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

Protocol Number: **Sobi.EMAPALUMAB-104**

Version 2.0, 01 Jun 2022

Sponsor: Swedish Orphan Biovitrum AB

Type of Study: **Therapeutic Use, Phase 4**

Sponsor's Medical Director	Principal Coordinating Investigator
[redacted]	[redacted]
Signature Date	Signature Date

Investigator statement

I have read the protocol entitled "An Open Label, Single Arm, Multi-Centre, Post-authorization Study to describe the safety and efficacy of Emapalumab for the Treatment of Primary Hemophagocytic Lymphohistiocytosis in Treatment Experienced Chinese Patients" and the accompanying current investigator's brochure. I agree to conduct the clinical investigation in compliance with the Final Protocol, Version version 2.0, 01 Jun 2022, the International Council for Harmonisation (ICH) harmonised guideline E6(R2): Guideline for Good Clinical Practice (GCP) [1], applicable regulatory/government regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki [2]. I will not implement any changes to study procedures or conduct without prior approval from the sponsor and, when applicable, the Independent Ethics Committee/Institutional Review Board and Regulatory Authority. I will supervise any individual or party to whom I delegate study-related duties and functions conducted at the study site and ensure qualification of individuals or parties who perform delegated tasks.

I agree to maintain the confidentiality of this study protocol, as described on the title page. Further, I will not publish results of the study without authorization from Swedish Orphan Biovitrum.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

Table of contents

Table of figures

Table of tables

Synopsis

STUDY IDENTIFIERS	
Title of study:	An Open Label, Single Arm, Multi-Center, Post-authorization Study to describe the safety and efficacy of Emapalumab for the Treatment of Primary Hemophagocytic Lymphohistiocytosis in Treatment Experienced Chinese Patients
Clinical study number:	Sobi.EMAPALUMAB-104
Type of study:	Therapeutic use, Phase 4
STUDY OBJECTIVES	
Primary objective:	To collect safety data on emapalumab in treatment-experienced Chinese pHLH patients
Secondary Objective:	To collect efficacy data on emapalumab in treatment-experienced Chinese pHLH patients
STUDY ENDPOINTS	
Primary endpoint:	• Permanent discontinuation of study drug due to emapalumab-related adverse events as judged by the investigator
Secondary endpoints supporting the primary objective:	• Treatment-emergent adverse events (AEs) • Treatment-emergent serious adverse events (SAEs) • Treatment emergent laboratory abnormalities, • Treatment-emergent vital sign abnormalities.
Secondary endpoints supporting the secondary objective:	• Overall Response, i.e., achievement of either Complete or Partial Response or HLH Improvement, at EOT or Week 8 (whichever occurs earlier). • Time to first Overall Response, i.e., time from the date of first dose of emapalumab to the first achievement of response (Complete or Partial Response or HLH Improvement) • Cumulative duration of response, i.e., total time in response from the first achievement of an Overall Response until EOT • Ability to reduce glucocorticoids by 50% or more of the baseline dose during emapalumab treatment • Investigator assessed response • Survival: o To start of HSCT conditioning, i.e., time from the date of first dose of Emapalumab to date of death, with censoring at conditioning for HSCT or at last date of contact for patients who did not undergo conditioning for HSCT o After HSCT, i.e., time from HSCT to death, with censoring time at last date of contact for patients with no event. Only patients undergoing HSCT will be included in the analysis
Exploratory endpoint supporting the secondary objective:	[redacted]

STUDY DESIGN AND METHODS

Study design:	This will be an open-label, single-arm, multi-center study to collect safety and efficacy data on emapalumab in treatment-experienced male and female patients diagnosed with pHLH.
Number of patients planned:	At least 10 and up to 18 patients
Diagnosis and main criteria for inclusion:	Male and female HLH patients of any age. Patients diagnosed with confirmed or suspected pHLH defined by; a molecular diagnosis or familial history consistent with pHLH or fulfilment of at least five out of eight HLH-2004 diagnostic criteria Presence of active disease Presence of at least one of the following criteria, as assessed by the Investigator: • Unsatisfactory or no response to conventional therapy • Worsening on conventional therapy • Reactivation after initial response to conventional therapy • Intolerance to conventional therapy Expectation of survival beyond 1 week as judged by the investigator Patient has expectation of proceeding to HSCT
Main criteria for exclusion:	Diagnosis of secondary HLH consequent to a proven rheumatic, metabolic or neoplastic disease. Active mycobacteria, Histoplasma capsulatum, Salmonella, or Leishmania infections. Evidence of latent tuberculosis. Presence of malignancy. Existence of any severe co-morbidity or any other medical condition which, in the opinion of the investigator, makes the patient unsuitable for the treatment Receipt of a Bacillus Calmette-Guérin (BCG) vaccine within 12 weeks prior to Screening. Receipt of a live or attenuated live (other than BCG) vaccine within 4 weeks prior to Screening. Pregnant or lactating female patients.
Assessments:	See schedule of events in Table 3 and Table 4
Test product; dose and mode of administration:	Emapalumab 5 mg/mL solution for intravenous infusion to be administered over a period of 1-2 hours in doses of 1, 3, 6 or 10 mg/ kg body weight twice weekly. Starting dose is 1mg/kg.
Reference product; dose and mode of administration:	Not applicable
Duration of treatment(s):	The duration of treatment is expected to last until HSCT.
Determination of sample size:	Sample size is not based on statistical considerations but the data from 10 up to 18 Chinese patients will add sufficient information to the safety and efficacy profile established during the global clinical development program for emapalumab in pHLH patients.
Statistical methods:	Safety and efficacy analyses will be conducted on the “All treated analysis set” which will comprise all patients who received at least one infusion of IMP.

2 Abbreviations and definition of terms

2.1 List of Abbreviations and definitions

Term	Definition
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
BP	Blood pressure
CBC	Complete blood count
CDASH	Clinical data acquisition standards harmonization
CDC	Complement dependent cytotoxicity
CDISC	Clinical data interchange standards consortium
CMV	Cytomegalovirus
CRO	Contract research organization
CRF	Case report form
CsA	Cyclosporine A
CSR	Clinical study report
EBV	Epstein-Barr virus
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
FDA	US Food and Drug Administration
GCP	Good clinical practice
GDPR	General data protection regulation
GPV	Global Pharmacovigilance & Patient Safety
HLH	Hemophagocytic lymphohistiocytosis
HSCT	Hematopoietic stem cell transplantation
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IFNγ	Interferon gamma
IgG	Immunoglobulin G
IGRA	Interferon gamma release assays
IMP	Investigational medicinal product
IRR	Infusion related reactions

IRS	Interactive response system
IT	Intrathecal
IV	Intravenous
JAK	Janus kinase
LCMV	Lymphocytic choriomeningitis virus
LPLV	Last patient last visit
ORR	Overall response rate
PD	Pharmacodynamic
pHLH	Primary hemophagocytic lymphohistiocytosis
PK	Pharmacokinetic
PRIME	Priority medicines
SAE	Serious adverse event
SD	Study day
SDTM	Study data tabulation model
Sobi	Swedish Orphan Biovitrum
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMDD	Target-mediated drug disposition
US	Ultrasound
VZV	Varicella zoster virus

3 Ethics

3.1 Independent ethics committee and/or institutional review board

It is the responsibility of the investigator to obtain approval of the study protocol, possible amendments and the written patient information and informed consent form from the IEC. The investigator should file all correspondence with the IEC. Copies of IEC correspondence and approvals should be forwarded to the CRO/Swedish Orphan Biovitrum (Sobi).

3.2 Ethical conduct of the study

This study will be conducted in compliance with this protocol, the ICH GCP [1], applicable regulatory requirements, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki) [2].

3.3 Patient information and consent

It is the responsibility of the investigator to give each patient and/or the patient's legally acceptable representative prior to any study-related activities, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The patients and/or the patient's legally acceptable representative must be informed about their right to withdraw from the study at any time without prejudice. The written patient information and/or informed consent form must not be changed without prior approval from Sobi. Before any revisions are implemented, the revised written patient information and/or informed consent form must also be approved by the IEC and assent form for patients not being able to provide full consent (i.e., minors).

It is the responsibility of the investigator to obtain signed informed consent/assent from all patients prior to any study-related activities. The patients should receive a copy of the written information and the signed informed consent form.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.

If approved by the IEC the task of obtaining informed consent can be delegated to an appropriately qualified site staff although the responsibility and the oversight of the procedure remains with the Investigator.

If approved by the IEC the consent process can be conducted remotely, outside of the study site without physical presence of the site personnel, for example by sending the patient information and informed consent form to the patient's home and answering questions via phone.

If remote consenting is used the Investigator should have methods in place to ensure that the informed consent process allows patients to ask questions and to prevent fraudulent use of remote/electronic signatures. Irrespective of where the consent process takes place, on-site or

remotely, the responsibility for obtaining informed consent remains with the Investigator and the study personnel to which responsibility has been appropriately delegated.

