applied

[d] **Allowed time-windows:** a ±2 day window is allowed until D+30 visit. A ±1 week window is allowed for D+60 and D+100 visits. A ±4 week window is allowed for 6-mo and 1-yr visits

[e] **WD (Withdrawal visit):** assessments as indicated for last study visit are to be performed in case of premature study discontinuation

[f] **UV (Unscheduled visit):** assessments to be performed as clinically indicated

[g] **Physical examination:** includes as a minimum: spleen and liver size (by abdominal palpation), height/length (at Pre-Conditioning and 6 month visit only) and neurological examination

[h] **Post-HSCT outcome:** applies to patients who undergo HSCT. Includes engraftment rate, donor chimerism achieved (as available), incidence of acute and chronic graft versus host disease

[i] **Chest X-ray**: to be performed at pre-conditioning and then only if clinically indicated. Other imaging modalities (e.g. CT) performed as part of pre-transplant work-up are also acceptable.

[j] **Abdominal ultrasound:** must include longitudinal measure of spleen

[k] **PK/PD:** in patients who receive HSCT, assessment of PK/PD to be also performed at D+3 after HSCT

[l] **PK:** if serum levels of emapalumab were detectable at the previous visit; **PD**: if serum levels of emapalumab were detectable at the previous visit; thereafter only if clinically indicated

[m] **TB**: as clinically indicated, at minimum at D+30, D+60, D+100, 6 month and 1 year/WD visits; until serum levels of emapalumab are no longer detectable

[n] **AE recording**: all AEs are collected after signing of ICF up to Study Completion or until serum levels of emapalumab are no longer detectable (whichever occurs first). After elimination of emapalumab only SAEs will be reported.

1 BACKGROUND INFORMATION

1.1 HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by a severe impairment or absence of cytotoxic function by natural killer (NK) and CD8+ T cells leading to striking activation of the immune system.

HLH comprises primary (genetic/familial) and secondary forms, both clinically characterized by a dysregulation of the immune system leading to a profound hypercytokinemia with deleterious consequences on various tissues and organs (Henter 1991).

Primary HLH (pHLH) is a heterogeneous autosomal recessive disorder. Primary HLH is mostly seen in infancy and early childhood with an estimated prevalence in Europe of 1/50,000 live births (Henter 1991). The disease is invariably fatal with a median survival of less than 2 months after onset of symptoms, if untreated (Janka 1983, Arico 1996).

The impaired cytotoxic function present in HLH leads to hypercytokinemia and hemophagocytosis. These, in turn, cause all of the typical signs and symptoms of HLH (Dhote 2003, Risdall 1979, Risdall 1984):

- Prolonged fever
- Splenomegaly
- Cytopenia
- Hyperferritinemia
- Hypertriglyceridemia
- Hypofibrinogenemia
- Lymphohistiocytic infiltrate, bone marrow hypoplasia, meningeal infiltrate.

Secondary forms of HLH (sHLH) are reported to occur during the course of an infection, of an autoimmune or auto-inflammatory disease, or of a malignancy. While pHLH is a predominantly childhood disease, sHLH is a condition that can also be diagnosed in adults, and increased awareness indicates this may occur more often than recognized in the past.

Secondary HLH presents with the same signs and symptoms of primary forms and can be equally severe. Of note, the presence of certain infections, in particular viral infections such as those due to cytomegalovirus (CMV) or Epstein-Barr virus (EBV), is very often the trigger for the manifestation of primary forms of HLH.

During the last years, evidence has been accumulating in support of the pivotal role of interferon gamma (IFNγ) in the development of both primary (Jordan 2004; Pachlopnik 2009) and secondary (Behrens 2011, Bracaglia 2017, Buatois 2017) forms of HLH.

Perforin knock-out mice represent a relevant model for pHLH since, once infected with Lymphocytic choriomeningitis virus (LCMV), they develop an HLH-like disease dependent on activation and proliferation of CD8+ T cells and increased IFNγ production, with many of the clinical and laboratory characteristic features of the human disease. When the high circulating levels of IFNγ are neutralized with the administration of an anti-IFNγ antibody, not only are the clinical and laboratory abnormalities reverted, but also survival rate is dramatically improved. On the contrary, the ablation of many other cytokines had no impact on survival (Jordan 2004).

Two animal models of sHLH have been investigated to elucidate the pathogenetic role of IFNγ, a murine model that mimics an infection-driven HLH through repeated administrations of CpG oligodeoxynucleotides and activation of toll-like receptor-9 (TLR9) (Strippoli 2012), and a model of interleukin-6 (IL-6) transgenic mice expressing high levels of IL-6 that mimics the condition of patients with systemic juvenile idiopathic arthritis (sJIA), the rheumatic disease most frequently associated with secondary forms of HLH (Prencipe 2017). In both models, when IFNγ was neutralized by the administration of an anti-IFNγ antibody, clinical and laboratory features of the disease were reverted (Strippoli 2012), and survival markedly improved (Prencipe 2017).

Further strengthening the importance of IFNγ in HLH are the high concentrations of circulating IFNγ levels found in pHLH patients (Browne 2012, Remus 2001), with IFNγ levels above the upper limit of normal (17.3 pg/mL) in all patients, and above 1000 pg/mL in 53.5% of cases.

With regard to sHLH, evidence has been recently gathered in two observational studies conducted in patients with secondary forms of HLH: one study in sHLH consequent to infections or of unknown origin (Buatois 2017), and another one in macrophage activating syndrome (MAS) occurring in the context of sJIA (Bracaglia 2017). Levels of IFNγ and IFNγ-induced chemokines (CXCL9 and CXCL10) were markedly higher in the active phase compared to disease remission and significantly correlated significantly with parameters of disease severity, such as neutrophil and platelet counts, ferritin and alanine transaminase (ALT) (Bracaglia 2017, Buatois 2017).

At present, no drug, other than emapalumab (in the USA), is approved for the treatment of pHLH. Most commonly used conventional therapy for the initial treatment of pHLH and severe forms of sHLH is immunochemotherapy. Hematopoietic stem cell transplantation (HSCT) is required to cure pHLH and is indicated in forms (independently of the trigger, if known) of HLH which appear recurrent or progressive despite intensive therapy, or which present central nervous system (CNS) involvement (Jordan 2004). It has been shown that a reduction or abrogation of signs of HLH activity prior to HSCT is an important step in order to improve HSCT outcome and survival.

The most commonly used immunochemotherapy is the so called HLH-94 regimen which includes the use of high doses of dexamethasone and etoposide. The results of prospective study of this regimen, initially published by (Henter 2002) and subsequently by (Trottestam 2011) showed a 5-year cumulative probability of survival of 54%.

In an attempt to improve survival, two alternative treatment regimens have been proposed and assessed: the HLH-2004 one based on addition of cyclosporine A to the HLH-94 treatment protocol (Henter 2007), and the treatment investigated in the 'HIT-HLH' study (Hybrid Immunotherapy for HLH) combining treatment with anti-thymocyte globulin (ATG), etoposide and dexamethasone.

Despite these more aggressive immunochemotherapies, no significant improvement in mortality was obtained with either of the two regimens, as reported at the latest Histiocyte Society meeting in October 2016 (Henter for the HLH-2004 study oral presentation, Jordan 2016 for the HIT-HLH study).

A significant number of patients with HLH either fail to respond to current therapies or relapse prior to HSCT. Furthermore, withdrawal of the drugs commonly used for the treatment of HLH may be required due to their toxicities (e.g., severe infections, myelosuppression, malignant hypertension), thus leaving HLH patients without alternative treatment options and significantly increasing the risk of death. No conventional salvage therapy is available at present, although the use of rescue alemtuzumab has been reported in a retrospective series of 22 patients (Marsh 2013).

With mortality and morbidity remaining high, the scientific community concurs that new therapeutic approaches are needed.

The possibility to treat HLH by means of the targeted neutralization of the most relevant recognized pathogenic player, namely IFNγ, offers an innovative approach towards the management of this disease, aimed at ensuring efficacy with minor toxicity. The USA approval of emapalumab in pHLH in patients with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy confirms the strength of this rationale.

1.2 EMAPALUMAB

1.2.1 Description and Mode of Action

Emapalumab (previously referred to as NI-0501) is a fully human immunoglobulin G1 (IgG1) anti-interferon gamma (IFNγ) monoclonal antibody which binds and neutralizes IFNγ. Emapalumab binds to both free and receptor (IFNγR1)-bound forms of IFNγ.

Since emapalumab is a human IgG1, it retains the characteristics of this immunoglobulin isotype, including the capacity to engage Fcγ receptors and to bind complement.

IFNγ is produced predominantly by NK and NK T cells, as part of the innate immune response, and by CD4 Th1 and CD8 cytotoxic T lymphocyte effector T cells, once antigen-specific immunity develops. IFNγ is one of the most potent and pleiotropic cytokines of the immune system. After binding to its receptor, IFNγ acts to produce a variety of physiological and cellular responses. Numerous studies over the last 20 years have associated IFNγ with the pathogenesis and the maintenance of inflammatory diseases (Billiau 1996, Schoenborn 2007, Zhang 2008).

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1.2.2 Preclinical Data

1.2.2.1 Non-clinical Pharmacology

Emapalumab has shown similar binding affinity and blocking activity for IFNγ from non-human species, including Rhesus and Cynomolgus monkeys, but not from dogs, cats, pigs, rabbits, rats, or mice.

Due to emapalumab capacity to bind free and IFNγR1-bound IFNγ, studies were performed to investigate the potential of emapalumab to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) activities, in the presence of target. A lack of ADCC activity was demonstrated and no induction of CDC activity was observed.

As to safety pharmacology, no abnormalities in electrocardiograms (ECGs), histopathology of organs and behavior of the animals were observed throughout the pre-clinical emapalumab program.

1.2.2.2 Toxicology

Binding and functional data demonstrated Rhesus or Cynomolgus monkeys to be relevant species to evaluate the safety of emapalumab. No off-target toxicity was attributed to the drug when administered to Cynomolgus monkeys in 13 weekly doses of up to 200 mg/kg. *Shigella* and *Campylobacter* infections were observed at all dose levels (10 to 200 mg/kg/week) in animals originally harboring gastrointestinal pathogens (*Shigella, Salmonella, Campylobacter*) prior to emapalumab administration. These findings were assessed to be in line with emapalumab pharmacological effect (i.e., neutralization of IFNγ), given the role played by IFNγ in controlling these pathogens. Subsequently, in a study where cynomolgus

monkeys were free from gastrointestinal pathogens at Screening, weekly administrations of emapalumab for 8 consecutive weeks at doses up to 30 mg/kg were well tolerated with no toxicity or gastrointestinal disturbances observed, and no need for antibiotic prophylaxis.

Results from a human tissue cross-reactivity study, involving a panel of 35 different human tissues, demonstrated that emapalumab did not cross-react with any of the human samples tested.

Embryo-fetal development, fertility and early embryonic development as well as peri- and post-natal development studies were performed in mice. No effects on embryo-fetal development, mating or fertility were observed. No effects on sexual maturation, organ weights, learning and memory, reproductive or immunological functions evaluated in the F1 generation mice were observed.

More details are available in the current Investigator Brochure (version 10.0, dated 24 January 2020).

1.2.3 Clinical Data

A Phase 1 randomized double-blinded placebo-controlled single ascending dose study, Study NI-0501-03, in 20 healthy adult volunteers investigating the safety, tolerability and pharmacokinetic (PK) profiles of single intravenous (IV) administrations of emapalumab took place between September 2011 and January 2013. During this study, 6 subjects received placebo, while 3, 3, 4, and 4 subjects (in total 14 subjects) received emapalumab doses of 0.01, 0.1, 1, and 3 mg/kg, respectively.

The PK analysis of emapalumab revealed the expected profile for an IgG1 with a long half-life (around 22 days), a slow clearance (approximately 0.007 L/h) and a low volume of distribution (< 6 L on average).

All emapalumab infusions were uneventful.

A similar incidence of commonly reported infections (e.g., upper respiratory tract infections) was observed after administration of emapalumab and in subjects who had received placebo.

A Herpes Zoster (HZ) infection was reported in one subject (male, aged 26), 14 days after infusion of 3 mg/kg of emapalumab. This event was assessed as related to the emapalumab infusion and considered as serious (medically significant) in the context of a Phase I study in healthy volunteers. Its intensity was moderate and its course normal under antiviral therapy. The subject recovered with no sequelae.

An increased susceptibility to HZ infections in patients having developed auto-antibodies against IFNγ (Browne 2012) or having received ustekinumab (a monoclonal antibody which decreases IFNγ production by inhibiting the p40 subunit of IL-12) has been described in the literature (Failla 2011).

In conclusion, the infusion of emapalumab was well tolerated and the effects observed during the 8-week monitoring after drug infusion did not reveal any serious or unexpected off-target safety or immunogenicity concerns.

An open-label, single arm, international, multicenter Phase 2/3 study is ongoing to evaluate the efficacy and safety of emapalumab treatment in patients with pHLH (protocol NI-0501-04). The protocol allows for inclusion of patients either treatment-naïve or reactivating after initial response to conventional therapy or not achieving a satisfactory response or showing intolerance to conventional therapy.

Upon completion of study NI-0501-04, patients were invited to enter a long-term safety follow-up (study NI-0501-05) of 1 year after HSCT or after last emapalumab infusion. NI-0501-05 study protocol made provision for continuation of emapalumab treatment if required by the treating physician as a bridge to transplantation.

An interim analysis of the data gathered in both NI-0501-04 and NI-0501-05 studies (cut-off date of 20 July 2017) has been conducted and these data have been the basis of the biologics license application (BLA) and the market authorization application (MAA) submissions.

At the BLA/MAA cut-off date, 34 patients have been treated in Study NI-0501-04. The primary efficacy endpoint of the study, overall response rate (ORR) at End of Treatment (EOT) was met. ORR was 64.7% (95% CI: 44%, 78%) in all patients, and 63% (95% CI: 42%, 81%) in second-line patients.

In both groups, the lower limit of the 95% CI was higher than the pre-defined null hypothesis of 40% (p=0.0031 and p=0.0134, respectively). Response occurred early during treatment and was generally sustained.

During pre-conditioning, the most frequently reported adverse events (AEs) were those related to HLH reactivation, flare or worsening. The most frequently reported AEs in post-conditioning were pyrexia and hypertension.

At the BLA/MAA cut-off date, a total of 34 patients were treated and 10 patients died in studies NI-0501-04/05. None of the deaths were assessed to be related to emapalumab by Investigator, Sponsor and independent data monitoring committee (iDMC).

In line with the risks due to the immune deficiency status in pHLH patients, 19 out of 34 patients (56 %) reported at least 1 infection from start of emapalumab treatment until start of HSCT conditioning. In 11 patients, infections were reported as a serious adverse event (SAE). Only 2 SAEs (both infections) were assessed as possibly related to emapalumab, one disseminated histoplasmosis (leading to treatment discontinuation) and one necrotizing fasciitis (assessed by the Investigator as possibly related based on the temporal relationship). Both events resolved with appropriate antibiotic therapy.

In second-line patients who were intolerant to previous conventional HLH therapies due to their toxicities, the administration of emapalumab did not aggravate these toxicities, while showing, in general, a favorable impact on disease activity.

Likewise, no safety concern related to the concomitant administration of emapalumab with other treatments (e.g., antimicrobial agents, anti-hypertensive drugs) has been reported so far. Of interest, tapering of glucocorticoids had no impact on the safety and tolerability of emapalumab infusions and has shown benefit for patients with steroid-related hypertension and generalized immunosuppression.

Study NI-0501-04 has currently completed enrolment, with a total of 45 patients recruited.

Study NI-0501-06 is a phase 2 study in sJIA patients with MAS/sHLH who have shown an inadequate response to high-dose glucocorticoid treatment. As of 24 August 2019, a total of 8 patients have been treated. In all 6 patients, complete response was achieved. Systemic glucocorticoids were weaned in all patients. Emapalumab infusions were well tolerated and none of the patients discontinued emapalumab prematurely. A CMV reactivation was reported by Investigator as a serious event possibly related to emapalumab, but resolved completely with treatment (De Benedetti F, 2019).

Overall, 6 out of the 8 patients experienced at least 1 treatment-emergent AE (TEAE). No AEs with fatal outcome or leading to study treatment discontinuation were reported.

For more details on the clinical experience, refer to the latest Investigator's Brochure (currently version 10.0, dated 24 January 2020).

Refer to Section 9.4.2 for the current benefit/risk assessment on the use of emapalumab in pHLH patients.

2 OBJECTIVES

- To gather additional safety and efficacy data on emapalumab in 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 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).

3 STUDY DESIGN

3.1 OVERALL DESIGN

Study NI-0501-09 is an open-label, single arm, multicenter, interventional study performed both in North America (NA) and in Europe.

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

The study is divided into three parts: screening, treatment, and follow-up.

Patients will be in the treating unit the day before the first administration of emapalumab (Study Day minus one; SD-1).

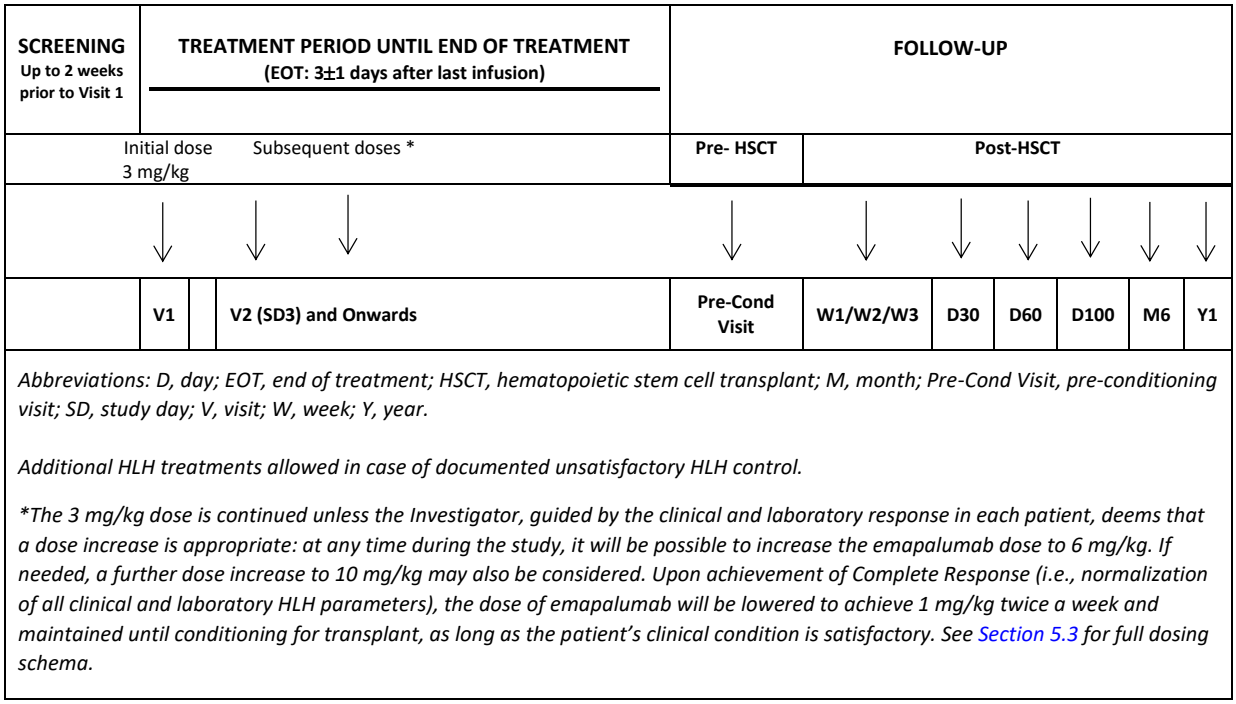
Patients are required to receive dexamethasone from SD-1.

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.

Figure 1: NI-0501-09 Study Design



Abbreviations: D, day; EOT, end of treatment; HSCT, hematopoietic stem cell transplant; M, month; Pre-Cond Visit, pre-conditioning visit; SD, study day; V, visit; W, week; Y, year.

Additional HLH treatments allowed in case of documented unsatisfactory HLH control.

**The 3 mg/kg dose is continued 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. If needed, a further dose increase to 10 mg/kg may also be considered. 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 condition is satisfactory. See Section 5.3 for full dosing schema.*

3.2 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 (ICF).

Samples for infection screening need to be collected for analysis prior to first administration of emapalumab according to the protocol requirements. However, if a patient's medical condition warrants rapid treatment initiation, availability of the results is not required prior to initiation of emapalumab provided that there are no clinical findings suggestive of any of the infections which represent exclusion criteria.

3.3 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 wash-out period is required between the last administration of emapalumab and the start of conditioning.

3.4 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).

If patient experiences HLH reactivation during the follow-up period, patient may be re-treated with emapalumab, upon discussion with Sponsor. Re-treated patient will follow the same schedule of assessments as applicable during initial treatment (i.e., starting from Visit 1), and will enter follow-up period after completion of re-treatment.

If the patient is unable to return to the site for all follow-up visits, every effort should be made to schedule visits until emapalumab is no longer detectable in the blood.

3.5 STUDY END

The end of the study is defined as last patient last visit (LPLV) at 1 year after either HSCT or last emapalumab infusion (as applicable).

In case of an ongoing 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.

3.6 STUDY COMMITTEES

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. Moreover, the iDMC will be specifically tasked with regular assessment of extent of benefit and fatal events prior to transplant in the treatment-naïve subgroup of patients.

iDMC operations will be described in the iDMC charter.

4 TARGET POPULATION

The criteria for study eligibility are provided below. 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 having shown signs of intolerance to HLH therapy. Of note, enrolment of patients who have failed previous conventional HLH therapy will continue until emapalumab is commercially available for a given indication, or until sample size is reached, whichever comes first; thus, US enrolment will be limited to treatment-naïve patients.

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.

4.1 ELIGIBILITY CRITERIA

Patients will be included in the study if they meet all the inclusion criteria and none of the exclusion criteria.

4.1.1 Inclusion Criteria

1. Male and female pHLH patients, from birth up to and including 18 years at diagnosis of HLH.
2. A molecular diagnosis or familial history consistent with pHLH or fulfilment of HLH-2004 diagnostic criteria, i.e., five out of eight of the criteria below:
    - Fever
    - Splenomegaly

- Cytopenias affecting 2 of 3 lineages in the peripheral blood (hemoglobin <90 g/L; platelets <100 x 10^9/L; neutrophils <1 x 10^9/L)
- Hypertriglyceridemia (fasting triglycerides ≥3 mmol/L or ≥265 mg/dL) and/or hypofibrinogenemia (≤1.5 g/L)
- Hemophagocytosis in bone marrow, spleen or lymph nodes, with no evidence of malignancy.
- Low or absent NK-cell activity[i]
- Ferritin ≥500 µg/L
- Soluble CD25 (sCD25; i.e., soluble IL-2 receptor) ≥2400 U/mL[ii]

3. Presence of active HLH disease as assessed by the treating physician.

4. Patients having already received conventional HLH therapy must fulfil one of the following criteria as assessed by the treating physician:
    - Having not responded
    - Having not achieved a satisfactory response or worsened
    - Having reactivated[iii]
    - Showing intolerance to previous conventional treatment of HLH

    At the time of enrolment, eligible patients might still be receiving treatment (induction or maintenance) or might have already discontinued it.

5. Informed consent signed by the patient (as required by local law), or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as applicable.

6. Having received guidance on contraception for both male and female patients sexually active and having reached puberty.

    Females of child-bearing potential require use of highly effective contraceptive measures (failure rate of less than 1% per year) from Screening until 6 months after receiving last dose of the study drug.

    Highly effective contraceptive measures include:

    - Sexual abstinence: refraining from heterosexual intercourse during the entire period defined above. The reliability of sexual abstinence needs to be evaluated in relation to its duration

[i] NK-cell degranulation testing is considered to be acceptable

[ii] Or equivalent as measured by the site's laboratory

[iii] Reactivation is defined as:

- Deterioration of two or more HLH clinical and laboratory criteria (following an initial response) with the following specifications:
    1. numerical laboratory values* must become abnormal and worsen by more than 30% compared to the previous evaluation, on two sequential assessments performed with an interval of minimum 1 day and maximum 1 week
    2. deterioration of clinical criteria must be confirmed by consistent observations of worsening over three consecutive days
- The development of new or recurrent CNS symptoms counts as a single criterion for reactivation.

* *The following laboratory parameters are specifically considered for determination of reactivation: platelets, neutrophils, fibrinogen, ferritin, sCD25 (i.e., soluble IL-2 receptor).*
The assessment of NK function, red blood cells/hemoglobin and triglyceride levels cannot be considered for the determination of reactivation.

and compatibility with the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception)

- Hormonal contraceptives: combination or progesterone only
- Intrauterine methods: intrauterine devices or systems
- Bilateral tubal occlusion
- Vasectomised partner

Males with partner(s) of child-bearing potential must agree to take appropriate precautions (such as sexual abstinence, barrier contraception, vasectomy) to avoid fathering a child from Screening until 6 months after receiving last dose of the study drug.

4.1.2 Exclusion Criteria

1. Diagnosis of secondary HLH consequent to a proven rheumatic, metabolic or neoplastic disease.
2. Active mycobacteria*, Histoplasma capsulatum, Shigella, Salmonella, Campylobacter* or *Leishmania* infections.
3. Evidence of latent tuberculosis.
4. Presence of malignancy.
5. Patients who have another concomitant disease or malformation severely affecting cardiovascular, pulmonary, CNS, liver, or renal function that in the opinion of the Investigator may significantly affect the likelihood to respond to treatment and/or the assessment of emapalumab safety and/or efficacy.
6. History of hypersensitivity or allergy to any component of the study regimen (e.g., polysorbate).
7. Receipt of a Bacillus Calmette-Guérin (BCG) vaccine within 12 weeks prior to Screening.
8. Receipt of a live or attenuated live (other than BCG) vaccine within 6 weeks prior to Screening.
9. Pregnant or lactating female patients.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT

Emapalumab (previously referred to as NI-0501) is a fully human high affinity anti-IFNγ monoclonal antibody that binds to and neutralizes human IFNγ.

Emapalumab is manufactured by a third-party manufacturing facility duly qualified by Swedish Orphan Biovitrum AG and is supplied to study sites in 2 mL and/or 10 mL filled single-use glass vials at a concentration of 5 mg/mL, for dilution prior to administration.

The nominal composition of the emapalumab sterile concentrate for infusion (per mL) is as follows:

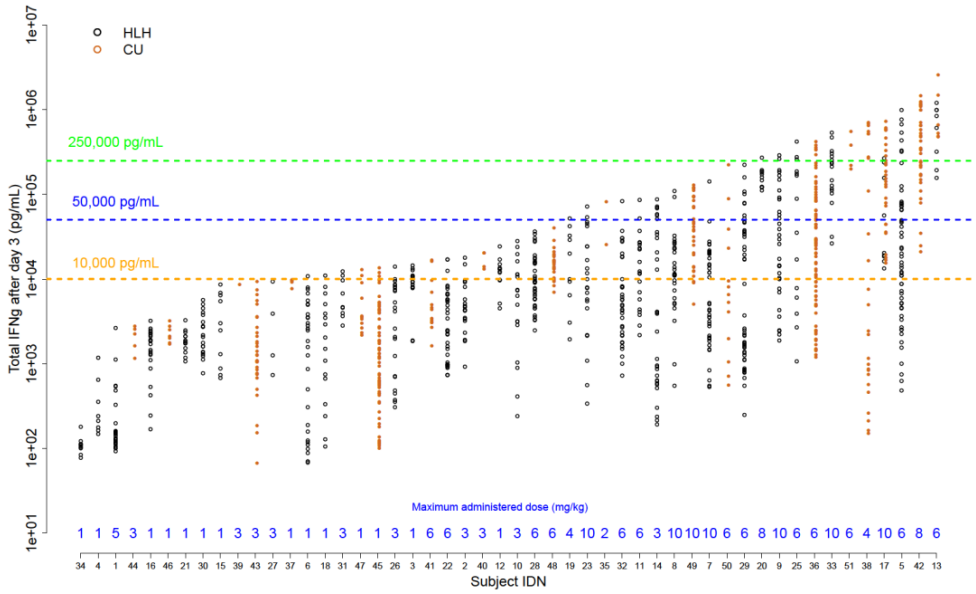
Ingredient	**Quantity (per mL)**
Emapalumab	5 mg
L-Histidine	1.55 mg
L-Histidine monohydrochloride, monohydrate	3.14 mg
Sodium chloride (NaCl)	7.31 mg
Polysorbate 80	0.05 mg
pH	6.0 ± 0.2

The solution contains no antimicrobial preservative, and therefore each vial must be used only once.

5.2 RATIONALE FOR DOSING SCHEMA

The dosing regimen for emapalumab is determined based on patient outcomes and PK/PD data collected in the ongoing NI-0501-04 and NI-0501-05 studies. Preliminary analyses indicate that the administered dose needs to be adapted to the IFNγ production, which varies significantly between subjects but can also significantly change over time within a subject, e.g. in case of infection (Figure 2).

Figure 2: Total IFNγ Concentrations up to the Last Dose or HSCT in HLH Patients Treated with Emapalumab in Studies NI-0501-04 and NI-0501-05 (HLH) and in Compassionate Use (CU) Patients



Results of preliminary PK/PD analyses demonstrate that: 1) the higher the total IFNγ production, the higher the clearance of emapalumab due to target mediated drug disposition and 2) the higher the IFNγ concentration, the higher the required emapalumab concentration to reach neutralization.

In the 34 pHLH patients enrolled in the NI-0501-04 study as of 15 May 2017, emapalumab has been administered at a dose ranging from 1 to 10 mg/kg. Out of these 34 patients, 14 remained at the dose of 1 mg/kg and 20 required a dose increase at any time during the course of treatment, with 12 patients requiring a dose increase by Day 9. These dose adaptations were based on PK observations and on clinical/laboratory parameters (in the initial pilot phase of the study) and on clinical criteria only thereafter. Specifically, in this later phase, in which 8 patients were enrolled, dose increase occurred in 7 patients and only 1 remained at 1 mg/kg. These dose increases did not lead to any safety concerns.

Based on these learnings from the NI-0501-04 study, a starting dose of 3 mg/kg is applied in this study, with a simplified schema for dose escalation up to 10 mg/kg (refer to Section 5.3).

The impact on the PK and PD of the proposed dosing schema is shown by the simulations reported in Figure 3, Figure 4 and Figure 5.

The concentration of emapalumab (graphs on the left) and CXCL9 (graphs on the right) are represented at three different production rates of IFNγ (represented by total IFNγ levels) that exemplify the variability of IFNγ: namely a “relatively low” production of 10,000 pg/mL (orange line), a “medium” production of 50,000 pg/mL (blue line), and a “high” production of 250,000 pg/mL (green line). As reference:

The grey area on the left graph indicates the mean of the individual three highest peak and trough concentrations observed in Studies NI-0501-04 and NI-0501-05, and in compassionate use patients (cut-off date 20 July 2017).

The black line (mean) and grey shadowed area on the right graph indicates CXCL9 levels at week 2 and end of treatment that appear to be associated with the probability of clinical response at end of treatment as indicated by preliminary Receiver Operating Characteristic (ROC) analyses (*data on file*). The right y-axis gives the probability of overall response at the end of treatment as estimated by logistic regression analysis.

The simulation with the dose increase up to 10 mg/kg (Figure 5) shows that patients with a low production of IFNγ (TIFNγ=10,000 pg/mL) reach emapalumab concentrations close to the highest ones already observed in studies NI-0501-04 and NI-0501-05 and in compassionate use patients. However, this condition is unlikely to occur as these patients are expected to respond primarily at the dose of 3 mg/kg. As shown in Figure 2, none of the NI-0501-04 study patients with maximal total IFNγ levels remaining below 10,000 pg/mL required a dose increase up to 10 mg/kg.