If a female study participant or a female partner of a male participant becomes pregnant during the study period a separate consent form should be collected before collecting any details on the pregnancy, its outcome and the birth and health of the baby, if required per local regulations.

4 Introduction

4.1 Background

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome of pathologic immune activation. HLH comprises primary (genetic/familial) HLH and secondary HLH (sHLH), both clinically described by a dysregulation of the immune system leading to a profound hypercytokinemia with deleterious consequences on various tissues and organs [3].

Primary HLH (pHLH) is a heterogeneous recessive disorder characterized by a severe impairment or absence of cytotoxic function by natural killer (NK) and CD8+ T cells with striking activation of the immune system. While pHLH is mostly seen in infancy and early childhood with an estimated prevalence in Europe of 1/50,000 live births [4], adult cases are described [5-7]. The incidence of HLH in China has not been reported in literature. The disease is invariably fatal if untreated, with a median survival of less than 2 months after diagnosis [8, 9].

Typical features of HLH are [10]:

- Prolonged fever
- Splenomegaly and hepatomegaly
- Cytopenia
- Hyperferritinemia
- Hypertriglyceridemia
- Hypofibrinogenemia
- Lymphohistiocytic infiltrate
- Hypercytokinemia.

There is mounting evidence supporting the pivotal pathogenic role of interferon gamma (IFNγ) in the development of both primary [11, 12] and secondary forms of HLH [13-16].

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 CD8+ T cells and IFNγ production, with many of the clinical and laboratory features of the human disease. When the high circulating levels of IFNγ are neutralized by 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 inhibition of many other cytokines had no impact on survival [11].

Further strengthening the importance of IFNγ in pHLH are the high concentrations of circulating IFNγ levels found in pHLH patients[3, 17, 18], with IFNγ levels above the upper limit of normal in all patients, and above 1000 pg/mL in 53.5% of the cases.

No drugs had been specifically developed and approved for the treatment of HLH until emapalumab was approved in the United States for the treatment of refractory, recurrent or progressive pHLH in November 2018. Nonetheless, during the last decades, experts in the field have established guidelines for the management of HLH patients [10, 19, 20].

The management of pHLH patients currently comprises the following steps [19, 21]:

- 8-weeks induction therapy based on a combination of glucocorticoids and etoposide, administered with or without cyclosporine A.
- Patients with central nervous system involvement receive intrathecal injection of methotrexate and glucocorticoids.
- Hematopoietic stem cell transplantation (HSCT).

The main goal of the induction therapy is to suppress the life-threatening inflammatory process that characterizes pHLH, enabling HSCT in those patients who require it [22]. HSCT is the only curative treatment for HLH associated with high penetrance genetic mutations [20].

Despite the adoption of the above guidelines, no significant improvement in mortality rates have been seen for pHLH during the last 20 years. The overall mortality rate for pHLH remains high, around 40%, as shown by the results of the HLH-1994 and of the HLH-2004 studies and as reported for the HIT study [20, 23, 24]. The known short- and long-term toxicities, in particular myelosuppression and immunosuppression, of the current treatment of HLH further contributes to the already high mortality [24, 25].

Currently, there is limited literature concerning the salvage therapy of patients with resistant or refractory disease, and there are no consensus guidelines regarding treatment options. [26]

Overall, there is a lack of adequate literature upon which to confidently base decisions regarding salvage therapy of HLH or predict outcomes of patients with refractory HLH. Prospective clinical trials of salvage and/or alternative therapies are urgently needed. [26]

The 2018 Expert Consensus on the Diagnosis and Treatment of Hemophagocytic Syndrome in China describes the DEP or L-DEP treatment protocol for salvage therapy. In this protocol, patients' response to the HLH-94 protocol should be evaluated after 2-3 weeks of initiating induction therapy, with salvage therapy begun if suboptimal response to first-line therapy. While there is no standardized recommendation for salvage therapy, a protocol combining liposomal doxorubicin, etoposide and methylprednisolone is described.

The efficacy of emapalumab administered with dexamethasone was assessed in an open-label, single-group, phase 2/3 study, involving European and North American patients who had received conventional therapy before enrollment (treatment experienced patients) and treatment

naïve patients who were 18 years of age or younger and had pHLH. The primary analysis of the study (cut off July 2017) included a total of 34 patients (27 treatment experienced patients and 7 treatment naïve patients). 63.0 % (95 % confidence interval 42 to 81 %) of the treatment experienced patients and 64.7 % (95 % confidence interval 46 to 80 %) of all treated patients (treatment experienced and treatment naïve) had a response; these percentages were significantly higher than the prespecified null hypothesis of 40% (P=0.02 and P=0.005, respectively). [27].

4.1.1 Emapalumab

4.1.1.1 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 [28-30]

4.1.1.2 Pre-Clinical data

4.1.1.2.1 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.

4.1.1.2.2 Toxicology

Binding and functional data demonstrated Rhesus and 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 version of the Investigator Brochure (IB).

4.1.1.3 Clinical Data

Since the start of the clinical development program for emapalumab, more than 100 patients have received emapalumab in clinical trials and through compassionate use. Furthermore, more than 130 patients have been treated to date in the US following Federal Food and Drug Administration (FDA) approval, and post-marketing surveillance has not revealed any additional safety concerns with the use of emapalumab.

Emapalumab has been granted Orphan Drug Designation in the United States (US) on 26 March 2010 and in Europe (EU) on 09 June 2010. Emapalumab has obtained Breakthrough designation in US on 11 March 2016 and PRIME designation in EU on 26 May 2016.
On 20 November 2018 the FDA approved emapalumab for the treatment of adult and pediatric (newborn and older) patients with pHLH with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.

The FDA approval was based on data from study NI-0501-03, interim data from the pivotal study NI-0501-04 and interim data from the long-term follow-up study NI-0501-05.

4.1.1.3.1 Study NI-0501-03

Study NI-0501-03 was a phase 1 randomized double-blinded placebo-controlled single ascending dose study, 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.

Emapalumab PK data from healthy volunteers were evaluated using a population modeling approach. The PK of emapalumab was best described by a two-compartment model (NI-0501-03 - Modelling and Simulation support to NI-0501 PK analysis of study NI-0501-03). In healthy

volunteers, emapalumab has the typical PK profile expected for a mAb, with low central and peripheral volumes of distribution (3.02 L and 2.83 L), slow clearance (0.007 L/h) and long distribution and terminal half-lives (1.55 and 25.4 days).

The infusions of emapalumab were well tolerated and the effects observed during the 8-week monitoring after drug infusion did not reveal any unexpected off target safety or immunogenicity concerns. One case of Herpes Zoster was reported as a serious adverse reaction in the highest dose group (3 mg/kg). This is considered a consequence of the expected pharmacological effect of emapalumab. Its intensity was moderate and healed with antiviral therapy. The subject recovered with no sequelae. An increased susceptibility to Herpes Zoster infections in patients having developed auto-antibodies against IFNγ [31] 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 [32].

In conclusion, the infusion of emapalumab was well tolerated and the effects observed during the 8-week monitoring after drug infusion, then extended up to week 44, did not reveal any serious or unexpected off-target safety or immunogenicity concerns. The tolerability/safety profile, as well as the PK characteristics observed after administration of emapalumab in healthy volunteers supported the continuation of the development program for emapalumab for the treatment of HLH.

4.1.1.3.2 Study NI-0501-04 and NI0501-05

Study NI-0501-04 was designed to investigate the safety and tolerability profile of multiple intravenous (IV) administrations of emapalumab and its efficacy in primary hemophagocytic lymphohistiocytosis (pHLH) patients. The evaluation of the pharmacokinetic (PK) profile and the pharmacodynamic (PD) effects of emapalumab is also an important objective of the study to define the appropriate therapeutic dose regimen for the treatment of pHLH patients. The study was conducted according to twin protocols in EU and in the US.

Study NI-0501-05 is a long-term, follow-up study that includes patients treated in Study NI-0501-04. Of note, HLH patients who received emapalumab treatment in the pilot NI-0501-06 study (patients with systemic Juvenile-onset Idiopathic Arthritis developing Macrophage Activation Syndrome) and in compassionate use (CU) were also followed-up long-term in this study. The objectives of the long-term follow-up NI-0501-05 study are the long-term monitoring of the safety profile in patients treated with emapalumab, the assessment of survival after emapalumab treatment, the assessment of emapalumab immunogenicity and the evaluation of its elimination profile.

The primary analysis for Study NI-0501-04 was completed on 20 July 2017 (last patient last visit, LPLV). A supplemental analysis for Study NI-0501-04 including 11 additional patients was completed on 04 January 2019. Study NI-0501-05 is ongoing.

In the primary analysis population, 34 patients were treated whereof 27 (79.4%) were treated as second-line (treatment-experienced) patients and 7 (20.6%) as first-line (treatment-naïve i.e., prior to starting emapalumab the sole medication received is dexamethasone at doses of 10 mg/m^2/day for not more than 7 days) patients. A total of 26 (76.5%) patients completed Study NI-0501-04, i.e.,

- completed emapalumab treatment, i.e., received a minimum of 4 weeks of treatment [from SD0 to end of treatment (EOT)] unless discontinued subsequently due to lack of efficacy or safety reason, and
- completed the 4-week short-term follow-up or continued treatment in the NI-0501-05 study.