Figure 3: Emapalumab and CXCL9 Concentrations at the Initial Dose of 3 mg/kg (Maintained TWICE A WEEK During the Treatment Course)

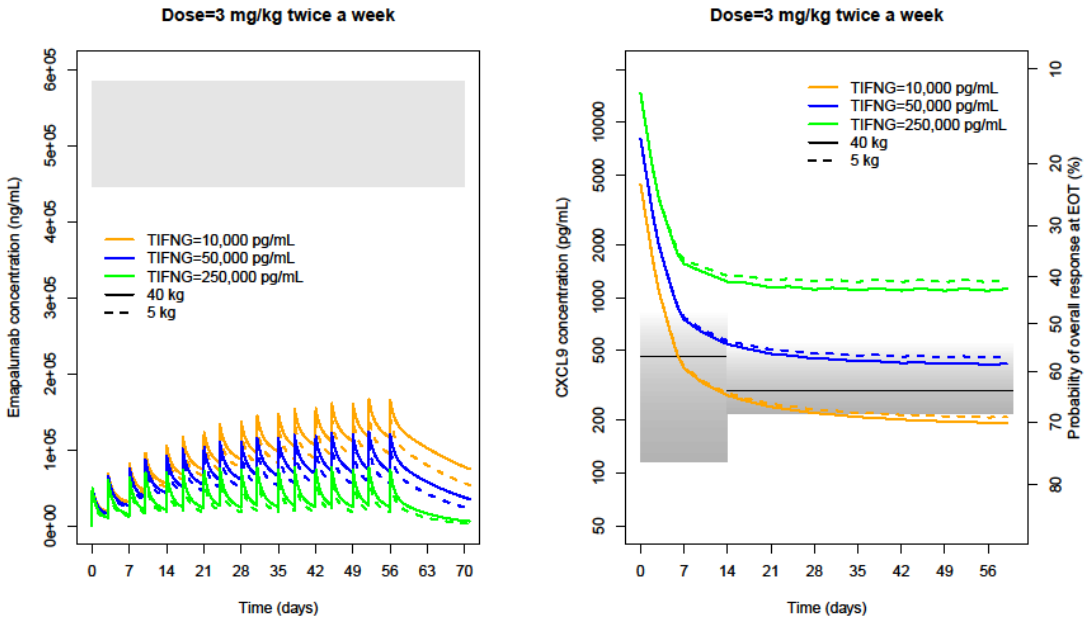


Figure 4: Emapalumab and CXCL9 Concentrations at the Initial Dose of 3 mg/kg, Increased to 6 mg/kg ON DAY 6 and Maintained TWICE A WEEK During the Treatment Course

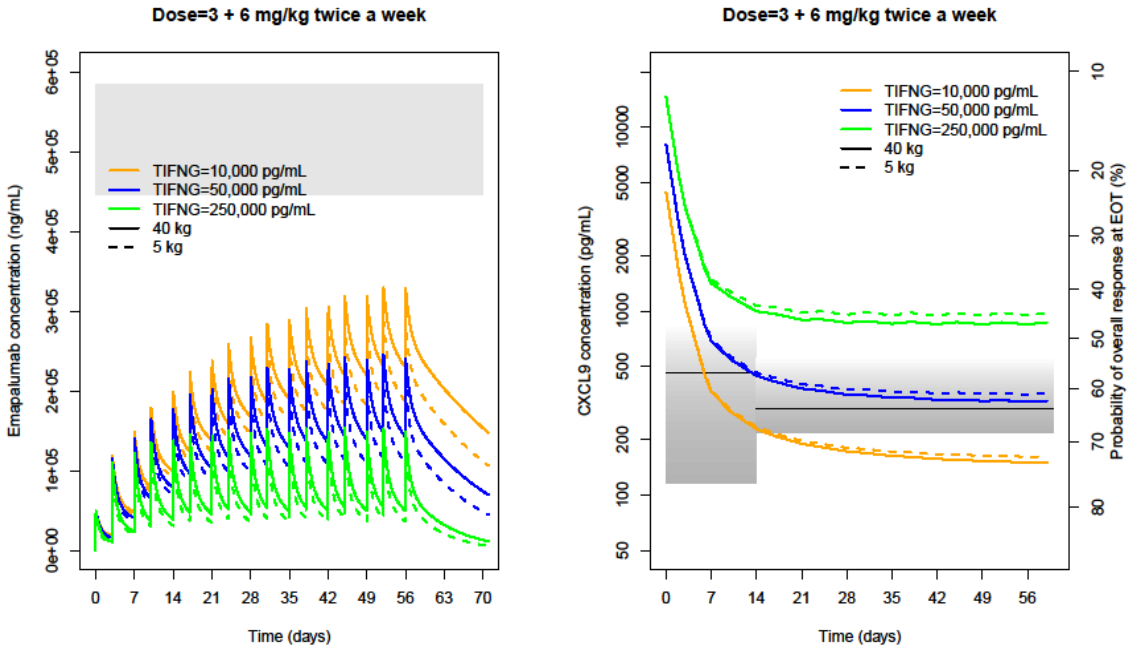
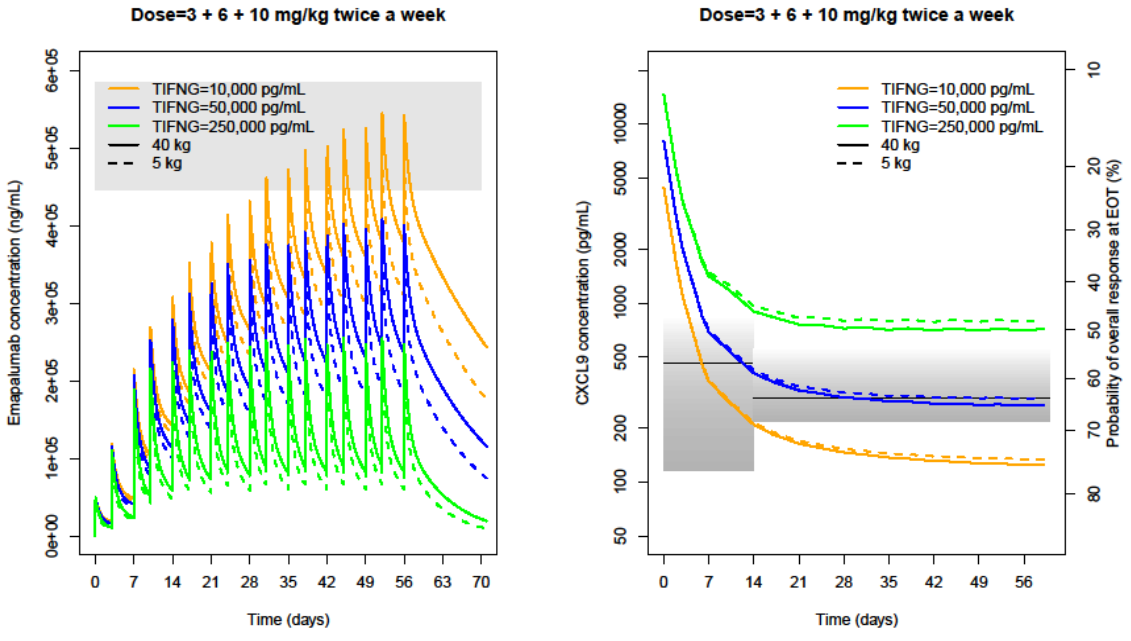


Figure 5: Emapalumab and CXCL9 Concentrations at the Initial Dose of 3 mg/kg, increased to 6 mg/kg on day 3, to 10 mg/kg on day 7 and Maintained TWICE A WEEK During the Treatment Course



5.3 DOSING SCHEMA

Emapalumab will be administered by 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 SD3.

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 emapalumab dose to 6 mg/kg (Table 3). A further dose increase to 10 mg/kg can be considered per Investigator's decision based on the patient's condition and appreciation of some benefit from the administration of emapalumab.

Upon achievement of Complete Response (i.e., normalization of all clinical and laboratory HLH parameters), the dose of emapalumab should be lowered to achieve 1 mg/kg twice a week and maintained until conditioning for transplant, as long as the patient's clinical conditions is satisfactory. Decrease of emapalumab dose will occur in a stepwise fashion (e.g. if patient was on 6 mg/kg, emapalumab will be administered in 3 mg/kg for at least one infusion before achieving 1 mg/kg).

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 described above (Table 3).

The Investigators' assessments for emapalumab dose increase will be documented in the Dose Notification form (Appendix E) to be completed for each infusion and provided to Sponsor in a timely manner.

Upon regaining a Complete Response, the dose of emapalumab should be lowered again to achieve 1 mg/kg twice a week. Should 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.

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 the performance of HSCT.

No wash-out period is required between the last administration of emapalumab and the start of conditioning.

If patient experiences HLH reactivation during the follow-up period, patient may be re-treated with emapalumab, upon discussion with Sponsor. Re-treated patients will follow the same schedule of assessments as applicable during initial treatment (i.e., starting from Visit 1), and will enter the follow-up period after completion of re-treatment.

Table 3: Clinical and Laboratory Criteria to Guide Dose Increase

On Visit / Study Day (SD)	Emapalumab Dose	
On Visit 1/SD0	Starting dose of 3 mg/kg	
On Any Visit, from Visit 2/SD3 onwards	Increase to 6 mg/kg[5]	Upon an overall assessment by the Investigator that improvement in clinical conditions[1] is unsatisfactory and presence of at least 1 of the following: *Fever* → persistence or reoccurrence *Platelet counts* → lack of normalization[2] or Worsening *ANC* → lack of normalization[3] or Worsening *Ferritin* → less than 30% decrease or Worsening *Splenomegaly* → worsening (at clinical exam or US examination) *Coagulopathy* (either D-dimer or fibrinogen) → lack of normalization[4] or Worsening
On Any Visit, from Visit 3 onwards	Increase up to 10 mg/kg (if deemed necessary)	Upon assessment by the Investigator that a further increase of emapalumab dose may provide a better benefit/risk ratio than administration of alternative HLH treatments (see Section 6.3.5) and presence of 1 of the criteria listed above

Abbreviations: ALC = absolute lymphocyte count; ANC = absolute neutrophil count; SD = study day; US = ultrasound

Note: the table is based on an initial dose of emapalumab of 3 mg/kg.

[1] Features to be assessed may include patient's overall performance and well-being, as well as evolution of clinical and laboratory signs that significantly contribute to or indicate overall severity of the patient's disease, e.g. signs of CNS involvement or liver impairment, dynamics of ALC, sIL2Ra

[2] Normalization of platelet counts is defined as values >100 x 10^3/mcl, as per HLH diagnostic criteria

[3] Normalization of ANC is defined as values >1000 count/mcl, as per HLH diagnostic criteria

[4] Normalization of D-dimer is defined as values <1.0 μg/mL; normalization of fibrinogen is defined as values >150 mg/dL

[5] The dose of 6 mg/kg may be maintained as long as deemed appropriate by the Investigator to obtain a satisfactory improvement.

5.4 INVESTIGATIONAL MEDICINAL PRODUCT HANDLING

5.4.1 Packaging and Labelling

Emapalumab will be supplied to study sites in glass vials containing either 2 or 10 mL solution at a concentration of 5 mg/mL. Labelling and packaging will be prepared to meet local regulatory requirements.

5.4.2 Investigational Medicinal Product Supply

Emapalumab will be supplied to the study sites as open-label supplies.

5.4.3 Investigational Medicinal Product Receipt and Storage

Emapalumab vials will be transported with temperature deviation alarms (TempTale 4 or equivalent device), to confirm consistent temperatures during transit. When the study drug is received at the site, the Investigator or Pharmacist will check for accurate delivery and absence of temperature deviation alarms.

Emapalumab should be stored between 2 - 8°C (36 - 46°F). All vials must be stored in a secure locked location in a temperature-controlled refrigerator or cold room. Any deviations from the recommended storage conditions should be immediately reported to the Sponsor and responsible study monitor or contract research organization (CRO). Affected vials should not be used and should be quarantined until the Sponsor has authorized their use, return or destruction.

Documentation of the storage conditions of the study drug must be maintained for the duration of the time the study drug is stored at the site, until the time it is used, disposed of, or returned to Swedish Orphan Biovitrum AG or designee.

Regular inspections of the emapalumab vials are required, as detailed in the Investigational medicinal product (IMP) manual's directions for the Preparation and Administration of Individual Doses of Study Drug Emapalumab.

5.4.4 Investigational Medicinal Product Preparation, Administration, Accountability, and Destruction

5.4.4.1 Preparation

The study drug must be prepared only by a Pharmacist or other appropriately qualified staff member, specifically authorized by the Investigator/Pharmacist and appropriately licensed to perform the task.

The specific dose to be administered for an individual infusion is determined as detailed in Section 5.3. As emapalumab is dosed in mg/kg, the weight of the patient must be taken within 24 hours before preparation of the study drug for administration.

Full instructions for the preparation, including dilution steps, and method for administration of emapalumab are available in the IMP manual's directions for the Preparation and Administration of Individual Doses of Study Drug Emapalumab.

5.4.4.2 Administration

The patient should receive the designated volume of the infusion material through an infusion pump over 1 to 2 hours depending on the volume to infuse. A 0.2 µm filter must be added to all infusion lines.

It is recommended that an IV central line remain in place to ensure venous access during the treatment period. This will improve patient's comfort and ensure a reliable drug administration, in particular in infants and toddlers, or in case of foreseen difficulties with peripheral venous access. However, peripheral infusions have been successfully performed in some patients.

Since no data are available on the compatibility of emapalumab with other IV substances or additives, other medications/substances should not be added to the infusion material or infused simultaneously

through the same IV line. If the same IV line is used for subsequent infusions of other drugs, the line should be flushed appropriately with saline before and after infusion of emapalumab.

The infusion of emapalumab will be performed under the direct supervision of the Investigator (or delegate), preferably in the morning at the same time for each infusion. Details of the infusion must be recorded in the patient's Medical Notes or other source documents and have to include:

- Dose prescribed (in mg/kg)
- Date of administration
- If flushing was performed
- Start time & End time
- Rate of administration
- Total volume infused (ml)
- Total dose infused (mg)
- In case infusion was interrupted
    - Reason for interruption
    - What was the stop time of the infusion
    - What was the new start time of the infusion
    - What was the new rate of administration
- Any untoward signs and/or symptoms, event or illness experienced by the patient during the infusion
- Any other event(s) judged relevant by the site personnel.

5.4.4.3 Accountability

When the study drug is received at the site, the Investigator or Pharmacist (or appropriate designee) should acknowledge its receipt by signing (or initialing) and dating the documentation, and updating the Interactive response technology (IRT) system. Documentation should be returned to Swedish Orphan Biovitrum AG (or its designee) and a copy retained in the Investigator's file.

The dispensing of the study drug shall be carefully recorded on Drug Accountability Forms and an accurate accounting must be available for verification by the Monitor at monitoring visits.

The used (or unused) infusion material should be sent back to the Pharmacist at the end of the infusion, if possible, for later inventory.

Drug accountability records shall include:

- Confirmation of the study drug's delivery to the study site.
- The inventory at the study site.
- The use of study drug by each patient.
- The return to the Sponsor or alternative disposition of unused products.

The records should include dates, quantities, expiration dates, batch number, and if applicable patient number.

Unused study drug vials must not be used for any purpose other than the present study without Sponsor's approval. Study drug vials that have been allocated to a patient and remain unused must not be re-allocated to a different patient without Sponsor`s approval.

Unused study drug vials must not be discarded prior to verification by the Monitor.

5.4.4.4 Destruction, Return, and Disposal

Periodically during the study and at the conclusion of participation of the study by the site, the clinical research associate (CRA) will monitor and perform drug accountability via the IRT system, before making arrangements for study drug return or authorizing destruction by the study site.

6 PATIENT BACKGROUND TREATMENT AND CARE

6.1 BACKGROUND THERAPY WITH DEXAMETHASONE

Initially, emapalumab will be administered on a background of dexamethasone.

Patients are required to receive dexamethasone from not later than SD-1.

In treatment-naïve patients, a background therapy of 10 mg/m^2 of dexamethasone will be required. In patients receiving emapalumab after having 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 at study entry are allowed in case of documented intolerance to glucocorticoids.

During the study, dexamethasone can be tapered depending on patient`s condition. The tapering scheme can be selected by the treating physician, and should take into account the potential risk of disease (HLH) reactivation.

In the event of disease reactivation/worsening after tapering of dexamethasone, the dose of dexamethasone can be increased and maintained until a satisfactory response is achieved according to the treating physician.

6.2 PROPHYLACTIC TREATMENT

Prophylaxis for HZ virus (HZV) infection will be performed to mitigate the potential risk associated to emapalumab administration (see Section 9.4) and has to be in place from the day before initiation of emapalumab treatment until serum levels of emapalumab are no longer detectable.

Patients will receive any additional required prophylactic antimicrobial treatment according to local recommendations in pHLH.

Consider the following:

- For HZV prevention, according to Institution Guidelines/Recommendations (e.g., Acyclovir 200 mg four times daily for children over two years, for children under two years 100 mg four times daily).
- For tuberculosis (TB) prophylaxis (if required as indicated above) according to Institution Guidelines/ Recommendations (e.g., Isoniazid).

These treatments will be given orally, whenever possible, otherwise intravenously.

6.3 CONCOMITANT THERAPY

6.3.1 Cyclosporin A

Cyclosporin A (CsA) can be continued, if already administered prior to Screening. CsA can be withdrawn at any time, upon the judgment of the Investigator. CsA is not to be introduced (or re-introduced) during the course of the study once emapalumab administration has started.

6.3.2 Intrathecal Therapy

For patients receiving intrathecal (IT) therapy (e.g., methotrexate and glucocorticoids) at the time of emapalumab treatment initiation, this therapy will be continued until clinically indicated. The introduction of IT therapy during emapalumab treatment is allowed should CNS signs and symptoms occur during the study, as clinically indicated.

6.3.3 Other Concomitant Therapies

Intravenous immunoglobulin (IVIG) are only allowed as replacement treatment (i.e., not at doses expected to produce an immunomodulatory effect) according to the clinical judgement of the Investigator. Any IVIG infusion within the previous 4 weeks prior to Screening, as well as any infusion during emapalumab treatment, should be documented in the Case Report Form (CRF; dose, date of administration).

Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, IV parenteral nutrition, inotropic support, antibiotics, anti-fungal and anti-viral treatment, hemofiltration or hemodialysis, as well as general supportive care (e.g., gastro-protective agents, anti-hypertensive etc.) are permitted within the study.

The use of any prescription or over-the-counter medication, including herbal and homeopathic preparations with the exception of multi-vitamins, needs to be notified to the Investigator.

Contraception guidance: see Section 6.4.

6.3.4 Not Allowed Concomitant Therapies

As long as emapalumab is being administered, the concomitant use of other biologic drugs (for indications other than additional HLH treatments) is generally not allowed, except for the following:

- Granulocyte-colony-stimulating factor (G-CSF), in case of prolonged neutropenia
- Rituximab, in case of documented EBV infection.

Administration of Janus kinase (JAK) inhibitors concomitantly with emapalumab is not allowed.

Vaccination with a live or attenuated-live (including BCG) vaccine must be avoided until serum levels of emapalumab are no longer detectable, unless the investigator has a specific reason for overcoming this recommendation, and upon discussion with the Sponsor.

6.3.5 Additional HLH treatments

The administration of additional HLH treatments (e.g., etoposide, T-cell depleting agents) will be allowed concomitantly with emapalumab.

In a patient in whom an HLH worsening or no initial response has been observed after an increase of emapalumab dose to 6 mg/kg on SD3, at SD6 the Investigator may consider the therapeutic option of adding an alternative HLH treatment while continuing emapalumab.

Benefit/risk of administering an additional HLH treatment (with or without emapalumab dose increase) must be assessed, taking into consideration e.g. possible drug toxicities, trends of relevant clinical/ laboratory parameters in that individual patient, extent of past response to conventional HLH therapy (if a second-line patient).

The administration of an additional HLH treatment is also allowed later during the course of emapalumab treatment in case of unsatisfactory HLH control, provided that emapalumab has been administered at a dose of 6 (or 10 mg/kg if the Investigator decided to do so) for at least 2 infusions.

Unsatisfactory HLH control is defined as follows:

- patients who have not achieved or maintained a disease control and general conditions that would allow to proceed to transplant
- patients who present a clinically relevant worsening.

If an additional HLH treatment is needed, etoposide is the drug of choice, unless there is evidence indicating that an alternative agent should be selected. The rationale for administration of additional HLH treatments (including the choice of an agent alternative to etoposide, if applicable) has to be documented in the patient's medical file and in the Dose Notification Form (Appendix E).

At any time, the Investigator can decide to discontinue emapalumab treatment and opt for a different HLH regimen in the patient's best interest, as described in the Section 10.1.3.

6.4 CONTRACEPTION

Females of child-bearing potential require the use of highly effective contraceptive measures (failure rate of less than 1% per year) from Screening until 6 months after receiving last dose of the study drug.

Highly effective contraceptive measures include:

- Sexual abstinence: refraining from heterosexual intercourse during the entire period defined above. The reliability of sexual abstinence needs to be evaluated in relation to its duration and compatibility with the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception)
- Hormonal contraceptives: combination or progesterone only
- Intrauterine methods: intrauterine devices or systems
- Bilateral tubal occlusion
- Vasectomised partner.

Males with partner(s) of child-bearing potential must agree to take appropriate precautions (such as sexual abstinence, barrier contraception, vasectomy) to avoid fathering a child from Screening until 6 months after receiving last dose of study drug.

6.5 EMERGENCY TREATMENT

Severe allergic reactions such as anaphylactic shock require prompt IV treatment with adrenaline and antihistamines. Oxygen shall be supplied through a face mask. Patients must have an appropriately sized IV line that allows rapid infusion of colloid volume substitution. In case of an anaphylactic reaction patients shall be transferred as soon as possible to the intensive care unit of the hospital.

Following the first administration of emapalumab and before leaving their reference center, each patient (and/or patient's legal representative) will be given a card to carry at all times in case of any emergency. The card gives details of the name of the drug, name of the responsible physician, and the address and telephone number of the study site.

7 ENDPOINTS

7.1 EFFICACY ENDPOINTS

Criteria for the definitions of response are reported in Table 4.

Primary efficacy endpoint

- Overall Response, i.e., achievement of either Complete or Partial Response or HLH Improvement, at EOT or Week 8 (whichever occurs earlier).

Secondary efficacy endpoints:

- Overall Survival, including survival to 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 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™ (link to examples of questionnaires are placed in (Appendix A) and BASES questionnaires (Appendix B). While PedsQL (Varni JW, 1999) is a validated tool, BASES (Phipps S, 1994; Phipps S, 2002) is not, but it is of potentially great interest given the fact it focuses on HSCT; BASES will be used in an exploratory fashion.

Table 4: Definition of Response

Overall Response	
Complete Response	Complete Response is adjudicated if: - No fever = body temperature <37.5°C - Normal spleen size - No cytopenia = Absolute Neutrophil Counts ≥1.0x10^9/L and platelet count ≥100x10^9/L [absence of G-CSF and transfusion support must be documented for at least 4 days to report no cytopenia] - No hyperferritinemia = serum level is <2000 µg/L - No evidence of coagulopathy, i.e., normal D-Dimer and/or normal (>150 mg/dL) fibrinogen levels - No neurological and CSF abnormalities attributed to HLH - No sustained worsening of sCD25 (as indicated by at least two consecutive measurements that are > 2-fold higher than baseline)
Partial Response	Partial Response is adjudicated if: - At least 3 of the HLH clinical and laboratory abnormalities (including CNS abnormalities) meet the above mentioned criteria for "Complete Response" - In the case of "reactivated patients" who enter the study with 3 abnormal HLH features, Partial Response is adjudicated if at least 2 parameters normalize

	- In case of reactivated patients who enter the study with 2 abnormal HLH clinical and laboratory parameters only, Partial Response is adjudicated if one of the 2 parameters normalizes - There is no progression of other aspects of HLH disease pathology
HLH improvement	- Improvement (>50% change from baseline or normalization) of at least 3 HLH clinical and laboratory abnormalities (including CNS abnormalities). - In the case of "reactivated patients" who enter the study with only 2 abnormal HLH features, a change from baseline greater than 50% for both will define HLH as improved.

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; G-CSF, granulocyte-colony-stimulating factor; HLH, hemophagocytic lymphohistiocytosis

7.2 SAFETY ENDPOINTS

Safety and tolerability of emapalumab will be assessed as follows:

- Incidence, severity, causality and outcomes of 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

7.3 PHARMACOKINETIC ENDPOINTS

The serum concentration of emapalumab will be measured as a function of time to determine the emapalumab PK profile.

Pharmacokinetic data will be visually examined using appropriate graphical analysis.

Individual emapalumab concentration-time profiles will be subject to population PK analysis using non-linear mixed effects modelling. The anticipated covariate effects of body weight and time-varying total IFNγ will be included in the model. Additional covariate effects might be investigated. Individual and mean PK parameters will be tabulated.

Measurement of emapalumab concentrations may be performed in an exploratory manner, if clinically indicated, in other matrices, e.g., cerebrospinal fluid (CSF), bronchoalveolar lavage (BAL).

7.4 PHARMACODYNAMIC ENDPOINTS

Determination of PD parameters as a function of time will include the followings:

- 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)

Population PK/PD analysis using non-linear mixed effects modelling will be undertaken. The main PD biomarker investigated will be CXCL9.

Additional PD biomarkers will also be evaluated (e.g., sCD25 and other exploratory biomarkers). The anticipated covariate effect of time-varying total IFNγ will be included in the CXCL9 model. Additional covariate effects might be investigated. Individual and mean PD parameters will be tabulated.

Measurement of PD parameters may be performed in an exploratory manner, if clinically indicated, in other matrices, e.g., cerebrospinal fluid CSF, BAL.

PD samples may be used to investigate potential drug-drug interactions.

8 OUTLINE OF STUDY PROCEDURES

Patients will be recruited from specialized study sites, equipped with an intensive care unit and access to a bone marrow transplant unit.

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

For a detailed description of the schedule of visits and assessments, refer to the Schedule of Assessment Table 1 (Screening and Treatment Period) and Table 2 (Follow-up Period).

Informed consent form must be signed by the patient or his/her legally authorized representative prior to any study-related procedures, with the assent of patients who are deemed suitable to provide it.

During the emapalumab treatment period, visits for infusion and efficacy/safety assessments will occur on SD0, SD3 and twice-a-week thereafter (not more than 4 days apart). In the circumstances when HSCT is scheduled beyond 12 weeks from emapalumab initiation and Complete Response is maintained (see Section 5.3), the treatment with emapalumab may continue once a week; acceptable time-window for visits in this case will be ±1 day. An EOT visit has to be performed 3±1 days after last emapalumab infusion.

Furthermore, during the follow-up period, the following time-windows are allowed around visits:

- Pre-conditioning: can be combined with EOT visit provided the two visits are not more than 2 days apart
- Week (Wk) 1-2-3, D+30 post-HSCT: ±2 days
- D+60, D+100 post-HSCT: ±1 week
- 6-mo, 1-yr post-HSCT: ±4 weeks

If HSCT is not performed, the described schedule applies to the follow-up visits required to occur after the last emapalumab infusion.

Following windows can be applied to the vital signs measurement:

- When measured every 15 minutes: ±5 minutes
- When measured every 30 minutes: ±10 minutes
- When measured at 1 hour and 2 hours after infusion: ± 15 minutes

Some procedures are not to be done systematically but only if clinically relevant. For example:

- ECG is mandatory at Screening and at EOT visits, however it should be done at any other time-point during the study, if deemed appropriate.
- Brain magnetic resonance imaging (MRI) is mandatory at Screening only in case of CNS disease, but should be done at any other time-points during the study to monitor evolution or to confirm onset of CNS involvement, as clinically indicated.
- Lumbar puncture for CSF analysis is to be performed at Screening providing that coagulation function allows, but should be done at any other time-points during the study to monitor evolution (if the initial analysis was abnormal), or to confirm new onset of CNS involvement.

- Search for pathogens (other than TB) at Screening and during the study should be done if there is any suspicion of infection, and should be performed at relevant time intervals to follow the evolution of infections, either pre-existing or emerging during the study.
- Chest X-ray should be performed at Screening and during the study in case of clinical suspicion of a pulmonary infection or to follow-up a pre-existing infection at Screening/baseline.

If planned as standard of care, alternative imaging methods will be accepted as a replacement for per protocol imaging (with exception of abdominal ultrasound): namely, brain computerized tomography (CT) or cranial ultrasound will be accepted as a replacement of brain MRI, and chest CT will be accepted as a replacement of chest X-Ray.

If CBC, coagulation, biochemistry and imaging assessments cannot be performed on the day of the scheduled visit, assessments within ±1 day window from scheduled visit date will be accepted as a replacement.

Analysis done on blood samples will favor as much as possible the use of micro-sampling techniques.

When blood drawing needs to be limited, laboratory safety parameters (which would have been done as normal disease monitoring) will be prioritized.

Volumes of blood are calculated assuming a maximum 2-week screening, 6-month treatment period with infusions twice a week, 1-year follow-up with emapalumab detectable at all timepoints, pregnancy test performed (total study duration of 18.5 months), and amount to 98 mL for study-specific assessments (PK, PD, ADA); 253 mL for CBC, biochemistry, coagulation and pregnancy test; 31.5 mL for search for infections. Amount of blood drawn per 8 weeks of study (41.4 mL) is therefore within acceptable[iv] 5-10% total blood volume draw for patients of the first year of life, and under 5% of total blood volume for older children.

8.1 SCREENING

Patients will be screened for eligibility prior to enrolment into the study. An Eligibility Review Form (Appendix C) will be completed and shared with the Sponsor after the patient is consented, to guide the joint review of patient's eligibility.

A pre-screening checklist (Appendix D) is an additional tool to assist the Investigator to make decisions such as patient transfer,. This checklist enables rapid preliminary assessment of patient's eligibility based strictly on the information available from routine patient care. The pre-screening checklist does not need to be shared with the Sponsor

A screening log will be maintained by the Investigator with specification of reasons for non-eligibility.

Screening evaluations should be completed within the 2 weeks prior to the first administration of study drug (Visit 1). Evaluations performed before ICF signature, but within this window and as per routine care, will be accepted for screening purposes. Patient's medical record should clearly denote these evaluations as standard of care.

The following information must be collected and the following procedures must be performed:

[iv] WHO | Blood Sample Volumes in Child Health Research: Review of Safe Limits." n.d. WHO. https://doi.org//entity/bulletin/volumes/89/1/10-080010/en/index.html.

Patient information:

- Demographic and medical history, including race, ethnicity and country of origin, if allowed per local Regulations
- Medications at Screening
- Any conventional HLH therapy previously received
- Date of HLH diagnosis and HLH history
- Molecular diagnosis of HLH, as available
- Perforin expression and other functional tests performed for the diagnosis of HLH, as available
- Date and criteria of eligibility

Clinical Assessment:

- Vital signs, including body temperature, heart rate, blood pressure, and oxygen saturation
- Physical examination, including at a minimum, weight, height/length, spleen and liver size (by abdominal palpation), and neurological examination
- Quality of Life questionnaire: PedsQL™, Pediatric Quality of Life Inventory™

Procedure:

- ECG

Search for infections[v]:

- *Tuberculosis mycobacteria* via interferon-gamma release assays (IGRA)/ purified protein derivative (PPD) test and polymerase chain reaction (PCR). In a patient having received BCG vaccination, a PPD test must be performed and combined with IFNγ-release assay if the PPD result is ≥5 mm. In addition, search for Tuberculosis via PCR in any relevant specimen should be performed to have a baseline, as this test will be used during the course of the study to perform regular TB monitoring.
- Infection search at Screening should be performed according to the patient's clinical presentation. At a minimum EBV and CMV viral loads should be assessed.
- *Atypical mycobacteria*, *Histoplasma capsulatum*, *Shigella*, *Salmonella*, *Campylobacter* and *Leishmania*[vi], as appropriate. The presence of *Leishmania* can also be ascertained by direct bone marrow observation. A first screening for *Histoplasma capsulatum* may be performed using galactomannan assay, however -if the test

[v] A patient with a clinical assessment (including chest X-ray) not indicative of the presence of the above mentioned infections, provided that a usable specimen has been taken, and the microbiological analysis is ongoing, can be enrolled prior to the availability of the results, if a patient's medical condition warrants rapid treatment initiation.

[vi] As *Leishmania* is not endemic in North America, only patients who have been in endemic regions (e.g., South America) during the 6 months prior to Screening, are required to be actively screened for *Leishmania*.

	is positive- confirmation should be obtained by using a *Histoplasma capsulatum* specific test.
Laboratory:	▪ CBC with differential count (including large unstained cells count, whenever performed as routine) ▪ Coagulation tests: activated partial thromboplastin time and/or ratio, prothrombin time and/or International Normalized Ratio (INR), D-dimers and fibrinogen ▪ Biochemistry: glucose, ferritin, C-reactive protein (CRP), liver function (aspartate amino transferase [AST], ALT, gamma glutamy transferase [γGT], lactate dehydrogenase [LDH], alkaline phosphatase [ALP], bilirubin), renal function (albumin, creatinine and urea) and triglycerides (fasting whenever possible) ▪ Pregnancy test (blood or urine), if applicable
Imaging:	▪ Abdominal ultrasound (spleen longitudinal measure) ▪ Chest X-ray (or chest CT as an alternative) ▪ Brain MRI to be performed in case of CNS disease (brain CT or cranial ultrasound as an alternative)
Histopathology:	▪ CSF Analysis (if coagulation allows)
Safety:	▪ Recording of any AEs occurred since signature of the ICF

8.2 VISIT 1 (INFUSION 1 OF EMAPALUMAB; SD0)

The following assessments are to be performed pre-infusion at Visit 1 (SD0):

Clinical Assessment:	▪ Vital signs, including body temperature, heart rate, blood pressure, and oxygen saturation ▪ Physical examination, including as a minimum, weight, spleen and liver size (by abdominal palpation), and neurological examination
Laboratory:	▪ CBC with differential count (including large unstained cells count, whenever performed as routine) ▪ Coagulation tests: activated partial thromboplastin time and/or ratio, prothrombin time and/or INR, D-dimers and fibrinogen ▪ Biochemistry: glucose, ferritin, CRP, liver function (AST, ALT, γGT, LDH, ALP, bilirubin), renal function (albumin, creatinine and urea) and triglycerides (fasting whenever possible) ▪ Urinalysis: glucose, blood, protein and/or albumin, leucocytes, ketones, pH and specific gravity
Imaging	▪ Abdominal ultrasound (spleen longitudinal measure), if 2 weeks or longer elapsed between the screening visit and SD0
Safety:	▪ Recording of any AEs occurred since last screening visit or prior to infusion
PK:	▪ Emapalumab serum concentrations

PD:	▪ CXCL9, CXCL10, sCD25, total IFNγ
Immunogenicity:	▪ ADAs
IMP Handling:	▪ Preparation, dispensing, and accountability

The infusion will be administered over a period of 1 to 2 hours depending on the volume to be infused.

Blood pressure, heart rate and oxygen saturation (pulse oximetry) will be collected every 15 minutes during and until the end of the infusion.

The following assessments are to be performed post-infusion:

Vital sign assessment:	▪ Heart rate, oxygen saturation, blood pressure and temperature at the end of the infusion, 1 hour and 2 hours after completion of emapalumab infusion
PK:	▪ Emapalumab serum concentration.