In the primary analysis population 63.0 % (95 % confidence interval 42 to 81 %) of the treatment experienced patients and 64.7 % (95 % confidence interval 46 to 80 %) of all treated patients (treatment experienced and treatment naïve) had a response; these percentages were significantly higher than the prespecified null hypothesis of 40% (P=0.02 and P=0.005, respectively). In the treatment experienced group, 70% of the patients were able to proceed to transplantation, as were 65% of the all treated group. At the last observation, 74% of the treatment experienced patients and 71% of the patients who received emapalumab were alive.

The supplemental analysis efficacy endpoint in Study NI-0501-04, the Overall Response was 60.0% (27/45 patients) with exact 95% CI of 44.3%, 74.3% at EOT in the "All treated analysis set". The lower 95% CI is confirmed to be significantly higher than the pre-specified null hypothesis of 40%. These results were also supported by the investigator-assessed Overall Response, which was consistent with the primary efficacy analysis, to some extent more favorable. In the "All treated analysis set", the response was assessed in 30 (66.7%) patients compared to the 27 patients according to the protocol-defined algorithm.

The safety profile of emapalumab is favorable in this fragile, immunocompromised patient population, requiring high number of co-medications and procedures. Infusions were in general well tolerated, no anaphylaxis or severe hypersensitivity reaction have been associated with any emapalumab infusion, the infusion-related reactions (IRRs) being mild, self-limiting, and not requiring any treatment at any of the doses administered.

Infections caused by pathogens reported to be potentially favored by neutralization of IFNγ, occurred in 1 patient with Histoplasmosis disseminated during the course of emapalumab treatment, and in 1 patient with Salmonella gastroenteritis during the long term follow-up after HSCT; both infections resolved.

No patient reported Varicella or Herpes Zoster, including patients who could not receive the recommended anti-viral prophylaxis due to the presence of contraindications.

Emapalumab administration did not appear to be associated with any organ/function toxicity and emapalumab treatment was not discontinued as a result of any cardiac, respiratory, liver, or renal events.

4.1.1.3.3 Study NI-0501-09

Study NI-0501-09 is an ongoing phase 3 study in pediatric patients with confirmed or suspected pHLH who are either treatment-naïve, have failed conventional HLH therapy, or are intolerant to it. This study was initiated to gather additional safety and efficacy data on emapalumab, to assess the impact of emapalumab on quality of life indicators, and to evaluate a starting dose of 3 mg/kg.

As of 26 Feb 2021, 32 patients had been treated with emapalumab in the study. A total of 2 SAEs (acute respiratory failure and BCG adenitis) were assessed by the Investigator as possibly related to emapalumab, and one of which led to permanent emapalumab discontinuation (acute respiratory failure). Both events resolved. The reported SAEs generally reflected mortality and morbidity of the underlying pHLH and known complications, including events typically associated with HSCT. Based on the data collected so far, the tolerability and safety profile of emapalumab is consistent with previous observations in pHLH patients receiving emapalumab.

For more details on the clinical experience, see current IB.

4.2 Study rationale

Currently the diagnosis and first-line treatment of pHLH in China follows the HLH-2004 diagnostic criteria and the HLH-94 treatment protocol recommended by the Histiocyte Society and endorsed in the 2018 Expert Consensus on the Diagnosis and Treatment of Hemophagocytic Syndrome in China [21, 25]. Early assessment and salvage therapy is recommended in patients who do not respond. In a Chinese review paper, treatment suggestions and future research directions are described, and it is proposed that more attention should be paid to the treatment of refractory HLH. Refractory HLH accounts for 25% ~ 50% of all HLH patients [33]. These patients are in critical condition, with poor prognosis and high fatality rate, and treatment options are limited in clinical practice [33].

Given the reported high mortality rate in pHLH and the known toxicities of conventional therapies, the development of targeted therapies was warranted. Moreover, morbidity and mortality of patients with HLH remained significant in the HLH-94 and HLH-04 studies. Alternative treatment approaches are urgently needed and increasingly explored [34].

As there is limited experience of emapalumab in Chinese patients it is of interest to describe the safety and efficacy of emapalumab in Chinese patients diagnosed with pHLH and that have already received conventional HLH therapy (treatment experienced patients), without obtaining a satisfactory response according to the investigator or having shown signs of intolerance to it.

4.3 Potential risks and benefits

Emapalumab is approved by FDA since November 2018, for the treatment of patients with primary HLH who have refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.

Since the start of the clinical development program for emapalumab, more than 130 patients have received emapalumab in clinical trials and through compassionate use. Furthermore, it is estimated that more than 255 patients have received Gamifant® through commercial (market) distribution worldwide since the launch of the product, and post-marketing surveillance has not revealed any additional safety concerns with the use of emapalumab. Based on the analyses conducted to date, no sign of any off-target effect of emapalumab has been detected.

4.3.1 Potential benefits

Based on evidence available from comprehensive analysis of the NI-0501-04 and NI-0501-05 studies, emapalumab administration has shown the overall potential to improve or resolve relevant clinical and laboratory abnormalities of pHLH.

Also, in the cohort of the treatment experienced patients which corresponds to the patient population of the current study, emapalumab demonstrated a statistically significant and clinically relevant reduction in pHLH disease activity, the Overall Response Rate (ORR) was assessed through objective clinical and laboratory parameters as being 58.8% (20/34 patients). Response occurred early during treatment (the median time to response was 7.0 days) and was generally sustained. The median cumulative time at which the patients remained "in response" was 31.5 days and in 75% of patients the first response was maintained for at least 22 days. The reduction in HLH disease activity was sustained and was associated with an overall survival benefit that persisted following HSCT. 27 of 34 patients (79.4%) survived to HSCT and the post-HSCT survival probability estimates were 91% (95% CI: 68.3%, 97.6%) at 3 months and 89% (95% CI: 64%, 97%) at 1 year post-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.

4.3.2 Potential risks based on emapalumab's mechanism of action

Infusion related reactions and hypersensitivity:

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.

Cumulatively, among 108 subjects receiving emapalumab in clinical trials up to safety data cut-off point of 24-Aug-2020, no patient experienced anaphylactic or anaphylactoid reaction, including:

- Study NI-0501-03: Of 20 healthy volunteers participating in the study, 6 emapalumab and 2 placebo-treated subjects experienced IRRs. IRRs in subjects receiving emapalumab included ventricular tachycardia, paraesthesia, feeling cold, pyrexia, myalgia, and headache
- Study NI-0501-04: Of 45 patients participating in the study, a total of 12 patients (26.7 %) experienced at least one IRR. All were non-serious and, except for one which was moderate, all were mild and none of them led to emapalumab discontinuation. The majority were skin reactions (drug eruption 8.9 %; rash, 4.4 %; erythema, 4.4 % rash erythematous 2.2 %), hyperhidrosis (8.9 %), pyrexia (6.7 %), tachycardia (2.2 %) and lymphadenopathy (2.2 %).
- Study NI-0501-09: Of 26 patients participating in the study, one IRR (acute respiratory failure) was reported as serious, occurring during 8th emapalumab infusion, leading to permanent emapalumab discontinuation; it resolved with appropriate treatment. Two (2)

additional, non-serious IRRs of sinus tachycardia, one mild and one moderate were reported, both of which recovered within 24 hours.

From the clinical experience to date, the risk of IRRs associated with emapalumab treatment seems to be very low. Nevertheless, the infusion should be performed under medical supervision with monitoring of vital signs during and for 2 hours after emapalumab infusion as outlined in Section 6.5.6.1

Infections:

As emapalumab neutralizes IFNγ activity, emapalumab may increase the risk of infections caused by some specific pathogens potentially favored by IFNγ neutralization including mycobacteria (typical and atypical), salmonella, varicella zoster virus (VZV), and Histoplasma capsulatum. Study specific requirements should be followed for infections screening, prophylaxis, and monitoring.

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 [35, 36]. The mean age of the first environmental mycobacterial infection is 3.1 and 13.4 years in patients with complete and partial deficiency, respectively [37].

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*, VZV) [31].

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 active infections due to *Salmonella 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, cumulatively, among the 108 subjects receiving emapalumab in clinical trials up to the safety data cut-off point of 24-Aug-2020:

- Study NI-0501-03: One case of herpes zoster infection was reported in a healthy volunteer and recovered with antiviral treatment.
- Study NI-0501-04: One patient developed disseminated histoplasmosis which resulted in treatment discontinuation. The infection resolved with adequate antifungal therapy while emapalumab was still at measurable concentrations in the blood.
- Study NI-0501-09: One previously vaccinated patient developed BCG adenitis during the study, which resolved with appropriate therapy.

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

Therapeutic Protein-Drug Interactions (TP-DI):

The expression of CYP450 enzymes may be suppressed by increased levels of cytokines (such as IFNγ) during inflammation. By neutralizing IFNγ, the use of emapalumab may normalize CYP450 activities which may change the metabolism of drugs that are CYP450 substrates. The restoration of CYP activity may therefore alter the elimination of concomitant medications metabolized by these CYPs.