8.3 VISIT 2 (INFUSION 2 OF EMAPALUMAB; SD3)

The following assessments are to be performed pre-infusion at Visit 2 (SD3):

Clinical Assessment:	▪ Vital signs, including body temperature, heart rate, blood pressure, and oxygen saturation ▪ Physical examination, including as a minimum, weight, spleen and liver size (by abdominal palpation), and neurological examination
Laboratory:	▪ CBC with differential count (including large unstained cells count, whenever performed as routine) ▪ Coagulation tests: activated partial thromboplastin time and/or ratio, prothrombin time and/or INR, D-dimers, and fibrinogen ▪ Biochemistry: glucose, ferritin, CRP, liver function (AST, ALT, γGT, LDH, ALP, bilirubin), renal function (albumin, creatinine and urea) and triglycerides (fasting whenever possible)
Safety:	▪ Recording of any AEs occurred since start of first infusion
PK:	▪ Emapalumab serum concentrations
PD:	▪ CXCL9, CXCL10, sCD25, total IFNγ
IMP Handling:	▪ Preparation, dispensing, and accountability

The infusion will be administered over a period of 1 to 2 hours depending on the volume to be infused.

The second infusion must be administered on SD3.

During the infusion, monitoring of heart rate and oxygen saturation will be performed, with recording of values at 30 minutes after the beginning of the infusion. If this is the first infusion at an increased dose of emapalumab, and/or patient has experienced an infusion-related reaction, blood pressure, heart rate and oxygen saturation are to be collected every 15 minutes during and until the end of the infusion.

The following assessments are to be performed post-infusion:

Vital sign assessment:	▪ Heart rate, oxygen saturation, blood pressure and temperature at the end of the infusion, 1 hour and 2 hours after completion of emapalumab infusion
PK:	▪ Emapalumab serum concentration.

8.4 VISIT 3 AND ONWARDS (INFUSION 3 OF EMAPALUMAB AND ONWARDS)

The following assessments are to be performed pre-infusion at all visits from Visit 3 onwards, unless specified differently:

Clinical Assessment:	▪ Vital signs, including body temperature, heart rate, blood pressure, and oxygen saturation ▪ Physical examination, including as a minimum, weight, spleen and liver size (by abdominal palpation), and neurological examination ▪ Assessment of clinical response every 2 weeks
Search for infections:	▪ TB by PCR (every 4 weeks) ▪ *Infection search & monitoring* in case of suspicion of infection or if there is an active infection at screening/baseline to monitor evolution of viral load and positivity for an identified pathogen ▪ *Atypical mycobacteria, Histoplasma capsulatum, Shigella, Salmonella, Campylobacter, Leishmania* - if an infection is suspected
Laboratory:	▪ CBC with differential count (including large unstained cells count, whenever performed as routine) ▪ Coagulation tests: activated partial thromboplastin time and/or ratio, prothrombin time and/or INR, D-dimers and fibrinogen ▪ Biochemistry: glucose, ferritin, CRP, liver function (AST, ALT, γGT, LDH, ALP, bilirubin), renal function (albumin, creatinine and urea) and triglycerides (fasting whenever possible)
Imaging:	▪ Abdominal ultrasound with spleen longitudinal measure (every 2 weeks during emapalumab treatment) ▪ Chest X-ray - in case of clinical suspicion of pulmonary infection or to monitor existing abnormalities
Safety:	▪ Recording of any AEs occurred since last visit
PK:	▪ Emapalumab serum concentration (every other infusion starting from Visit 3)
PD:	▪ CXCL9, CXCL10, sCD25, total IFNγ (every other infusion starting from Visit 3)
Immunogenicity:	▪ ADAs (only at Week 4, together with a PK sample)
IMP Handling:	▪ Preparation, dispensing, and accountability

The infusion will be administered over a period of 1 to 2 hours twice a week (not more than 4 days apart). Monitoring of heart rate and oxygen saturation will be performed, with recording of values at 30 minutes after the beginning of the infusion. If this is the first infusion at an increased dose of emapalumab, and/or

patient has experienced an infusion-related reaction, blood pressure, heart rate and oxygen saturation are to be collected every 15 minutes during and until the end of the infusion.

The following assessments are to be performed post-infusion at Visit 3 and onwards:

Vital sign assessment:	▪ Heart rate, oxygen saturation, blood pressure and temperature at the end of the infusion, 1 hour and 2 hours after completion of emapalumab infusion
PK:	▪ Emapalumab serum concentration (every other infusion starting from Visit 3)
Clinical Assessment:	▪ QOL questionnaire - PedsQL™, Pediatric Quality of Life Inventory™ (at Visit 3 only)

During treatment, emapalumab and biomarker concentrations may be measured in other matrices, such as CSF or BAL, if samples obtained in procedures which are performed for diagnostic/therapeutic purposes can also be available for these exploratory investigations, and if clinically indicated.

8.5 WEEK 8 ASSESSMENT VISIT (3 DAYS AFTER WEEK 8 INFUSION) AND END OF TREATMENT VISIT (3 DAYS AFTER LAST EMAPALUMAB INFUSION)

These visits will include a full patient`s assessment.

The Week 8 Assessment Visit will be performed 3 (±1) days after the last Week 8 emapalumab infusion. If treatment with emapalumab is completed before Week 8, only an EOT visit will be performed 3 (±1) days after the last infusion.

For patients continuing treatment beyond Week 8, an EOT visit will be conducted 3 (±1) days after the last emapalumab infusion.

The following assessments are to be performed at the Week 8 Assessment Visit and at the EOT Visit:

Clinical Assessment:	▪ Vital signs, including body temperature, heart rate, blood pressure, and oxygen saturation ▪ Physical examination, including as a minimum, weight, spleen and liver size (by abdominal palpation), and neurological examination ▪ Assessment of clinical response ▪ QOL questionnaires - PedsQL™, Pediatric Quality of Life Inventory™, BASES (BASES only at EoT and if HSCT is planned)
Procedure:	▪ ECG (only at EOT)
Search for infections:	▪ TB by PCR (if not performed within the last 4 weeks) ▪ *Infection search & monitoring* in case of suspicion of infection or if there is an active infection at screening/baseline to monitor evolution of viral load and positivity for an identified pathogen*Atypical mycobacteria, Histoplasma Capsulatum, Shigella, Salmonella, Campylobacter, Leishmania* – only if an infection is suspected

Laboratory:	▪ CBC with differential count (including large unstained cells count, whenever performed as routine) ▪ Coagulation tests: activated partial thromboplastin time and/or ratio, prothrombin time and/or INR, D-dimers, and fibrinogen ▪ Biochemistry: glucose, ferritin, CRP, liver function (AST, ALT, γGT, LDH, ALP, bilirubin), renal function (albumin, creatinine and urea) and triglycerides (fasting whenever possible) ▪ Pregnancy test, if applicable (only EOT) ▪ Urinalysis: glucose, blood, protein and/or albumin, leucocytes, ketones, pH (only EOT), gravity
Imaging:	▪ Abdominal ultrasound with spleen longitudinal measure
Safety:	▪ Recording of any AEs occurred since last visit
PK:	▪ Emapalumab serum concentration
PD:	▪ CXCL9, CXCL10, sCD25, total IFNγ
Immunogenicity:	▪ ADAs
IMP Handling:	▪ Preparation, dispensing, and accountability (week 8 only)

If emapalumab treatment is continued, and **Week 8 Assessment Visit** is performed on the same day of the subsequent infusion, the infusion will be administered over a period of 1 to 2 hours. Monitoring of heart rate and oxygen saturation will be performed, with recording of values at 30 minutes after the beginning of the infusion. If this is the first infusion at an increased dose of emapalumab, and/or patient has experienced an infusion-related reaction, blood pressure, heart rate and oxygen saturation are to be collected every 15 minutes during and until the end of the infusion.

The following assessments will be performed post-infusion:

Vital sign assessment:	▪ Heart rate, oxygen saturation, blood pressure and temperature at the end of the infusion, 1 hour and 2 hours after completion of emapalumab infusion
PK:	▪ Emapalumab serum concentration

8.6 FOLLOW-UP PERIOD

A long-term follow-up will be conducted after the completion (or premature discontinuation) of emapalumab treatment, until 1 year after either HSCT or last emapalumab infusion (if HSCT is not performed). For patients not planned to receive HSCT, the long-term follow-up period will be conducted according to the same schedule of post-HSCT follow-up.

8.6.1 Follow-Up Pre-HSCT: Pre-Conditioning Visit

The following assessments have to be performed before starting the administration of conditioning agents for HSCT. This visit can be combined with the EOT visit, if the visits are not more than 2 days apart.

If the pre-conditioning and EOT visits are not combined, the following assessments are to be performed:

Clinical Assessment:	▪ Vital signs, including body temperature, heart rate, blood pressure, and oxygen saturation ▪ Physical examination, including as a minimum, spleen and liver size (by abdominal palpation), height/length and neurological examination ▪ Survival
Laboratory:	▪ CBC with differential count (including large unstained cells count, whenever performed as routine) ▪ Coagulation tests: activated partial thromboplastin time and/or ratio, prothrombin time and/or INR, D-dimers, and fibrinogen ▪ Biochemistry: glucose, ferritin, CRP, liver function (AST, ALT, γGT, LDH, ALP, bilirubin), renal function (albumin, creatinine and urea) and triglycerides (fasting whenever possible) ▪ Urinalysis: glucose, blood, protein, leucocytes, ketones, pH, gravity
Imaging:	▪ Abdominal ultrasound with spleen longitudinal measure ▪ Chest X-ray. Other imaging modalities (e.g. CT) performed as part of pre-transplant work-up are also acceptable.
Safety:	▪ Recording of any AEs occurred since last visit
PK:	▪ Emapalumab serum concentration
PD:	▪ CXCL9, CXCL10, sCD25, total IFNγ.

8.6.2 Follow-Up Post-HSCT (or After Last Emapalumab Infusion)

The following assessments will be performed at weekly visits after either HSCT or last emapalumab infusion (as applicable) until Day 30, and subsequently at Day 60, Day 100, and Month 6:

(In addition to the below, in patients undergoing HSCT, PK/PD samples will be collected at Day 3 post-transplant).

Clinical Assessment:	▪ Vital signs, including body temperature, heart rate, blood pressure, and oxygen saturation ▪ Physical examination, including as a minimum, spleen and liver size (by abdominal palpation), height/length (at 6 month visit only) and neurological examination ▪ Post HSCT outcome, if applicable ▪ Survival ▪ QOL questionnaires - PedsQL™, Pediatric Quality of Life Inventory™ and BASES if HSCT is performed (at Day 30, Day 100 and Month 6 visits)
Laboratory:	▪ CBC with differential count (including large unstained cells count, whenever performed as routine) ▪ Coagulation tests: activated partial thromboplastin time and/or ratio, prothrombin time and/or INR, D-dimers, and fibrinogen

- Biochemistry: glucose, ferritin, CRP, liver function (AST, ALT, γGT, LDH, ALP, bilirubin), renal function (albumin, creatinine and urea) and triglycerides (fasting whenever possible)
- Urinalysis: glucose, blood, protein and/or albumin, leucocytes, ketones, pH, gravity

Search for infections:
- TB by PCR in any relevant specimen, as clinically indicated, at minimum at D+30, D+60, D+100, 6 month and 1 year/WD visits; until serum levels of emapalumab are no longer detectable
- *Infection search & monitoring* according to the patient's clinical presentation – in case of suspicion of infection

Imaging:
- Chest X-ray – in case of clinical suspicion of pulmonary infection or to monitor existing abnormalities
- Abdominal ultrasound with spleen longitudinal measure (at Day 100 visit only)

Safety:
- Recording of any AEs occurred since last visit until serum levels of emapalumab are no longer detectable. After elimination of emapalumab only SAEs will be reported.

PK:
- Emapalumab concentrations (if serum levels of emapalumab were still measurable at the previous visit). *Also at D+3 after HSCT, if performed*

PD:
- CXCL9, CXCL10, sCD25, total IFNγ (if serum levels of emapalumab were still measurable at the previous visit; then only if clinically indicated). *Also at D+3 after HSCT, if performed*

Immunogenicity:
- Assessment for ADAs (at Day 100 visit only)

8.6.3 End of Study: 1-Year Visit Post-HSCT (or After Last Emapalumab Infusion)/Withdrawal Visit

This visit represents the last visit of the study. The following assessments will be performed:

Clinical Assessment:
- Vital signs, including body temperature, heart rate, blood pressure, and oxygen saturation
- Physical examination, including as a minimum, spleen and liver size (by abdominal palpation), and neurological examination
- Post HSCT outcome, if applicable
- Survival
- QOL questionnaires - PedsQL™, Pediatric Quality of Life Inventory™ and BASES if HSCT is performed

Laboratory:
- CBC with differential (including large unstained cells count, whenever performed as routine)
- Coagulation tests: activated partial thromboplastin time and/or ratio, prothrombin time and/or INR, D-dimers, and fibrinogen

	▪ Biochemistry: glucose, ferritin, CRP, liver function (AST, ALT, γGT, LDH, ALP, bilirubin), renal function (albumin, creatinine and urea) and triglycerides (fasting whenever possible)
	▪ Urinalysis: glucose, blood, protein, leucocytes, ketones, pH, gravity
Search for infections:	▪ TB by PCR in any relevant specimen (if serum levels of emapalumab were still measurable at the previous visit)
	▪ *Infection search & monitoring* according to the patient's clinical presentation – in case of suspicion of infection
Imaging:	▪ Abdominal ultrasound with spleen longitudinal measure
Safety:	▪ Recording of any AEs occurred since last visit until serum levels of emapalumab are no longer detectable. After elimination of emapalumab only SAEs will be reported.
PK:	▪ Emapalumab concentrations (if serum levels of emapalumab were still measurable at the previous visit)
PD:	▪ CXCL9, CXCL10, sCD25, total IFNγ (if serum levels of emapalumab were still measurable at the previous visit, or if clinically indicated)
Immunogenicity:	▪ Assessment for ADAs

8.7 ASSESSMENTS IN CASE OF UNPLANNED/UNSCHEDULED VISITS

Unplanned visits may occur should the patient need to be assessed or treated for any clinical condition that arises during the study. This includes the evaluation and follow-up of AEs and SAEs.

8.8 UNPLANNED ASSESSMENTS

Additional PK/PD samples may be required to better characterize the PK/PD profile and/or for safety reasons. The number of additional samples taken will depend on the weight and health status of the patient, and will be taken only if the amount of blood required is acceptable in the context of the EMA guideline and USA pediatric recommendations (see Section 8).

9 SAFETY MONITORING

9.1 DESCRIPTION OF SAFETY PARAMETERS

Evaluation of emapalumab tolerability and safety will be based on the following parameters:

- AEs (serious and non-serious)
- Laboratory parameters, including:
  - CBC with differential counts
  - Coagulation tests (activated partial thromboplastin time and/or ratio, prothrombin time and/or INR), d-Dimer, and fibrinogen
  - Biochemistry: glucose, ferritin, CRP, liver function (AST, ALT, γGT, LDH, ALP, bilirubin), renal function (albumin, creatinine and urea) and triglycerides (fasting whenever possible)

- TB PCR results

- Vital signs: body temperature, heart rate, blood pressure, oxygen saturation
- If present at baseline or emerging during treatment, the following parameters will be collected until resolution:
  - evolution of viral load and positivity for an identified pathogen(frequency of collection driven by site local practices).

9.2 RECORDING AND REPORTING SAFETY PARAMETERS

9.2.1 Adverse Events

Adverse events (AEs) are defined as any undesirable experience occurring to a patient during the study, whether or not considered related to the IMP. All AEs occurring during the study, i.e., from the date of ICF signature up to and including the end-of-study visit must be recorded on the AE page of the electronic CRF (eCRF). Once emapalumab serum levels are no longer detectable, only serious AEs (SAEs) will be recorded on the AE page of the eCRF.

Medical conditions present at Screening or diagnosed at the Screening visit will be recorded in the medical history section of the eCRF.

An AE which occurs between the Screening visit and the start of first IMP administration will be considered as a pre-treatment AE.

Any AE that occurs after the start of first IMP administration will be considered as a Treatment Emergent Adverse Event (TEAE), including the specific situations described below. AEs are collected after signing of ICF up to Study Completion or until serum levels of emapalumab are no longer detectable (whichever occurs first). After elimination of emapalumab only SAEs will be reported.

Should a pre-existing medical condition worsen (clinically significant change in intensity or frequency), it must be recorded as an AE in the eCRF and, depending on the time of its occurrence, will be considered as a pre-treatment AE or a TEAE. Should a medical condition recorded as a pre-treatment AE worsen after start of IMP administration, it will be recorded in the eCRF as a separate TEAE, specifying `Worsening of xxx`.

For all AEs, the following will be assessed and recorded: onset and end dates (and -when relevant- time), intensity, seriousness, relationship to IMP, action taken regarding IMP, any treatment received, and outcome.

Intensity of AEs will be graded on a three-points scale (mild, moderate, severe) using the modified World Health Organization (WHO) toxicity scale (Grade 3 and 4 are considered to be the severe grade). If AE severity is not mentioned in the scale, assessment will be made using the following definitions:

- Mild: Discomfort noticed but no disruption of normal activity
- Moderate: Discomfort sufficient to reduce or affect normal daily activity
- Severe: Inability to work or perform normal daily activity

For a given AE, the assessment of its intensity should reflect the highest grade (on the three-point scale mentioned above) reported during its course (except when the intensity of a pre-treatment AE increases after treatment initiation, as indicated above).

The relationship of AEs to the IMP will be assessed by the Investigator using a “Yes/No” classification. A “Yes” relationship infers that there is a reasonable suspected causal relationship to the IMP. The

expression “reasonable causal relationship” is meant to convey that there are facts, evidence or arguments to suggest a causal relationship. In this study, emapalumab is the only IMP.

Specific situations:

- Common HLH signs and symptoms (e.g., anemia, neutropenia, thrombocytopenia, pancytopenia, splenomegaly, hepatomegaly) will not be reported as separate AEs unless clearly attributed to a cause different from HLH, and the verbatim term should indicate the cause.
- If changes in the above mentioned HLH signs and symptoms indicate HLH worsening or reactivation, worsening or reactivation will be reported as an AE.
- Fever will only be reported when not linked to an identified cause with the highest temperature considered during the period. If it is a recurrent fever it can be entered as intermittent fever with no need to specify the temperature (the intensity should be a reflection of the highest temperature observed). If fever is considered as a sign of a confirmed infection or of HLH worsening or reactivation, only the diagnosis should be reported as an AE, and not `fever`.
- Viral load positivity, in particular for EBV, CMV and adenovirus, and evolution will be collected on a dedicated eCRF module.
- Active infections will be reported as AEs, indicating whether constituting a primary infection or a reactivation (whenever possible). Pathogen positivity and evolution will be collected in a dedicated eCRF module.
- Expected effects of conditioning (i.e., pancytopenia during conditioning and until engraftment) will not be reported.

9.2.2 Serious Adverse Events

Any AE is considered “serious” if it:

- results in death (note: death is an outcome, not an event);
- is life-threatening; (note: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe);
- requires in-patient hospitalization or prolongs an existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is an important medical event, i.e., refers to an event that may not result in death, be life-threatening, or require hospitalization but may be considered as serious when, based upon appropriate medical judgment, may jeopardize the patient, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition above.

The following reasons for hospitalization are exempted from being reported:

- elective hospitalizations for surgical procedures that are a result of a patient’s pre-existing condition(s) which have not worsened during the study;
- hospitalization requested for emapalumab infusion and study visits (including a possible hospital stay overnight, if due to logistic convenience);
- post-HSCT hospitalization as a measure of caution in this fragile population, to investigate a clinical sign or symptom (e.g. fever), provided that the hospital stay has a duration of less than 72 hours and does not result in any confirmed new diagnosis (e.g., negative search of infection in

presence of fever which resolves with symptomatic measures); in this case the sign will be recorded as an AE.

For the initial SAE report, the Investigator should report all available case details concerning the patient and the event, using the Swedish Orphan Biovitrum AG SAE reporting form within 24 hours of awareness.

Swedish Orphan Biovitrum AG contact information for SAE reporting:

E-mail: **NI-0501drugsafety@sobi.com**

Relevant follow-up information on SAEs should be forwarded to Swedish Orphan Biovitrum AG as soon as it becomes available. In addition, the Investigator must be available to answer without delay any request for follow-up information or questions that Swedish Orphan Biovitrum AG may have regarding the SAE.

All SAEs will be recorded on the appropriate page of the eCRF. They will be reviewed, evaluated and followed up until the event resolves or is considered stable by a study physician.

If either the Sponsor or Investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

9.2.3 SUSAR reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are both:

- related, i.e., there must be a certain degree of probability that the event is a harmful and undesirable reaction to the IMP under investigation, regardless of the administered dose
- unexpected, i.e., the event is not listed as an expected serious adverse reaction in the Reference Safety Information (RSI) of the Investigator's Brochure

All SUSARs will reported by the sponsor to relevant Health Authorities, Ethics Committees (ECs)/Institutional Review Boards (IRBs)/Research Ethics Boards (REB) and investigators as per applicable regulations.

Under the USA 21 Code of Federal Regulation (CFR) 312.32(c), the Sponsor (directly or through a delegated third party) is required to notify the Food and Drug Administration (FDA) and all participating Investigators in an Investigational New Drug (IND) safety report (i.e., 7- or 15-day expedited report) of potentially serious risks from clinical trials or any other source as soon as possible, but no later than 15 calendar days after the Sponsor receives the safety information and determines that the information qualifies for reporting.

Investigators in the USA are required to promptly report to the IRB all unanticipated problems involving risk to human subjects or others, including AEs that should be considered unanticipated problems (21 CFR 312.66), such as IND safety reports.

In countries other than the USA, the Sponsor will promptly evaluate all SAEs and against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, REBs and applicable health authorities based on applicable legislation.

Swedish Orphan Biovitrum AG will also report all SUSARs to the EMA's EudraVigilance database within 15 days, as well as to the relevant National Competent Authorities when required. Fatal and life-threatening SUSARs will be reported within 7 calendar days, with another 8 days for completion of the report.

9.2.4 Managing Abnormal Laboratory Test Values

All laboratory tests (hematology, coagulation, blood chemistry) will be captured in the database from the local laboratory.

Laboratory test abnormalities must be considered as AEs and recorded on specific AE pages of the CRF only if they:

- require specific intervention for correction, or
- lead to a change in study medication (e.g., dose modification, interruption or permanent discontinuation), or
- qualify as grade 4 severity as per modified WHO toxicity scale

If a laboratory test abnormality leads to a new clinical diagnosis, the new clinical diagnosis should be reported as an AE rather than the laboratory abnormality.

Laboratory test abnormality that qualifies as an AE as per the definition above, will follow the AE/SAE reporting process described in this section.

Laboratory abnormalities which are considered to be part of HLH signs and symptoms (see Section 9.2.1) will not be reported as AEs. If laboratory abnormalities are indicative of an HLH reactivation or worsening, the reactivation or worsening of HLH will be reported as the AE, and not the laboratory abnormalities themselves.

9.3 FOLLOW-UP OF SAFETY PARAMETERS

9.3.1 Follow-up of Adverse Events

Adverse events should be followed up to resolution or stabilization or until they return to baseline status (in the event of an exacerbation of a pre-existing condition).

For AEs still ongoing at study completion or withdrawal, where return to baseline status or stabilization cannot be established, an explanation should be recorded.

9.3.2 Follow-up of Abnormal Laboratory Test Values

Abnormal laboratory findings that qualify as AEs should be followed-up as per Section 9.3.1.

9.3.3 Pregnancy

Occurrence of pregnancy in a study participant will require discontinuation of the IMP and entry into the study follow-up period.

Pregnancies, including pregnancies of female partners of male study participants must be reported to Swedish Orphan Biovitrum AG within 24 hours of awareness on the Swedish Orphan Biovitrum AG Pregnancy form.

A pregnancy must be followed until its conclusion. Any AE associated with the pregnancy occurring during the follow-up period after study treatment discontinuation must be reported in the eCRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 9.2.2.

9.4 BENEFIT/RISK MANAGEMENT

9.4.1 Safety Surveillance Management

HLH is a rare disease, and experience gathered from previous exposure of patients to emapalumab is still limited. It is therefore required that patients are monitored during and for 2 hours after each infusion of emapalumab, and that infusions are administered under medical supervision within a unit having emergency equipment.

The iDMC will ensure that any emergent safety concern will be assessed in a timely manner and appropriate measure taken for the patients, if relevant. Moreover, iDMC will be specifically tasked with regular assessment of the extent of benefit and fatal events prior to transplant in the treatment-naïve subgroup of patients.

9.4.2 General Benefit/Risk Considerations

9.4.2.1 Potential benefits

Based on evidence available from comprehensive analysis of the NI-0501-04 and NI-0501-05 studies that formed the basis of the BLA and MAA submissions, emapalumab administration has shown the potential to improve or resolve relevant clinical and laboratory abnormalities of HLH. Emapalumab demonstrated a statistically significant and clinically relevant reduction in HLH disease activity, assessed through objective clinical and laboratory parameters, in 64.7% of patients. Response occurred early during treatment and was generally sustained. The reduction in HLH disease activity was sustained and was associated with an overall survival benefit that persisted following HSCT. The observed treatment effect was consistent across all efficacy endpoints. Emapalumab was well tolerated in doses up to 10 mg/kg and no off-target toxicity has been identified. Emapalumab treatment could be continued safely and effectively beyond 8 weeks in patients for whom the search for a donor was longer than expected.

The response to emapalumab seems independent of:

- the presence and type of causative mutations
- the presence and type of an infectious trigger

On 20 November 2018, emapalumab was approved by the FDA "for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy".

For more details, refer to the latest Investigator's Brochure (currently version 10.0, dated 24 January 2020).

9.4.2.2 Risks

- Infusion-related reactions

Infusion-related reactions (IRRs) are commonly associated with monoclonal antibody infusions and are defined as signs or symptoms with a temporal relationship to the administration of an infusion and assessed as related, typically occurring soon after the start of the infusion, although symptoms may be delayed for up to 24h. They might be limited (skin reaction) or systemic.

After more than 1000 infusions administered to HLH patients up to the dose of 10 mg/kg, no anaphylactic/anaphylactoid or other significant reactions were observed with emapalumab. IRRs were mainly transient skin reactions observed during and shortly after emapalumab infusions (corresponding

to less than 2% of the infusions performed). They resolved spontaneously and did not lead to emapalumab permanent discontinuation.

From the clinical experience to date, the risk of IRRs associated with emapalumab treatment seems to be very low. However, the infusion should be performed under medical supervision with monitoring of vital signs during and for 2 hours after emapalumab infusion as outline in Section 8.

- Immunogenicity

Occurrence of ADAs inactivating therapeutic effects of the treatment and, in rare cases, inducing adverse reactions, is a potential risk associated with the administration of monoclonal antibodies (mAbs). As of 24 August 2019, treatment-emergent ADAs were detected in:

- 1 out of 14 healthy subjects participating in study NI-0501-03; a low titer of ADAs was measured at the last follow-up visit (at week 44 post-emapalumab administration
- 3 out of 45 patients treated in the context of NI-0501-04/05 studies
- 1 patient treated in compassionate use developed transient ADAs

No AEs, including decreased efficacy, attributable to antibodies have occurred in these patients. In addition, in ongoing studies in patients with sJIA/MAS (NI-0501-06, N=8) and in patients with pHLH (NI-0501-09, N=9), no ADA were detected.

- Drug-drug interactions

High IFNγ production and subsequent hyper production of other cytokines during active pHLH might downregulate cytochrome P450 enzymes (CYPs), resulting in suppression of CYP isoenzymes activity during active disease. Anti-cytokine mAbs have the potential to restore CYP activity back to normal, through neutralization of the pro-inflammatory cytokine which is targeted by the antibody and the ensuing reduction in inflammation (Morgan, 2009). The restoration of CYP activity may therefore alter the elimination of concomitant medications metabolized by these CYPs. During the clinical trials with emapalumab, no events of Therapeutic Protein-Drug Interactions (TP-DI) were reported in pHLH patients.

- Infections

The impact on the immune defense caused by the neutralization of IFNγ is known from patients with inborn errors of the IL-12/23-IFN-γ circuit, particularly patients with complete or partial IFNγ receptor (R) deficiency, and patients developing neutralizing auto anti-IFNγ antibodies. Patients with IFNγ R deficiency are prone to develop mycobacterial infections and, although to a lesser extent, *Salmonella* infections (Dorman 2000, Jouanguy 1997). The mean age of the first environmental mycobacterial infection is 3.1 and 13.4 years in patients with complete and partial deficiency, respectively (Remus 2001).

No systematic prophylaxis is recommended in these patients. If an infection occurs, appropriate antibiotic therapy based on sensitivity of isolated species is prescribed.

Individuals with anti-IFNγ auto-antibodies are also susceptible to develop mycobacterial infections (for the vast majority atypical mycobacterial infections), but also opportunistic infections (e.g., caused by *Histoplasma capsulatum, Salmonella*, HZV) (Browne 2012).

Toxicological studies carried out with emapalumab have shown an increased susceptibility to enteral pathogen infections in monkeys having received emapalumab, when the enteral pathogen was present in the intestinal tract prior to emapalumab administration. Therefore, presence of infections due to *Shigella, Salmonella* and *Campylobacter* pathogens is part of the exclusion criteria.

As to the development of infections caused by pathogens known to be favored by the absence of IFNγ biological activity, a reactivation of HZV (which resolved after a normal course with no sequelae) was observed in one healthy volunteer, at a dose of 3 mg/kg; and one HLH patient enrolled in the NI-0501-04 study developed a disseminated histoplasmosis which resulted in treatment discontinuation. This infection resolved with adequate antifungal therapy, even though emapalumab was still at detectable concentrations in blood.

Other infections reported during or after administration of emapalumab are the same ones commonly observed in immunocompromised patients or are the same ones described in pediatric populations (seasonal viral infections). Patients with active infections (except for the exclusionary ones) were enrolled and treated in the study. The presence of active infections did not lead to the discontinuation or dose decrease of emapalumab treatment, and infections resolved on study drug when treated appropriately and not associated with a refractory disease status. Severe or serious infections were generally reported in patients with previous recent significant exposure to immunosuppressive treatments as they added an additional risk factor for infection development. Importantly, emapalumab treatment has not been associated with myelosuppression.

Active infections, as per patient's clinical presentation, must be carefully followed over time, including quantitative monitoring (e.g. viral loads, antigenemia, antigenuria), when relevant.

For more details refer to the latest Investigator's Brochure (currently version 10.0, dated 24 January 2020).

9.4.2.3 Risk minimization measures

In view of the above reported considerations, the benefit/risk profile of emapalumab in children diagnosed with pHLH is considered to be favorable.

Specific measures are implemented to minimize the potential risks described above as follows:

- As per eligibility criteria, patients with evidence of active Mycobacteria*, Histoplasma, Shigella, Salmonella, Campylobacter* or *Leishmania* infections, or latent tuberculosis will not be included in the study (for details see Section 4.1.2). Patients who received live or attenuated live vaccine within 6 weeks prior to screening are excluded from the studies with emapalumab.
- Monitoring of IRRs: infusions will be performed under medical supervision to immediately identify the occurrence of any IRRs. Each of the specialized centers will have personnel adequately trained in IRR management.
- Prophylaxis for HZV for all patients, and tuberculosis for a defined subpopulation (see Section 6.2), is required per protocol.
- Occurrence of emerging infections and evolution of pre-existing infections are monitored through regular physical examination and laboratory testing, including detection of tuberculosis. *Ad hoc* search for infections will be performed based on signs and symptoms indicating a suspicion of infection. Empirical antibiotherapy will be introduced when deemed appropriate, and proper monitoring of active pre-existing infections or emerging infections will be conducted.

10 STOPPING RULES

10.1 AT PATIENT LEVEL

10.1.1 Decision to Slow Down or Stop Emapalumab Infusion due to Systemic Reaction

During the infusion of emapalumab, any significant change compared to pre-infusion values in vital signs, such as those listed below, should trigger appropriate immediate care:

- Sudden and sustained increase or paradoxical decrease of heart rate (duration of more than 5 minutes) compared to pre-infusion value and not linked to child's anxiety or fear;
- Sustained (an episode of more than 5 minutes duration or more than 3 episodes of shorter duration, i.e., 3 minute) oxygen desaturation (below 90%);
- Any clinical sign or complaint indicative of patient distress

The decision to interrupt the infusion might be taken by the physician in the event of any of the above mentioned occurrences.

The decision to restart the infusion will be based on the evolution of the patient`s status (i.e., resolution of symptoms after appropriate symptomatic measures, e.g., oxygenation or administration of anti-histamine treatment), and upon physician's own medical judgment. The infusion will generally be restarted at a lower rate.

All changes in infusion rate will be recorded in the patient's medical chart and the eCRF each time there is a rate modification, as well as at the end time of premature or delayed termination of the infusion.

10.1.2 Local Issues During Emapalumab Infusion

Unless related to a hypersensitivity reaction, a local infusion issue such as catheter displacement, obstruction or product extravasation, will trigger the infusion of the remaining quantity through a new venous access as soon as possible. All information related to the incident will be recorded accurately in the patient's medical chart prior to being entered in the eCRF. This includes reasons, volume of IMP potentially lost (to calculate the quantity of drug infused), time at which the infusion stopped, time at which the infusion was resumed and time of end of the infusion.

To avoid this type of incident, it is preferable that a central venous access is used: this will improve patient's comfort and ensure a reliable drug administration in particular in infants and toddlers or in case of foreseen difficulties with peripheral venous access.

10.1.3 Decision to Discontinue Treatment or to Withdraw from the Study

The Investigator can decide at any time during the study to discontinue the treatment for an individual patient based on his/her own medical judgment, taking into account the individual benefit/risk ratio for his/her patient. After treatment discontinuation (for any reason), the patient will continue in the study for a long-term follow-up.