During the clinical trial program with emapalumab, no events of TP-DI were reported in pHLH patients treated with emapalumab.

Immunogenicity:

The immunogenicity of emapalumab has been evaluated in all prior clinical studies.
In the emapalumab development program in the studies completed up to safety data cut-off point of 24-Aug-2020 anti-drug antibodies (ADAs) against emapalumab have been detected in 4 subjects with no impact on safety or efficacy parameters:

- one out of 14 (or 7.1%) of healthy subjects participating in study NI-0501-03 after administration of a single dose of emapalumab
- three out of 43 (or 7%) patients with post-baseline test participating in study NI-0501-04 with 2 patients tested positive for neutralizing antibodies

Antibodies against emapalumab may potentially cause decreased efficacy, allergic reactions, or infusion related reactions. However, no adverse events, including decreased efficacy, attributable to antibodies have occurred. For the most recent information about emapalumab, please refer to the current IB. The current risk benefit analysis supports this clinical trial to assess Safety and tolerability of Emapalumab in Chinese Patients with pHLH

4.3.2.1 Risk minimization measures and safety monitoring

In view of the above reported considerations, the benefit/risk profile of emapalumab in children and adults 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, Salmonella, or Leishmania infections, or latent tuberculosis will not be included in the study (for details see Section 6.3.2). Patients who received live or attenuated vaccine within 4 weeks prior to screening are excluded from the studies with emapalumab.
- Monitoring of IRRs: The infusion related reactions will be closely monitored by the investigator. 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. Should severe allergic reactions (such as anaphylactic shock) occur, the patient would be managed according to the local standard treatment guidelines.
- Monitoring of infections is requested throughout the study. Type of investigation, specimen, result, and pathogen identified will be captured in the eCRF. Details see section 6.5.5.1.2
- Prophylaxis for Pneumocystis jirovecii, and for fungal infections for all patients according to local practice. Prophylaxis for Herpes Zoster for all patient 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 or prophylactic antimicrobial therapy will be introduced when deemed appropriate according to local practice, and proper monitoring of active pre-existing infections or emerging infections will be conducted.
- It’s not recommended to treat patients with emapalumab beyond 6 months as safety data to support treatment beyond 6 months is limited.

4.3.3 Confidentiality of personal data

The following risk mitigations are in place to maintain confidentiality of personal data collected within the study.

Personal data collected and processed in the study will be coded. (The coded personal data can only be directly traced back to a specific patient by using the code key. The code key will never leave the study site and only authorized personnel will have access to it.)

Any reports, publications or presentations resulting from the study will never contain personal data that directly identifies a patient.

As Sobi has it’s headquarter in Europe, personal data will be handled in accordance with the European data protection regulation, GDPR. It may be necessary that coded personal data are transferred to, or processed in, countries outside the EU/EEA, where the laws may not protect personal data to the same extent as the laws in the EU/EEA. When personal data are transferred to, or processed in such countries outside the EU/EEA, Sobi is responsible to take all reasonable steps to ensure that the level of protection and confidentiality of personal data is the same as required in the EU/EEA.

5 Study objectives and endpoints

5.1 Primary objective

- To collect safety data on emapalumab in treatment-experienced Chinese pHLH patients

5.1.1 Primary endpoint

- Permanent discontinuation of study drug due to emapalumab-related adverse events as judged by the investigator

5.1.2 Secondary endpoints supporting the primary objective

- Treatment-emergent adverse events (AEs)
- Treatment-emergent serious adverse events (SAEs)
- Treatment emergent laboratory abnormalities,
- Treatment-emergent vital sign abnormalities.

5.2 Secondary objective

- To collect efficacy data on emapalumab in treatment-experienced Chinese pHLH patients

5.2.1 Secondary endpoints supporting secondary objective

- Overall Response, i.e., achievement of either Complete or Partial Response or HLH Improvement, at EOT or Week 8 (whichever occurs earlier).
- Time to first Overall Response, i.e., time from the date of first dose of emapalumab to the first achievement of response (Complete or Partial Response or HLH Improvement)
- Cumulative duration of response, i.e., total time in response from the first achievement of an Overall Response until EOT
- Ability to reduce glucocorticoids by 50% or more of the baseline dose during emapalumab treatment
- Investigator assessed response
- Survival:
    - To start of HSCT conditioning, i.e., time from the date of first dose of Emapalumab to date of death, with censoring at conditioning for HSCT or at last date of contact for patients who did not undergo conditioning for HSCT

- After HSCT, i.e., time from HSCT to death, with censoring time at last date of contact for patients with no event. Only patients undergoing HSCT will be included in the analysis

5.2.2 Exploratory endpoint supporting the secondary objective

[redacted]

6 Investigational plan

6.1 Overall study design and plan

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

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

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

Figure 1 summarizes the study design.

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

Figure 1 Overview of the study design

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

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

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

First emapalumab infusion, at a dose of 1 mg/kg, marks the start of the treatment period. The treatment period is foreseen to continue until start of conditioning for HSCT, if deemed indicated for this patient. Infusions will take place twice weekly, at a dose determined by the Investigator for each infusion, as described in Section 6.4.4. Emapalumab will be administered on the background of dexamethasone, which can be tapered or increased as needed. No wash-out is required prior to conditioning for HSCT.

Last visit of the treatment period is the end of treatment, which occurs 3 days after the last infusion of emapalumab. Assessment of efficacy objectives occurs at end of treatment.

After the start of conditioning for HSCT (or treatment completion, if HSCT is not deemed indicated), the patient proceeds to follow-up period. Follow-up visits are planned in relation to the date of the HSCT, or last emapalumab infusion (if HSCT is not deemed indicated). Duration of the follow-up is one year after HSCT, or after the last emapalumab infusion.

The end of study visit (EOS) for each patient will occur at the latest 18 months from first dose of emapalumab.

Patient will be considered screened after informed consent is obtained.

6.1.1 Number of patients planned

The goal is to recruit at least 10 patients and up to 18 patients, if enrolled within the recruitment period, receiving at least one dose of emapalumab.

6.2 Discussion of study design, including the choice of control groups

Open-label, single arm design of this prospective study is chosen, considering extreme rarity of the disease under study, its life-threatening nature, and lack of licensed alternative therapeutic approaches for the patients who have already received conventional HLH therapy without satisfactory response, or developed intolerance to it. For the same reasons, sample size is not driven by the statistical calculations, but rather by pragmatic considerations.

HLH is a challenging condition to manage, and disease control is known to be impacted by intercurrent conditions, such as infections. This is reflected in the flexible dosing schedule, which is the basis of the current established emapalumab dosing regimen for pHLH. Background treatment with dexamethasone with at least 5 mg/m^2/day, or at the same dose administered prior to screening if higher, will be put in place. Additional HLH treatments (etoposide as a drug of choice) will be allowed, provided specific conditions, outlined in Section 6.4.5.2.3 are fulfilled.

It is expected that most patients with pHLH will proceed to HSCT whenever possible

Treatment duration, which is expected to last until start of conditioning for HSCT, has been defined based on previous experience and observed time required to proceed to HSCT; logistical considerations (e.g., donor unavailability) that may at times delay HSCT, were also considered. Treatment is thus allowed to be flexible but is not recommended to exceed 6 months.

Schedule of Assessments takes into consideration the limitations imposed by the expected young age of the patients, and a significant number of standard of care assessments and interventions that may be needed for HLH management. Windows are implemented to minimize the study burden.

6.3 Selection of study population

The study population comprises male and female treatment experienced Chinese patients of any age diagnosed with primary Hemophagocytic Lymphohistiocytosis (pHLH).

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

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

6.3.1 Inclusion criteria

A patient must fulfill the following criteria in order to be included in the study:

1. Male and female HLH patients of any age.
2. Patients diagnosed with confirmed or suspected pHLH, based on; 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 investigator.
4. Patients must fulfil one of the following criteria as assessed by the investigator:
    - Having not responded to previous conventional treatment of HLH
    - Having not achieved a satisfactory response to previous conventional treatment of HLH or worsened
    - Having reactivated [iii]
    - Showing intolerance to previous conventional treatment of HLH

    At the time of enrollment, eligible patients might still be receiving treatment (induction or maintenance) or might have already discontinued it.
5. Expectation of survival beyond 1 week as judged by the investigator.
6. Patient has expectation of proceeding to HSCT
7. 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.
8. Willing to use highly effective methods of contraception from study drug initiation to 6 months after the last dose of study drug, if female and of childbearing potential.

In case of use of oral contraception women should have been stable on the same brand (or generic equivalent) for a minimum of 3 months before taking study treatment. Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago.

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.

6.3.2 Exclusion criteria

The presence of any of the following will exclude a patient from inclusion in the study:

1. Diagnosis of secondary HLH consequent to a proven rheumatic, metabolic or neoplastic disease.
2. Active mycobacteria, Histoplasma capsulatum, Salmonella, or Leishmania infections.
3. Evidence of latent tuberculosis.
4. Presence of malignancy.
5. Existence of any severe co-morbidity or any other medical condition which, in the opinion of the investigator, makes the patient unsuitable for the treatment
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 4 weeks prior to Screening.
9. Pregnant or lactating female patients.
10. Enrollment in another concurrent clinical interventional study, or intake of an IMP, within three months prior to inclusion in this study
11. Any condition or circumstance that in the opinion of the Investigator may make the patient unlikely to complete the study or comply with study procedures or requirements.

6.3.3 Withdrawal of patients from treatment or study

6.3.3.1 Withdrawal from treatment or study

A patient should be withdrawn from the study for any one of the following reasons:

- if, in the opinion of the investigator, it is medically necessary
- if the patient or their legally authorized representative(s) withdraws consent
- if the patient enrolls into an interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered

There are no predefined rules for permanent study drug discontinuation based on the current safety profile of the drug. The Investigator can decide to interrupt or discontinue the treatment for his/her patient at any time during the study, based on his/her medical judgment taking into account the individual benefit/risk ratio for the patient. The Investigator may request a discussion with the Sponsor, if relevant prior to taking a decision; however, the ultimate decision remains the Investigator`s responsibility.

Pregnancy in a patient will lead to permanent discontinuation of study treatment.

The date of last IMP dose and the date and reason for treatment and/or study withdrawal should be clearly described in the relevant sections of the eCRF. If a patient is withdrawn because of an AE, the reason for withdrawal should always be stated as ‘adverse event’ irrespective of whether this was the investigator’s or the patient’s decision. All serious and non-serious AEs assessed by the investigator as related to the IMP should continue to be followed until they resolve or until the investigator assesses them as “chronic” or “stable”, even after the patient's participation in the study is over, but without further recordings into the eCRF.

After treatment discontinuation for any reason, patient should be invited to continue the follow-up period in the study, and every effort should be made to obtain the data collected at the End of Treatment and the follow-up visits as complete as possible.

In any case, withdrawal from the treatment and/or study will have no impact on the patient’s care and on further standard of care treatments administered to him/her after withdrawal.

6.3.4 Replacement of withdrawn patients

Patients withdrawn before first dose will be replaced. Withdrawn patients who received at least one dose of emaplaumab will not be replaced.

6.3.5 Specific restrictions/requirements

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 the last emapalumab treatment have elapsed.

All women who are physiologically capable of becoming pregnant, will have a ß-hCG test (serum pregnancy test) performed at screening, baseline and at EOT. Urine pregnancy tests will

be performed monthly during the treatment period and at the scheduled visits day 30, 60, 100, and 6 months after HSCT (or last emapalumab treatment if HSCT is not performed) in the follow-up period.

6.4 Treatments

6.4.1 Investigational medicinal product

Emapalumab 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 the Sponsor and is supplied to study sites in 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
[redacted]	

The solution contains no antimicrobial preservative, and therefore each vial must be used only once. Further instructions on handling and storage of emapalumab are available in the Investigational Product Management Manual.

Table 1 Investigational medicinal products

Treatment	Dosage form	Route	Dose	Dosage regimen
emapalumab	Solution for infusion	i.v.	1, 3, 6, or 10 mg/kg	Every 3-4 days

6.4.2 Handling of investigational medicinal products

Possible deficiencies related to the handling and quality of the IMP(s) should be reported to the study monitor and also directly to [redacted]

Product accountability records will be kept. The pharmacy and investigator/head of site must maintain accurate records demonstrating date and amount of IMP received, to whom and by

whom administered or dispensed (patient-by-patient accounting), and accounts of used IMP and any IMP accidentally or deliberately destroyed. All unused IMP will be counted. At the end of the study, any remaining IMP will be returned to the depot for destruction. After destruction the depot will issue a certificate of destruction.

6.4.3 Selection of doses

Data from *in vitro* experiments investigating the binding kinetics of emapalumab to human IFNγ and the functional inhibition of human IFNγ by emapalumab have been used for predicting the concentrations of emapalumab expected to inhibit (e.g. 99%) the effect of circulating IFNγ concentrations.

These predictions were based on:

- the calculated neutralizing concentrations of emapalumab
- the PK parameters of emapalumab in healthy volunteers
- the PK information from recombinant IFNγ in humans.

Simulations were performed regarding the dose that would inhibit the effect of circulating and newly formed IFNγ by up to 99% over a period of 3 days in HLH patients.

Based on these simulations, the starting dose in HLH patients is 1 mg/kg. This dose is predicted to inhibit for 3 days at least 99% of IFNγ effect in patients with baseline IFNγ concentrations lower or equal to 3400 pg/mL. This dose is mainly driven by the estimated production of IFNγ which is expected to impact the clearance of emapalumab (due to target-mediated drug disposition) and varies considerably between patients.

These assumptions were confirmed in the clinical study NI-0501-04, which showed a wide range of baseline IFNγ concentrations observed in these patients. 13 (28.9 %) of 45 patients received the dose of 1 mg/kg every 3 to 4 days during the entire duration of the study; in some patients, the interval between infusions was elongated to 6-7 days. The dose of emapalumab was increased to 3-4 mg/kg in 11 patients (24.4 %) and 21 patients (46.7 %) received a dose of ≥6 mg/kg (up to 10 mg/kg). Among those 21 patients receiving a dose of ≥6 mg/kg, 10 patients (22.2 %) received a dose of 10 mg/kg on at least one occasion.

Due to the expected target-mediated drug disposition (TMDD) effect and to the high inter-individual variability of IFNγ concentrations in HLH patients, doses subsequent to the initial one can be increased in a step-wise fashion if required, as outlined in Table 2. This decision should be based on clinical and laboratory criteria, which are further outlined in Section 6.4.4 and Table 5.

6.4.4 Selection and timing of doses for each patient

Initial dose of emapalumab (Gamifant®) is 1 mg/kg and it will be administered by intravenous infusion over a period of 1 hour. Depending on the volume to infuse and the individual patient's condition, duration of infusion can be extended to maximum of 2 hours. Infusions will be

performed twice per week (not more than 4 days apart, e.g. every Monday / Thursday, or every Tuesday / Friday).

Dose increase may occur any time during the study, if the clinical and laboratory criteria listed in the Table 5 are met. Dose increase will occur in a stepwise manner, from 1 mg/kg to 3 mg/kg, from 3 mg/kg to 6 mg/kg, and from 6 mg/kg to 10 mg/kg.

After the patient's clinical condition is stabilized, decrease the dose to the previous level to maintain clinical response.

The duration of treatment is expected to last until start of conditioning for HSCT (if HSCT deemed necessary) or unacceptable toxicity, but is not recommended to exceed 6 months.

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

Table 2 Clinical and Laboratory Criteria to Guide Dose Increase

Study Visit	Emapalumab Dose	Criteria for Dose Increase
Day 1	1 mg/kg	N/A

Study Visit	Emapalumab Dose	Criteria for Dose Increase
Any visit from V2 onwards	Increase to 3 mg/kg	Upon an overall assessment by the Investigator that improvement in clinical conditions is unsatisfactory and presence of at least 1 of the following: • Fever – persistence or reoccurrence • Platelet count o If baseline <50,000/mm^3 and no improvement to >50,000/mm^3 o If baseline >50,000/mm^3 and less than 30% improvement o If baseline >100,000/mm^3 and decrease to <100,000/mm^3 • Neutrophil count o If baseline <500/mm^3 and no improvement to >500/mm^3 o If baseline >500 -1000/mm^3 and decrease to < 500/mm^3 o If baseline 1000-1500/mm^3 and decrease to <1000/mm^3 • Ferritin (ng/mL) o If baseline ≥3000 ng/mL and <20% decrease o If baseline <3000 ng/mL and any increase to >3000 ng/mL • Splenomegaly – any worsening • Coagulopathy (both D-dimer and Fibrinogen must apply) o D-Dimer – if abnormal at baseline and no improvement o Fibrinogen (mg/dL) ▪ If baseline levels ≤100 mg/dL and no improvement ▪ If baseline levels >100 mg/dL and any decrease to <100 mg/dL
Any visit from V3 onwards	Increase to 6 mg/kg	Previous dose was 3 mg/kg + same as above
Any visit from V4 onwards	Increase to 10 mg/kg	Previous dose was 6 mg/kg + Investigator assesses that based of initial signs of response, a further increase of emapalumab dose can be of benefit

6.4.5 Prior and concomitant therapy

A prior and concomitant therapy is any drug or substance administered from the screening visit until the EOS visit. The investigator must instruct patients and/or legal representatives to notify the study site about any new medications taken after the patient has been screened for the study. All medications, non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled must be recorded in the eCRF. Information about medication name, indication, dose, unit, frequency, route date and time is to be recorded for each medication.
Any conventional treatment for pHLH (including but not limited to plasmapheresis, HSCT) must be recorded, regardless of when it has been received.

No other medicinal product under investigation may be used concomitantly with the IMP in this study.