In addition, the patient (or their legal representative) can decide at any time to withdraw from the study.

The reason for premature treatment discontinuation or study withdrawal should be documented in the patient's chart and shared with the Sponsor.

The Investigator may request expert advice or a discussion with the Sponsor to receive additional information, if relevant prior to taking a decision; however, the ultimate decision remains the Investigator`s responsibility.

In any case, the decision to withdraw or be withdrawn from the study and/or treatment will have no impact on the patient's care and on further treatments administered to him/her after withdrawal. The management of these patients is described in Section 10.3.

10.2 AT STUDY LEVEL

Recruitment may be temporarily suspended in the following situations:

- occurrence of unexpected fatal or life-threatening adverse reactions;
- emergence of severe drug reactions linked to a common cause/ risk factor at different sites

Patients already enrolled in the study should continue receiving emapalumab per protocol unless decided otherwise by the Investigator.

The suspension will allow for the analysis of the available data by the Sponsor and the iDMC.

After re-evaluation of benefit/risk, the sponsor and iDMC may recommend any of the following:

- to resume recruitment without any change;
- to implement risk minimization measures that may require protocol amendment;
- to implement conditions for study termination, e.g., next occurrence of a particular serious drug reaction

The management of patients already enrolled in the study will also be part of the iDMC recommendations.

10.3 MANAGEMENT OF TREATMENT DISCONTINUATION

All patients who discontinue emapalumab treatment will be treated according to the standard care at the site. However, it is recommended they continue in the study for long-term follow-up monitoring.

11 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

Full details of all statistical issues and planned statistical analyses will be specified in a separate Statistical Analysis Plan (SAP), which will be finalized prior to the locking of the study database. This section contains an overview of the planned methods of analysis.

11.1 SAMPLE SIZE

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 NA sites in order to gather data in a reasonable timeframe.

11.2 ANALYSIS SETS

All analysis sets will be defined prior to final database closure. In addition to the analysis sets listed below, further exploratory analyses may be performed using other subgroups of patients.

11.2.1 All Treated Analysis Set

The All Treated Analysis Set will include all patients who receive any part of an infusion of study drug, and will be as the Primary Efficacy and Safety Analysis Set.

11.2.2 Evaluable Analysis Set

The Evaluable Analysis Set will consist of patients in the All Treated Analysis Set who are evaluable for efficacy, i.e.:

- Have received a minimum of 3 consecutive infusions of emapalumab
- Have not had a diagnosis of secondary HLH subsequent to the initiation of emapalumab treatment

11.2.3 Enrolled Population Analysis Set

The Enrolled Population Analysis Set will include all subjects who sign the inform consent. This population will be used for disposition and major protocol deviations summaries only.

11.3 STATISTICAL AND ANALYTICAL METHODS

For measurements of continuous endpoints, summary statistics will include n, mean, median, standard deviation, minimum and maximum values. For binary data (proportions of patients showing a defined response for example) numbers and percentages will be tabulated. For time to event data, Kaplan-Meier plots will be provided together with the median should this be available. Finally, 95% confidence intervals will be calculated for suitable summary statistics associated with endpoints of interest.

Efficacy analyses will be conducted on both the All Treated and Evaluable Analysis Sets. Safety analyses will be conducted on the safety set.

11.3.1 Efficacy Data

The analysis of the primary endpoint, Overall Response Rate, will utilize an exact binomial test to evaluate the null hypothesis that the response rate is at most 40%. This test will be undertaken at the one-sided 0.025 level.

Time to Response, Duration of Response, and Survival time will be presented using Kaplan-Meier curves with medians calculated if available. Ninety-five percent confidence intervals will be calculated for the median for each of these endpoints.

For maintenance of response achieved any time during the study, event of interest will be the loss of response, with patients in response being censored on the day starting conditioning.

Additional endpoints based on binary outcomes including number of patients who reduce glucocorticoids by 50% or more, and number of patients able to proceed to HSCT will be converted to proportions and associated 95% confidence intervals calculated.

Statistical significance in terms of p-values will only be obtained for the primary endpoint in both the All Treated and the Evaluable analysis sets. All other endpoints will be viewed as supportive for the primary endpoint and as a consequence no formal hierarchy of endpoints will be declared.

11.3.2 Safety Data

All data relating to safety will be listed and summarized using descriptive statistics.

AEs will be coded and tabulated by body system, and by individual events within each body system. AEs will also be tabulated by severity and relationship to the study medication. Summaries will also be produced for SAEs and AEs leading to withdrawal of treatment.

For each clinical laboratory test, individual patient values will be listed and summarized and change from pre-treatment baseline values calculated and summarized. Any values outside the standard reference range will be flagged. Summaries of marked abnormalities and shift tables or boxplots will be tabulated for each laboratory test.

In addition, other exploratory analyses of safety data, including summaries for different subsets of patients, may be conducted.

11.3.3 Pharmacodynamic Data

All PD data will be summarized using appropriate graphical and tabular presentations.

Exploratory statistical models will be fitted, and correlation analyses undertaken, to investigate the relationships between PD data and other biomarkers and the clinical measures of response. ROC curves may be used to summarize any relationships that are found.

In addition, other exploratory analyses of PD endpoints, including summaries for different subsets of patients, may be conducted.

11.3.4 Immunogenicity Data

The numbers of patients with anti-drug antibodies present at each assessment point will be summarized.

11.3.5 Missing Data

Imputation rules will be pre-defined in the SAP prior to final database close, in order to keep to a minimum the number of patients not being evaluated for the primary and key secondary endpoints.

11.4 REPLACEMENT POLICY

11.4.1 For Patients

Additional patients will be recruited into the study if patients are withdrawn from the study for reasons other than safety or lack of efficacy to ensure a sample size of a minimum of 34 patients.

11.4.2 For Centers

A center may be replaced for the following administrative reasons: excessively slow recruitment, poor protocol adherence.

12 ETHICAL AND LEGAL ASPECTS

12.1 GOOD CLINICAL PRACTICE

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Swedish Orphan Biovitrum AG, its authorized representative, and Investigators abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/IEC/REB prior to commencement and where applicable by law also from National Competent Authorities. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

12.2 INVESTIGATOR RESPONSIBILITIES

The Investigator should ensure that all persons assisting with the trial are appropriately qualified and adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The Investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all patients (or their legally authorized representative) who sign an informed consent document and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in their source documents and the study-screening log. The Investigator should maintain source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate and complete.

The Investigator, or a designated member of the Investigators' staff, must be available during monitoring visits, audits and inspections to review data, resolve queries and allow direct access to subjects' records (e.g., medical/hospital records, office charts, hospital charts, and study related charts) for source data and other types of verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

12.3 CONSENT

Before being admitted to the clinical study, the patient must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent document that includes both information about the study and the consent form will be prepared and given to the patient. This document will contain all ICH-GCP, and locally required regulatory elements (whichever is more stringent). The document must be in a language understandable to the patient and must specify who informed the patient, and when the informed consent was obtained.

Information to patients will be split into a Patient Information Sheet that provides detailed information about the trial and its benefits and risks, and the Informed Consent Form that summarizes the content of the Patient Information Sheet and is used to obtain the dated signature from the patient as evidence of the patient's agreement to partake in the study.

If applicable, since minors are involved in the trial, assent must be obtained from the minor and informed consent from at least one of the parents or as mandated by local rules (individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedures involved in the research). The language used in the Assent Form is adapted

to the maturity level of the minor involved in the trial. Since minors of different age groups are likely to be entered into the trial different versions of the Assent Form will be provided. The modalities for obtaining informed consent from the parents and Assent from the minor will be defined at the site initiation visit and documented in the clinical trial center Trial Master File (TMF).

After reading and understanding the informed consent document, the patient (or their legally authorized representative) must give consent in writing. The written informed consent will be obtained prior to conducting any study-related procedures or tests. The patient's consent (or the consent of the patient's legally authorized representative) must be confirmed at the time of consent by the personally dated signature of the person conducting the informed consent discussions. A copy of the signed consent document must be given to the patient or their legally authorized representative. The Investigator will retain the original signed consent document. The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

If an amended protocol impacts the content of the informed consent document, the consent document must be revised. Patients already participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. A copy of the revised informed consent document must be given to the patient or their legally authorized representative. The Investigator will retain the original signed updated consent document in the study files.

12.4 CONFIDENTIALITY AND DATA PRIVACY

Swedish Orphan Biovitrum AG affirms the patient's right to protection against invasion of privacy and to be in compliance with ICH-GCP and other local regulations (whichever is more stringent). Swedish Orphan Biovitrum AG requires the Investigator to permit Swedish Orphan Biovitrum AG representatives and when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws (any copies of patients' records must be duly anonymized to protect patients' confidentiality).

Should direct access to medical records require a waiver or authorization separate from the patient's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

12.5 PROTOCOL AMENDMENTS

Substantial amendments will be submitted to the IRB/IEC/REB for written approval and where applicable to National Competent Authorities. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC/REB should specifically reference the Principal Investigator's name, protocol number, study title and amendment number(s) that is/are applicable.

12.6 APPROVAL OF THE CLINICAL STUDY PROTOCOL AND AMENDMENTS

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB/IEC/REB with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Swedish Orphan Biovitrum AG can only supply study drug to an Investigator after Swedish Orphan Biovitrum AG or their authorized representative has received documentation on all ethical and legal requirements for starting the study. This documentation must also include a list of the members of the

IRB/IEC/REB and their occupation and qualifications. If the IRB/IEC/REB will not disclose the names of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. Formal approval by the IRB/IEC/REB should mention the study title, study code, study site, and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member (chairman or secretary of the IRB/IEC/REB. Before the first patient is enrolled in the study, all ethical and legal requirements must be met.

The IRB/IEC/REB and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The Investigator must keep a record of all communication with the IRB/IEC/REB. This statement also applies to any communication between the Investigator and regulatory authorities.

All documents handed over to patients or their legal representative prior to use must first be reviewed and approved by Swedish Orphan Biovitrum AG, and upon approval by Swedish Orphan Biovitrum AG submitted to and reviewed and approved by, the competent IRB/IEC/REB. This includes but is not limited to the informed consent form, patient information sheet, assent form, advertisements, training materials, etc.

12.7 ONGOING INFORMATION FOR IRB/IEC/REB

If required by legislation or the IRB/IEC/REB, the Investigator must submit to the IRB/IEC/REB:

- Information on SAEs, SUSARs, or any other safety measure, as per local applicable rules and timelines;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects

12.8 CLOSURE OF THE STUDY

Swedish Orphan Biovitrum AG reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB/IEC/REB, regulatory authorities).

In addition, Swedish Orphan Biovitrum AG reserves the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Significant non-compliance with contractual enrolment timelines and targets
- Serious or continued GCP non-compliance
- Inaccurate, incomplete or delayed data collection
- Failure to adhere to the study protocol
- Failure to provide requested follow-up information for data queries

12.9 RECORD RETENTION

The Investigator will ensure that essential records are kept in a secure archiving facility for the retention period stipulated in the study contract and should maintain a record of the location(s) of the essential documents. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects
- Subject identification code list, screening log (if applicable), and enrolment log
- Record of all communications between the Investigator and the IRB/IEC/REB
- Composition of the IRB/IEC/REB
- Record of all communications between the Investigator, Swedish Orphan Biovitrum AG and their authorized representative
- List of sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties, together with their roles in the study, curricula vitae and their signatures
- Copies of CRFs and of documentation of corrections for all subjects
- "Drug accountability" records
- Record of any body fluids or tissue samples retained
- All other source documents (subject records, hospital records, laboratory records, etc.)
- All other documents, as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, the Investigator must ask Swedish Orphan Biovitrum AG for permission to make alternative arrangements. Details of these arrangements should be documented in the clinical trial center's TMF.

12.10 LIABILITY AND INSURANCE

Liability and insurance provisions for this study are provided in the Investigator contract.

12.11 FINANCIAL DISCLOSURE

Investigators are required to provide financial disclosure information to allow Swedish Orphan Biovitrum AG to submit complete and accurate certification or disclosure statements in accordance with applicable national and local regulations, including FDA CFR21 requirements. In addition, Investigators must provide Swedish Orphan Biovitrum AG with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

12.12 DISCLOSURE OF PROTOCOL AND STUDY RESULTS AND PUBLICATION POLICY

Information about this trial will be posted following the principles of the International Committee of Medical Journal Editors (ICMJE), the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) Industry Position Paper and applicable national or regional regulations and laws.

Swedish Orphan Biovitrum AG will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Swedish Orphan Biovitrum AG will support publication of multicenter trials only in their entirety and not as individual center data.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements. Any formal publication of the study in which contribution of Swedish Orphan Biovitrum AG personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Swedish Orphan Biovitrum AG personnel.

So-called 'ghost writing' is not permitted. All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chairperson who provided only general support.

The results of this study may be presented at scientific meetings. If this is foreseen, the Investigator agrees to submit abstracts to Swedish Orphan Biovitrum AG prior to submission. This allows Swedish Orphan Biovitrum AG to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of Swedish Orphan Biovitrum AG, except where agreed otherwise.

13 MONITORING AND AUDITING

All aspects of the study will be monitored by Swedish Orphan Biovitrum AG or its representative for this study (Swedish Orphan Biovitrum AG authorized representative), for compliance with applicable government regulations with respect to current GCP and standard operating procedures. Direct access to the on-site study documentation and medical records must be ensured.

13.1 STUDY MONITORING AND SOURCE DATA VERIFICATION

As part of the responsibilities commensurate with participating in the study, the Investigator agrees to maintain and have available for monitoring, adequate case records (accurate source documents and CRFs) for the patients treated under this protocol. In addition, the Investigator agrees to maintain all administrative documents (e.g., IRB/IEC/REB correspondence, investigational product and supplies shipment manifests, monitoring logs, or correspondence with Swedish Orphan Biovitrum AG and with any of its representative for this study). When a copy is used to replace an original document, the copy should fulfil the requirements for certified copies.

The Investigator/institution should maintain a record of the location(s) of the essential documents. The storage system (irrespective of the media used) should provide for document identification, search and retrieval.

13.2 ON-SITE AUDITS

Investigators and institutions involved in the study will permit trial-related monitoring, audits, IRB/IEC/REB review, and domestic or foreign regulatory inspection(s) by providing direct access to source documents, CRFs, and all other study documentation.

The Investigator should promptly notify Swedish Orphan Biovitrum AG of any inspections scheduled by any regulatory authorities and promptly forward to Swedish Orphan Biovitrum AG copies of any audit reports received.

13.3 SERIOUS GCP BREACHES

Swedish Orphan Biovitrum AG is required to report a serious GCP Breach within 7 days of awareness of the breach to applicable health authorities.

A serious GCP breach is a breach likely to affect to a significant degree the safety (both physical and mental) and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

Therefore, should an Investigator become aware of a possible serious GCP breach, e.g., an important protocol deviation, or non-reporting of critical safety information that has the potential of jeopardizing patients' safety, Swedish Orphan Biovitrum AG must be notified within 24 hours.

14 DOCUMENTATION AND USE OF STUDY FINDINGS

14.1 DOCUMENTATION OF STUDY RESULTS

An eCRF is used in this study and a specific eCRF will correspond to each subject.

All required information must be entered on the eCRFs. If an item is not available or is not applicable, this fact should be indicated and no blank spaces must be left. The data collected on the eCRF will be entered into the study database. If the Investigator authorizes other personnel to enter data into the CRF, the names, positions, signatures, and initials of these persons must be supplied to Swedish Orphan Biovitrum AG or their authorized representative before these individuals start completing CRF information.

Swedish Orphan Biovitrum AG will ensure that the Investigator has control of and continuous access to the eCRF data reported to the Sponsor. Swedish Orphan Biovitrum AG will not have exclusive control of those data.

The eCRF pages must be reviewed and signed by the Investigator named in the study protocol or by a designated sub-Investigator. Swedish Orphan Biovitrum AG will ensure that the CRF copies left with the Investigator (print-outs and/or CD-ROM) are an exact copy of the data maintained in the database.

14.2 USE OF COMPUTERIZED SYSTEMS AT THE CLINICAL TRIAL CENTRE

When clinical information of patients are entered directly into an investigational site's computerized medical record system (electronic Health Records System; i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable electronic Health Records System allows preservation and integrity of the original entry of data by ongoing review, change control processes and audit trails. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, the name of the person making the change, the date and the hour of the change. The investigator should be able to demonstrate medical oversight of the trial when electronic Health Records Systems are used, e.g. verifying entries of study nurses on ongoing basis.

The system must allow the sponsor, clinical research associates, auditors or inspectors to verify source data without infringing privacy rights of other patients, e.g., access must be restricted to records pertaining to the study patients and access to other patients must not be possible. This should include

access to the audit trail. If the electronic Health System does not comply with these requirements, the sponsor reserves the right to be provided with paper print outs from the System containing the same information as the electronic original records.