6.4.5.1 Background therapy

Emapalumab will be administered on a background of dexamethasone. At least 5 mg/m^2/day of dexamethasone should be administered from not later than the day before SD initiation, unless there is a known intolerance to glucocorticoids, which must be documented in the patient's medical chart and eCRF. Lower dexamethasone doses at study entry are allowed in case of documented intolerance to glucocorticoids.

For patients who were receiving baseline dexamethasone, they may continue their regular dose provided the dose is at least 5 mg/m^2.

During the study, dexamethasone can be tapered depending on patient`s condition. The tapering scheme can be selected by the investigator 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 investigator.

Dexamethasone may be substituted for another glucocorticoid at an equivalent dose according to clinical judgement or local availability. Equivalent dosage should be converted using a steroid conversion calculator

6.4.5.2 Concomitant therapy

6.4.5.2.1 Cyclosporine A

Cyclosporine A (CsA) can be continued if already being administered to the patient prior to screening. CsA can be withdrawn at any time, upon the judgement of the Investigator. CsA is not to be introduced de novo during the course of the study once emapalumab administration has started.

6.4.5.2.2 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.

6.4.5.2.3 Additional HLH therapies

Administration of additional HLH treatments can be considered 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, as well as later during the course of emapalumab treatment in case of unsatisfactory HLH control.

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. In this circumstance, the Investigator has to fully document the rationale for an alternative choice in the patient's medical file and in the eCRF.

6.4.5.2.4 Other treatments

Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, antibiotics, antifungal and anti-viral treatment, and general supportive care (e.g. gastro-protective agents) are allowed. 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.

6.4.5.3 Prohibited treatments and treatments with specific restrictions

6.4.5.3.1 Intravenous immunoglobulin (IVIG)

IVIG is only allowed as replacement treatment (i.e., not at doses expected to produce an immunomodulatory effect) according to the clinical judgement of the Investigator.

6.4.5.3.2 JAK inhibitors

Administration of JAK inhibitors concomitantly with emapalumab is not allowed.

6.4.5.3.3 Vaccinations

Vaccination with a live or attenuated (including BCG) vaccine must be avoided for 44 days (corresponding to 2 half-lives) after last emapalumab administration.

6.4.5.3.4 Other treatments

Concomitant use of other biologic drugs for indications other than additional HLH treatments is generally not allowed. Rituximab for documented EBV infection, colony stimulating factor in case of prolong neutropenia and blood products are allowed.

The use of traditional Chinese medicine treatments must be avoided during the treatment period until 44 days (corresponding to 2 half-lives) after last emapalumab administration, if used for treatment of HLH.

6.4.5.4 Prophylactic treatments

6.4.5.4.1 Herpes Zoster

Patients will receive prophylactic treatment for *Herpes Zoster* from the day before initiation of emapalumab treatment and must be maintained for 44 days (corresponding to 2 half-lives) after the last emapalumab treatment according to local practice.

6.4.5.4.2 Antimicrobial and antifungal prophylaxis

Patients will receive any other required prophylactic antimicrobial and antifungal treatments according to local recommendations for the management of pHLH.

6.4.6 Treatment compliance

Compliance with IMP and mandatory prophylaxis will be assessed by the study investigator and/or study personnel at each visit. IMP will be administered intravenously by hospital staff twice per week. The amount, date and time of the IMP administrations will be recorded in the eCRF.

6.5 Safety and efficacy assessments

6.5.1 Study schedule

All visits should take place as close to planned dates as possible. Infusions should not take place more than 4 days apart. Detailed information on assessments and timing could be found in Sections 6.5.2 - 6.5.8 and Table 3 and Table 4

In the follow-up period, the following time-windows are allowed:

Pre-conditioning: can be combined with EOT visit provided the two visits are not more than 5 days apart

- Week (W) 1-2-3, Day+30 post-HSCT: ±2 days
- Day+60, Day+100 post-HSCT: ±1 week

- 6-months, 1-year post-HSCT: ±4 weeks

6.5.1.1 Schedule of events

Table 3 Schedule of events – Treatment period

Assessments		Screening Visit (up to 2 Weeks prior to Visit 1)	Week 1		Week 2 →	Week 8	Week 9 – start of conditioning for HSCT	EOT (3±1 days after last inf.)[b]
			Visit 1 / SD0	Visit 2	Visit 3 onwards [a]	Primary assessment timepoint if treatment continues [a]	if treatment continues [a]	Visit X [a] Primary assessment timepoint if treatment stopped before week 8 [a]
Dexamethasone or other glucocorticoid [c]		X	X	X	X	X	X	X
Prophylactic treatment [c]		X	X	X	X	X	X	X
Informed Consent/Assent		X						
Study Drug Infusion [d]			X	X	X	X	X	
Medical history [e]		X						
Prior and concomitant medications [e]		X	X	X	X	X	X	X
Eligibility criteria		X						
Clinical Assessments	Vital Signs [f]	X	X (Pre/post-inf.)	X (Pre/post-inf.)	X (Pre/post-inf.)	X	X (Pre/post-inf.)	X
	Physical Examination [g]	X	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X	X (Pre-inf.)	X
	Height	X				X		X
	Weight	X	X (Pre-inf.)	X	X	X	X	X
	ECG	X				X		X
	Assessment of clinical response		X	X	X	X	X	X
Procedure	HSCT					X		X
Search for Infections	TB [h]	X	X monitoring clinical signs and symptoms of TB (every two weeks) [h].					
	Adenovirus, EBV & CMV viral loads	X	X monitoring clinical signs and symptoms of viral infection (every two weeks) In case of suspicion of infection, viral load test should be performed					
	Atypical mycobacteria, *Histoplasma capsulatum*, Salmonella, *Leishmania,*	X	In case of suspicion of infection					
	Brucella	In case of suspicion of infection	In case of suspicion of infection					
Laboratory [k]	Genetic confirmation [i]	X						
	Hematology	X	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X
	Biochemistry	X	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X
	Coagulation	X	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X

Assessments		Screening Visit (up to 2 Weeks prior to Visit 1)	Week 1		Week 2 →	Week 8	Week 9 – start of conditioning for HSCT	EOT (3±1 days after last inf.)[b]
			Visit 1 / SD0	Visit 2	Visit 3 onwards [a]	Primary assessment timepoint if treatment continues [a]	if treatment continues [a]	Visit X [a] Primary assessment timepoint if treatment stopped before week 8 [a]
	sCD25	X	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X
	Pregnancy test (if applicable) [s]	X	X (Pre-inf.)		X [s]	X [s]	X [s]	X
	CSF analysis (if coagulation allows) [l]	X [l]	If clinically indicated (to monitor evolution of CSF abnormalities or in case of occurrence of new CNS symptoms)					
	Urinalysis [m]		X			X		X
Imaging [k]	Abdominal Ultrasound [n]	X	X (every 2 weeks)					X
	Chest X-ray [o]	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 [p]	(X) [p]	If clinically indicated (to monitor evolution or to confirm occurrence of new CNS symptoms)					
AE recording [q]			X	X	X	X	X	X
SAE recording [r]		X (from signing ICF)	X	X	X	X	X	X
IMP Handling (Preparation, Dispensing, Accountability)			X	X	X	X	X	X (accountability)

Abbreviations 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; PPD, purified protein derivative; PT, prothrombin time; SD, study day; TB, tuberculosis; US, ultrasound

Hematology: 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] **EOT**: indicates a full patient assessment performed 3 days after last emapalumab infusion

[c] **Dexamethasone and prophylactic treatment:** starting from SD-1 (at latest). A prophylaxis for herpes zoster virus infection must be in place from the day before initiation of emapalumab treatment until 44 days (corresponding to 2 half-lives) after last emapalumab administration. Prophylaxis for Pneumocystis jirovecii, and for fungal infections for all patients according to local practice. Patients will receive any other required prophylactic antimicrobial treatment according to local recommendations in pHLH. Dexamethasone may be substituted for another glucocorticoid at an equivalent dose according to clinical judgement or local availability. Equivalent dosage should be converted using a steroid conversion calculator

[d] **Infusion:** to be performed over a period of 1 to 2 hours, twice weekly, not more than 4 days apart

[e] **Medical history and concomitant medications:** 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.

[f] **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.

[g] **Physical Examination** includes as a minimum: spleen and liver size (by abdominal palpation), neurological examination

[h] **TB:** search for tuberculosis mycobacteria: at screening: IGRA/PPD and PCR; after screening, if clinically indicated (e.g. any clinical signs and symptoms suggestive of TB infection as per investigator discretion), a PCR testing should be performed.

[I] **Genetic Confirmation:** sample to be collected if this is not available in the medical records

[k] **Laboratory 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.

[l] **CSF sample:** to be performed in case of CNS disease and/or onset of neurological signs and/or symptoms.

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

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

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

[p] **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.

[q] **AE recording**: All AEs are collected from start of the first infusion of study drug, until study completion

[r] **SAE recording:** SAEs are collected after signing of ICF until study completion. Thereafter only related SAEs will be reported

[s] **Pregnancy test:** Female of childbearing potential will have a serum pregnancy test taken at Screening and Baseline and at EOT and then local urine pregnancy test will be taken monthly (week 4, 8, 12 etc.) until 44 days (corresponding to 2 half-lives) after last emapalumab administration

Table 4 Schedule of events – Follow-up period

Assessments		EOT [n]	Follow-up pre-HSCT [a]	Follow-up post-HSCT (or after last emapalumab infusion, as applicable) [b]					
			Pre-conditioning visit	Weekly visits wk 1 – 2 – 3 [c]	D+30 visit [c]	D+60 visit [c]	D+100 visit [c]	6 months visit [c]	EOS 1 year visit[c]/ WD [d]
Clinical Assessments	Vital signs	As indicated in Table 1	X	X	X	X	X	X	X
	Physical Examination [e]		X	X	X	X	X	X	X
	Height								X
	Post-HSCT outcome [f]			X	X	X	X	X	X
	Survival		X	X	X	X	X	X	X
Laboratory	Hematology		X	X	X	X	X	X	X
	Coagulation		X	X	X	X	X	X	X
	Biochemistry		X	X	X	X	X	X	X
	sCD25		X	X	X	X	X	X	X
	Urinalysis		X	X	X	X	X	X	X
Search for infections	TB [g]				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		In case of suspicion of infection						
	Abdominal US [j]		X				X		X
Concomitant medications			X	X	X	X	X	X	X
Prophylactic treatment [m]			X	X	X [m]				
AE recording [k]			X	X	X	X	X	X	X
SAE recording [l]			X	X	X	X	X	X	X

Abbreviations: 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; EOS, end of study; 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; 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

Hematology: 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). **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] **Follow-up post-HSCT:** If search for a donor is longer than 6 months, the follow-up period will be reduced, and the EOS will take place no later than 18 months after the first dose of emapalumab.

[c] **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

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

[e] **Physical examination:** includes as a minimum: spleen and liver size (by abdominal palpation), and neurological examination

[f] **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

[g] **TB**: as clinically indicated, at minimum at D+30, D+60, D+100, 6 month and 1 year/WD visits; (e.g. any clinical signs and symptoms suggestive of TB infection as per investigator discretion), a PCR testing should be performed.

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

[k] **AE recording**: All AEs are collected from start of the first infusion of study drug, until study completion.

[l] **SAE recording:** SAEs are collected after signing of ICF until study completion. Thereafter only related SAEs will be reported

[m] **Prophylactic treatment:** Prophylaxis for herpes zoster virus infection must be in place from the day before initiation of emapalumab treatment until 44 days (corresponding to 2 half-lives) after last emapalumab administration. Prophylaxis for Pneumocystis jirovecii, and for fungal infections for all patients according to local practice. Patients will receive any required prophylactic antimicrobial treatment according to local recommendations in pHLH.

[n] **EOT:** indicated as reference only, refer to Table 3

6.5.1.2 Screening

Patients will be screened for eligibility prior to enrollment into the study.

A signed informed consent form must be obtained from the patient/patient's legally authorized representative prior to any study specific activities. If applicable assent will be obtained in accordance with local requirements. Once the informed consent is signed the patient will be assigned a patient number.

A pre-screening checklist is an additional tool that is made available to assist the Investigator to make decisions. This checklist enables rapid preliminary assessment of patient's eligibility based strictly on the information available from routine patient care. The pre-screening checklist will be kept at site and will not be shared with Sponsor.

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

Any SAE that occurs after informed consent has been signed must be reported.

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

6.5.1.3 Treatment period

Patients will be in the treating unit the day before the first administration of emapalumab SD-1.

During the treatment period, visits for infusion and safety /efficacy assessments will occur on SD0, and twice-a-week thereafter (not more than 4 days apart). After the patient's clinical condition is stabilized, decrease the dose to the previous level to maintain clinical response.

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 and based on the Investigator's decision.

Treatment period will last until pre-conditioning for HSCT.

An end of treatment (EOT) visit has to be performed 3±1 days after last emapalumab infusion.

6.5.1.4 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). This will represent the last visit in the study. If search for a donor is longer than 6 months, the follow-up period will be reduced, and the EOS will take place no later than 18 months after the first dose of emapalumab.

A patient who experiences HLH reactivation during the follow-up period, may be re-treated with emapalumab.

After the patient has completed the EOS visit, they should be treated and followed-up according to investigator judgment and local practice. No further investigational medicinal product will be provided.

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.

6.5.1.5 Unscheduled visits

Unplanned visits may occur anytime during the study 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. Data collected during such a visit should be entered in the eCRF. An unscheduled visit should not affect the regular visit schedule and assessments.

6.5.2 Medical history

Medical history will be collected during the screening period up until the day of the first dose.

Relevant medical history events with onset date at any time prior to ICF signature date will be recorded in the eCRF.

HLH history will be recorded to the best possible extent, including (as available):
molecular diagnosis of HLH and perforin expression and other functional tests performed for the diagnosis of HLH, disease features at diagnosis, date of diagnosis, family history of HLH, conventional treatments received to date, including procedures (such as plasmapheresis and HSCT), molecular diagnosis (genetic and functional test results), EBV load at diagnosis.

If results of genetic and/or functional tests are pending at inclusion, they shall be reported when they become available.

6.5.3 Demography

Date of birth, gender, race, and childbearing potential will be collected at screening.

6.5.4 Efficacy endpoints assessments

6.5.4.1 Overall Response

Overall Response is defined as achievement of either Complete or Partial Response or HLH Improvement, at EOT or week 8 (whichever occurs earlier).

Complete response, partial response and HLH improvement and time to first response will be assessed after the database lock via a programmed algorithm, based on the Table 5 below.

Table 5 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.

6.5.4.2 Time to first Overall Response

Time to first response will be assessed after the database lock via a programmed algorithm, based on the Table 5

6.5.4.3 Duration of response

Duration of Response, i.e., maintenance of the response achieved will be assessed after the database lock via a programmed algorithm, based on the Table 5

6.5.4.4 Glucocorticoids tapering

Reduction of glucocorticoids by 50 % or more of the baseline dose

6.5.4.5 HSCT

Information about conditioning for HSCT and of the HSCT will be recorded in the eCRF. This information will be used to calculate the number and proportion of patients able to commence conditioning for HSCT

6.5.4.6 Investigator's assessment of clinical response

Investigator's assessment of clinical response will be collected at every visit throughout the treatment period and will be based on the evaluation of clinical signs and laboratory parameters which characterize the disease; clinical signs, e.g. fever, splenomegaly, CNS symptoms, and laboratory parameters, e.g. CBC, fibrinogen, ferritin, sCD25 levels. The assessment will be assisted by the Investigator`s clinical judgment and previous experience in treating patients with pHLH and will be used to assess the achievement of response. The patient's clinical response will be rated as 'complete response', 'partial response', or 'no response' as judged by the investigator

6.5.5 Safety assessments

6.5.5.1 Adverse events

6.5.5.1.1 Definitions

Adverse event (AE)

An AE is any untoward medical occurrence in a patient or study patient administered a pharmaceutical product; the event does not necessarily have a causal relationship with the treatment or usage.

AEs include the following:

- Abnormal test findings, as specified below.
- Clinically significant signs and symptoms.
- Changes in physical examination findings.
- Progression/worsening of underlying disease.

In addition, signs and symptoms resulting from the following should also be handled according to the same principles as AEs:

- Overdose.
- Withdrawal of treatment.
- Interactions.
- Abuse.
- Misuse.

For pregnancies and breastfeeding, see 6.5.5.1.6

Abnormal test findings

An abnormal test finding, e.g. abnormal laboratory analysis results, vital signs, or ECG, should be recorded as an AE in any of the following situations:

- The investigator considers the abnormal test finding to be clinically significant.
- The abnormal test finding is associated with accompanying symptoms. Note, that the symptom, not the test result, should be recorded as an AE.
- The abnormal test finding leads to a medical/surgical intervention including withdrawal of IMP(s) or discontinuation from the study. Repeat/confirmatory testing is not considered a medical intervention.

Preexisting conditions

A preexisting condition (i.e., a disorder present before the AE reporting period started and noted on the pretreatment medical history/physical examination form) should not be reported as an AE unless the condition worsens, or episodes increase in frequency during the AE reporting period.

Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy entered in the comments section of the eCRF.

Lack of efficacy

"Lack of efficacy" or "expected pharmacological effect has not been reached" will not be reported as an AE or SAE. However, failure of pharmacologic action or therapeutic benefit shall be recorded as an AE when they associated with a SAE or Serious outcome.

Serious adverse event (SAE)

An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Results in death.
- Is life-threatening (i.e., at immediate risk of death).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect (i.e., in an offspring to the study patient).
- Is a medically important AE.

Medically important AEs are events that may not result in death, be life threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient, or patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Serious also includes any other event that the investigator or company judges to be serious. Any suspected transmission of an infectious agent via IMP shall also be considered serious.