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16 APPENDICES

Appendix A – QOL questionnaires: PedsQL™, Pediatric Quality of Life Inventory™ (link to examples of questionnaires)

Appendix B – QOL questionnaires: BASES

Appendix C – Eligibility Review Form

Appendix D – Pre-Screening Checklist

Appendix E – Dose Notification Form

APPENDIX A QOL QUESTIONNAIRES

PedsQL™, Pediatric Quality of Life Inventory™:

- Infant, version 1.0, Parent Report for Infants (ages 1-12 months)
- Infant, version 1.0, Parent Report for Infants (ages 13-24 months)
- Core, version 4.0, Parent Report for Toddlers (ages 2-4)
- Core, version 4.0, Young Child Report (ages 5-7)
- Core, version 4.0, Parent Report for Young Children (ages 5-7)
- Core, version 4.0, Child Report (ages 8-12)
- Core, version 4.0, Parent Report for Children (ages 8-12)
- Core, version 4.0, Teenager Report (ages 13-18)
- Core, version 4.0, Parent Report for Teenagers (ages 13-18)
- Core, version 4.0, Young Adult Report (ages 18-25)
- Core, version 4.0, Parent Report for Young Adults (ages 18-25)

http://www.pedsql.org

APPENDIX B QOL QUESTIONNAIRES

BASES (Behavioral, Affective and Somatic responses to pediatric BMT)

Bases-R: Parent Report

Subject ID: _____ **Date:** _____

Please complete the following ratings, based on how your child has been feeling and behaving over the past day (in the last 24 hours). Please circle your answer.

Physical Discomfort	**None**	**Mild**	**Mild-Moderate**	**Moderate-Severe**	**Severe**
1. Nausea/Vomiting	1	2	3	4	5
2. Mouth Sores	1	2	3	4	5
3. Loss of appetite	1	2	3	4	5
4. Tired/Run down	1	2	3	4	5
5. Overall level of discomfort	1	2	3	4	5
Cooperation/Compliance	**Very cooperative**	**Cooperative**	**Neutral**	**Uncooperative**	**Very uncooperative**
6. Taking medicines or doing mouth care	1	2	3	4	5
7. Bath or sitz bath	1	2	3	4	5
8. Hickman line care	1	2	3	4	5
9. Vital signs/physical exam	1	2	3	4	5
10. Overall level of cooperation	1	2	3	4	5
Mood/Behavior	**Very much like this**	**Somewhat like this**	**Neutral**	**Somewhat unlike this**	**Very much unlike this**
11. Sad/subdued	1	2	3	4	5
12. Withdrawn	1	2	3	4	5
13. Fearful/Anxious	1	2	3	4	5
14. Angry/Irritable	1	2	3	4	5
15. Complaining/Demanding	1	2	3	4	5
16. Restless/Fidgety	1	2	3	4	5
	Very negative	**Negative**	**Neutral**	**Positive**	**Very positive**
17. Overall Mood	1	2	3	4	5

Quality of interactions	**Very positive**	**Positive**	**Neutral**	**Negative**	**Very negative**
18. How did your child get along with staff today?	1	2	3	4	5
19. How did you and your child get along today?	1	2	3	4	5
20. In general, what was the quality of your child's interactions with others today?	1	2	3	4	5
Activity/Sleep	**Not at all; sleeping most of the time, watching TV**	**Not very active; mostly sleeping**	**A little active; sitting up in bed**	**Fairly active;** **Out of bed**	**Very active; energetic**
21. Please circle the number which best describes your child's activity level today:	1	2	3	4	5
	No problems, sleeping very well		**Some difficulty**		**Much difficulty, sleeping poorly**
22. To what extent has your child experienced difficulty sleeping (for example, days/night reversed, nightmares, can't sleep)	1	2	3	4	5

BASES – R, Nurse Report

Subject ID: _____ **Date:**_____

Please rate the patients' behavior based on your observations from the past shift, as well as reports from earlier shifts. Note that the meaning of the 5-point scale changes for some groups of items.

PHYSICAL DISCOMFORT	**None**	**Mild**	**Mild-Moderate**	**Moderate-Severe**	**Severe**
1. Nausea/Vomiting	1	2	3	4	5
2. Mucositis	1	2	3	4	5
3. Appetite Loss	1	2	3	4	5
4. Fatigue/Malaise	1	2	3	4	5
5. Overall level of discomfort	1	2	3	4	5
COOPERATION/COMPLIANCE	**Very cooperative**	**Cooperative**	**Neutral**	**Uncooperative**	**Very uncooperative**
6. Taking medicines or doing mouth care	1	2	3	4	5
7. Bath/sitz bath	1	2	3	4	5
8. Hickman line care	1	2	3	4	5
9. Vital signs/physical exam	1	2	3	4	5
10. Overall level of cooperation	1	2	3	4	5
MOOD/BEHAVIOR	**Very much like this**	**Somewhat like this**	**Neutral**	**Somewhat unlike this**	**Very much unlike this**
11. Sad/subdued	1	2	3	4	5
12. Withdrawn	1	2	3	4	5
13. Fearful/Anxious	1	2	3	4	5
14. Angry/Irritable	1	2	3	4	5
15. Complaining/Demanding	1	2	3	4	5
16. Restless/Agitated	1	2	3	4	5
	Very negative	**Negative**	**Neutral**	**Positive**	**Very positive**
17. Overall Mood	1	2	3	4	5
QUALITY OF INTERACTIONS	**Very positive**	**Positive**	**Neutral**	**Negative**	**Very negative**
18. Quality of patient-staff interaction this shift	1	2	3	4	5

19. Quality of patient-parent interaction this shift	1	2	3	4	5
20. In general, quality of patient interactions with others this shift	1	2	3	4	5
ACTIVITY/SLEEP	**Very little activity; almost always asleep**	**Frequent sleeping; passive activity (e.g. watching T.V.)**	**Mostly awake but in bed; quiet activities (e.g. drawing, puzzles)**	**Fairly active; interactive games; out of bed**	**Very active; physical play; energetic**
21. Please circle the number which best describes the patient's activity level today:	1	2	3	4	5
	No problems, sleeping very well		**Some difficulty**		**Much difficulty, sleeping poorly**
22. Rate the extent of patient's problems/ difficulties sleeping (e.g., days/night reverses, nightmares, can't sleep)	1	2	3	4	5

APPENDIX C ELIGIBILITY REVIEW FORM

Institution

Institution name and location:	
Treating physician:	

Patient information

Patient ID*:* *assigned sequentially*	
Age:	
Gender	☐ Male ☐ Female
If patient is a female, is she pregnant or lactating?	☐ Yes ☐ No ☐ Not applicable (patient is not a female)

Primary HLH diagnosis

Age at diagnosis of HLH:	
Date of diagnosis of HLH:	*DD/MMM/YYYY*

HLH-2004 criteria *(please indicate the values)*

☐ Fever	
☐ Splenomegaly	
☐ Cytopenias affecting 2 of 3 lineages (hemoglobin < 90 g/L; platelets <100 x 109/L; neutrophils < 1 x 109/L)	
☐ Hypertriglyceridemia (fasting triglycerides ≥ 3 mmol/L or ≥ 265 mg/dL) and/or hypofibrinogenemia (≤ 1.5 g/L)	

☐ Hemophagocytosis in bone marrow, spleen or lymph nodes	
☐ Low or absent NK-cell activity	
☐ Ferritin ≥ 500 µg/L	
☐ Soluble CD25 ≥ 2400 U/mL	

What elements led you to suspect primary HLH:

☐ Molecular diagnosis: *Indicate mutated gene and/or functional testing suggestive of pHLH*	
☐ Family history consistent with pHLH *Briefly describe affected relatives and their disease features, as available*	
☐ Other elements *Specify what other elements contributed to adjudication of primary nature of the disease, e.g. presentation during infancy, reactivations*	

Exclusion of secondary HLH:

☐ Rheumatic disease *Please indicate any known or suspected rheumatic conditions*	
☐ Metabolic disease *Please indicate any known or suspected metabolic conditions*	
☐ Neoplastic disease *Please indicate any known or suspected neoplastic diseases*	

Do you assess patient's HLH disease as active?

☐ Yes	

Indicate which disease features contribute most to overall disease activity	
• If patient reactivated following initial response to therapy, please indicate at least two clinical / laboratory criteria that worsened, and/or new or recurrent CNS symptoms	
☐ No	

Did the patient already receive any therapy for HLH?

☐ No	
☐ Yes:	
• Please describe therapy that patient received since HLH diagnosis	
• Please describe patient's response to this therapy	
• Does the patient have any contraindications to continuation of this therapy? (e.g. adverse reactions, intolerance, benefit/risk concerns)	☐ No
	☐ Yes

Overall patient's condition and infectious status

Patient's general condition	
Cardiovascular function	
Pulmonary function	
CNS function	
Liver function	
Renal function	
Other important concomitant diseases	☐ Yes (specify):
	☐ No
• recently resolved and ongoing infections (indicate duration and severity)	☐ Yes (specify):
	☐ No

Treatments / procedures ongoing at the time of request (other than HLH treatments)	
☐ Biologics	
☐ Transfusions	
☐ G-CSF	
☐ Antibioticotherapy	
☐ Antifungal treatments	
☐ Antiviral treatments	
☐ Cardiorespiratory support	
☐ Renal replacement therapy	
☐ Other	
Vaccinations within prior 12 weeks:	☐ Yes (specify):
	☐ No
Has the presence of active or latent TB infection been excluded?	☐ Yes (specify):
	☐ Waiting for test results. There are no clinical findings suggestive of this infection.
	☐ No
Has the presence of atypical mycobacterial infection been excluded?	☐ Yes (specify):
	☐ Waiting for test results. There are no clinical findings suggestive of this infection.
	☐ No
Has the presence of *Histoplasma capsulatum* infection been excluded?	☐ Yes (specify):
	☐ Waiting for test results. There are no clinical findings suggestive of this infection.
	☐ No
Has the presence of *Shigella, Salmonella, Campylobacter* infection been excluded?	☐ Yes (specify):
	☐ Waiting for test results. There are no clinical findings suggestive of these infections.
	☐ No
	☐ Yes (specify):

Has the presence of *Leishmania* infection been excluded?	☐ Waiting for test results. There are no clinical findings suggestive of this infection.
	☐ No

Does the patient have history of hypersensitivity or allergy to any of the following components of the study regimen?

☐ Emapalumab
☐ L-histidine
☐ L-histidine monohydrochloride, monohydrate
☐ Sodium chloride
☐ Polysorbate 80
☐ NONE OF THE ABOVE

By signing this document I confirm that that the above provided patient data are accurate and can be shared with Swedish Orphan Biovitrum AG.

Enter date

Investigator's name and signature *Date*

APPENDIX D PRE-SCREENING CHECKLIST

Date of assessment: _____

Patient Identifier (initials, complete or incomplete date of birth, other identifier as per your local regulations): _____

PATIENT MUST HAVE	
• Primary HLH:	☐
○ Diagnosed at the age of 0-18 years	☐
○ Molecular diagnosis, ○ OR family history consistent with HLH, ○ OR 5/8 HLH-2004 diagnostic criteria*	☐
• Active HLH disease	☐
• If already received HLH conventional therapy (applicable outside of US): ○ no response, ○ OR unsatisfactory response, ○ OR worsening, ○ OR reactivation**, ○ AND/OR intolerance	☐

***HLH-2004 diagnostic criteria (5/8 required)** ☐Fever ☐Splenomegaly ☐Cytopenias affecting 2 of 3 lineages (HGB <90 g/L; PLT <100 x 10^9/L; NEU <1 x 10^9/L) ☐Hypertriglyceridemia (fasting TG ≥3 mmol/L or ≥265 mg/dL) and/or hypofibrinogenemia (≤1.5 g/L) ☐Hemophagocytosis in bone marrow, spleen or lymph nodes, with no evidence of malignancy ☐Low or absent NK-cell activity ☐Ferritin ≥500 µg/L ☐Soluble CD25 (sCD25; i.e., soluble IL-2 receptor) ≥2400 U/mL	****Abbreviated definition of reactivation (1/2 required)** ☐ Deterioration of at least two of the below parameters over three days • Platelets • Neutrophils • Fibrinogen • Ferritin • sCD25 (i.e., soluble IL-2 receptor) ☐ Development of new or recurrent CNS symptoms (single criterion)

PATIENT MUST NOT HAVE	
• Secondary HLH consequent to proven ○ rheumatic, ○ metabolic, ○ neoplastic disease	☐
• Active infections ○ Mycobacteria ○ Histoplasma capsulatum ○ Shigella ○ Salmonella	☐

○ Campylobacter ○ Leishmania	
• Latent tuberculosis	☐
• Malignancy	☐
• Another disease or malformation that may impact likelihood to respond or assessment of safety or efficacy, severely affecting ○ cardiovascular, ○ pulmonary, ○ CNS, ○ liver, ○ kidney function	☐
• Hypersensitivity or allergy to any component of the study regimen: ○ emapalumab ○ polysorbate 80 ○ L-histidine ○ L-histidine monohydrochloride, monohydrate ○ sodium chloride	☐
• BCG vaccination within 12 weeks prior to Screening	☐
• Any other live or attenuated live vaccine within 6 weeks prior to Screening	☐
• Pregnancy or lactation	☐

To be completed after patient's consent

Was this patient consented? ☐ Yes

☐ No

If YES, please record patient ID

_____

If NO: ☐Patient did not meet eligibility criteria (above)

☐Other reason, specify:

_____

_____

APPENDIX E DOSE NOTIFICATION FORM

PART A

Dose of emapalumab	
☐ Unchanged at mg/kg	
☐ Decreased to mg/kg	
☐ ***Increased to mg/kg***	*Please complete the below fields*

Reasons for deciding to increase emapalumab dose

☐ Dose increase to 6 mg/kg	☐ Dose increase to 10 mg/kg
The improvement in the patient's clinical conditions is unsatisfactory based on the followings:	*There was an initial benefit after the previous dose increase, <u>however</u> the improvement in patient's clinical conditions is unsatisfactory based on the followings:*
☐ patient's overall performance and well-being status has not ameliorated as expected	☐ patient's overall performance and well-being status has not ameliorated as expected
☐ CNS signs and symptoms due to HLH remained unchanged or worsened	☐ CNS signs and symptoms due to HLH remained unchanged or worsened
☐ liver HLH involvement remained unchanged or worsened	☐ liver HLH involvement remained unchanged or worsened
☐ there is a clinically relevant increase of absolute lymphocyte count	☐ there is a clinically relevant increase of absolute lymphocyte count
☐ there is a substantial increase of sIL2Ra levels	☐ there is a substantial increase of sIL2Ra levels
☐ other, specify:	☐ other, specify:
<u>AND</u> at least one of the following criteria are met:	*<u>AND</u> at least one of the following criteria are met:*
☐ Fever: persistence or reoccurence	☐ Fever: persistence or reoccurence
☐ Platelet counts: lack of normalization (i.e. >100 x 10^3/mcl) or worsening	☐ Platelet counts: lack of normalization (i.e. >100 x 10^3/mcl) or worsening
☐ ANC: lack of normalization (i.e. >1000 count/mcl) or worsening	☐ ANC: lack of normalization (i.e. >1000 count/mcl) or worsening
☐ Ferritin: less than 30% decrease or worsening	☐ Ferritin: less than 30% decrease or worsening
☐ Splenomegaly: worsening	☐ Splenomegaly: worsening
☐ Coagulopathy (D-dimer OR fibrinogen): lack of normalization (i.e. D-dimer <1.0 mcg/mL and fibrinogen >150 mg/dL) or worsening	☐ Coagulopathy (D-dimer OR fibrinogen): lack of normalization (i.e., D-dimer <1.0 mcg/mL and fibrinogen >150 mg/dL) or worsening

PART B *if no additional HLH treatments is considered, please tick this box* ☐

Additional HLH treatments	
☐ Etoposide*	Emapalumab treatment is
☐ *Another HLH treatment*:*	☐ continued ☐ discontinued
If other than etoposide drug was chosen, please specify the reasons:	
☐ medical history records indicating poor response to etoposide ☐ medical history records indicating intolerance to etoposide ☐ other, specify:	

** Please complete the below fields*

Reasons for deciding to administer an additional HLH treatment

Unsatisfactory HLH control

☐ patient has not achieved a disease control and general clinical conditions that would allow him/her to proceed to transplant

☐ patient has not maintained a disease control and general clinical conditions that would allow him/her to proceed to transplant

☐ patient has presented a clinically relevant worsening

☐ other**, specify:

AND the following benefit/risk considerations have been made:

☐ another HLH treatment is expected to improve HLH control to rapidly move to transplant

☐ applied emapalumab dose increases have not achieved the desired HLH control

☐ another HLH treatment may be helpful to control disease activity since no previous chemotherapy/broad immunosuppression has been administered

☐ side effects of the additional HLH treatment do not seriously preclude its administration

☐ other**, specify:

***Please use the free text field for any additional information that can further elucidate your decision*