Hospitalization

Hospitalization includes transfers within a hospital (e.g. from the psychiatric unit to the intensive care unit) and also includes admissions less than 24 hours. The following situations are not considered hospitalizations (although other SAE criteria may still apply):

- Outpatient procedures / ambulatory care.
- Emergency department visits.

Hospitalization in the absence of an AE occurring during the study should not be considered an SAE. This includes:

- Hospitalization due to a pre-existing condition not associated with a worsening of the pre-existing condition.
- Protocol specified admission.
- Elective admission, e.g. due to cosmetic surgery.
- Pre-planned admission for a condition specified at baseline for the patient.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

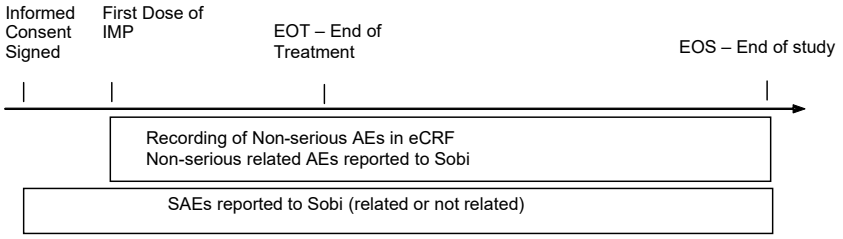
A SUSAR is an unexpected serious adverse event, suspected to be related to the study drug, which is not consistent with the reference safety information in the Investigator's Brochure.

6.5.5.1.2 Adverse event reporting period

The period for recording AEs in the eCRF, begins upon receiving the first dose of investigational medication until EOS. All AEs must be recorded on specific AE forms of the eCRF. AEs that are reported from start of infusion and over the next 24 hours will be considered infusion related, and they will be analyzed separately. The investigator should report the actual event, e.g. rash, hypotension.

Monitoring of suspicion of infections is requested throughout the study. Type of investigation, specimen, result, and pathogen identified will be captured in the eCRF. Any entry of new infection (assessed as serious and clinical suspicion of infections caused by pathogens potentially favored by IFN-γ neutralizations) in the eCRF will prompt to complete "infection log" to collect information regarding pathogen and specimen from which a pathogen has been isolated.

Figure 2 Overview of non-serious AE and SAE reporting period



6.5.5.1.3 Eliciting and recording adverse event information

The investigator is to record all directly observed AEs, and all AEs spontaneously reported by the patient, in the eCRF using concise medical terminology. In addition, each patient will be questioned about AEs at each clinic visit following initiation of treatment

When possible and appropriate, a diagnosis rather than individual signs and symptoms shall be recorded. The investigator is responsible for obtaining sufficient information to determine seriousness, causality, and outcome of each AE.

Severity assessment

The investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum severity of the AE. For the purpose of consistency, these severity grades are defined as follows:

MILD	Does not interfere with patient's usual function
MODERATE	Interferes to some extent with patient's usual function
SEVERE	Interferes significantly with patient's usual function

Note the distinction between the gravity (seriousness) and the severity of an AE. **Severe** is a measure of intensity; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

If the intensity of an AE worsens during the study, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

Events occurring during the screening period (i.e. after signature of informed consent up to IMP initiation) are considered medical history. If it worsens after IMP initiation or during the follow-up period, an AE form must be entered with the appropriated intensity.

Causality assessment

For each AE, the investigator must make a causality assessment to determine if there is a reasonable possibility that the IMP caused the AE. The AE is assessed as related or not related to

the IMP. The determination of the likelihood that the IMP caused the AE will be provided by an investigator who is a qualified physician.

- Related

  An AE that follows a reasonable temporal sequence from administration of the IMP (including the course after withdrawal of the IMP), or for which possible involvement of the IMP cannot be ruled out, although factors other than the IMP, such as underlying diseases, complications, concomitant drugs, and concurrent treatments, may also be responsible.

- Unrelated

  An AE that does not follow a reasonable temporal sequence from administration of the IMP and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.

6.5.5.1.4 Serious adverse event (SAE) and non-serious related AE reporting

Both serious and non-serious AEs are to be reported on the AE page of the CRF in English as specified in the CRF instructions and the investigator must assess the causal relationship of the event to study treatment.

The Sobi Global Pharmacovigilance & Patient Safety (GPV) department is to be notified by e-mail to [redacted] using the designated SAE reporting form / non-serious related AE reporting form, within 24 hours of the investigator's first knowledge of the following events:

- All SAEs (whether or not considered by the investigator to be related to study treatment)
- All non-serious related AEs (all non-serious AEs considered by the investigator to be related to study treatment)

The SAE reporting form/non-serious related AE reporting form is not always the same as the adverse event eCRF form. The forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. The investigator must assess the causal relationship of the event to IMP and sign the report.

If the patient is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE relevant information and documentation.

All new information obtained, relevant to an SAE and/or a non-serious related AEreport, should be forwarded to Sobi within the same timeframe as the initial information.

The investigator shall provide Sobi with sufficient information to enable a complete medical assessment of the reported event. Best efforts shall be made by the investigator to provide Sobi with additional information related to any SAE and/or a non-serious related AE as requested.

Prompt notification by the Investigator to the Sponsor of SAEs and non-serious related AEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor, will review it and will notify the IECs/IRBs, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy, and forwarded to investigators as necessary.
- The reference safety document to assess expectedness of a suspect serious adverse reaction and for reporting by the sponsor to Health Authorities, IECs/IRBs and investigators is the reference safety information section of the current version of the IB.

6.5.5.1.5 Follow-up of unresolved adverse events

All serious and non-serious AEs assessed by the investigator as related to the IMP should be followed until they are resolved or the investigator assesses them as chronic or stable, or the patient's participation in the study ends, i.e., until the EOS visit. How to report changes in an ongoing AE during a patient's participation in the study is described in the eCRF instructions.

In addition, all serious and non-serious AEs assessed by the investigator as related to the IMP should continue to be followed until they resolve or until the investigator assesses them as "chronic" or "stable", even after the patient's participation in the study is over, but without further recordings into the eCRF.

6.5.5.1.6 Exposure during pregnancy and breastfeeding

All events of exposure to the IMP during pregnancy (female patient or male patient's partner) or breastfeeding, shall be reported to Sobi Global Pharmacovigilance & Patient Safety by e-mail to [redacted] within 24 hours of awareness by any study personnel, whether the exposure is associated with an AE or not. This includes all situations where a female is or has been found to be pregnant after being exposed to IMP; directly, indirectly or via her partner (paternal exposure).

In all reported situations of exposure during pregnancy, Sobi will provide the investigator with a Pregnancy report form which shall be completed and returned by the investigator. The investigator is responsible for monitoring the outcome of the pregnancy and to inform Sobi of relevant information and any information requested related to the outcome of the pregnancy.

Any AEs and SAEs observed during and in relation to pregnancy, delivery or breastfeeding should be recorded in the eCRF and as applicable be reported to Sobi as described previously in this section.

6.5.5.2 Safety endpoint assessment

Number of patients who permanently discontinued study drug due to emapalumab-related adverse events. Occurrence and type of emapalumab-related adverse event as assessed by the investigator. Management and reporting of AEs related to these functions is described in Section 6.5.5.1.

The definitions of AEs related to the respective area above will be based on MedDRA System Organ Class (SOC) terms, High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Terms (PT), and Standardized MedDRA Queries (SMQ).

6.5.6 Clinical safety assessments

6.5.6.1 Vital signs

Vital signs (body temperature, heart rate, and systolic/diastolic BP and oxygen saturation) will be measured at every visit and recorded in the eCRF.
BP should be measured in the same body position consistently throughout the study, if possible.

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 (or the first infusion after an increased dose) BP and heart rate will be measured every 15 minutes during the infusion, at the end of infusion and 1 and 2 hr. post-infusion. Oxygen saturation will be measured continuously during the infusion and up to 2 hr. post-infusion.

For subsequent visits, if no infusion-related reactions have occurred, BP, heart rate and oxygen saturation will be measured every 30 minutes, at the end of infusion and 1 and 2 hr. post-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

Clinically significant abnormal vital signs should be reported as AEs (see Section 6.5.5.1.1 for details).

6.5.6.2 Height and weight

Body weight (in kg) will be recorded at each visit during the treatment period, at the EOT visit, and at the final 1-year visit during the follow-up period (EOS)/discontinuation visit. Height (in cm) will be recorded at screening, at the EOT visit, and at the EOS/discontinuation visit. For patients older than 18 years of age height is only recorded at enrollment visit.

6.5.6.3 Physical examination

A complete physical examination will be performed at screening and a brief examination (including spleen and liver size (by abdominal palpation) general appearance of the skin and neurological status) at all other visits indicated in the schedule of assessments, see Table 3 and Table 4. Information for all physical examinations must be included in source data and will not be recorded in the database.

Each component will be recorded in eCRF as “normal” or “abnormal” at each visit. Abnormalities should be described, and clinical significance assessed.

If any abnormalities are reported at baseline they should be recorded as medical history. New or worsening of abnormalities should be reported as AEs if clinically significant (see Section 6.5.5.1.1 for details).

6.5.6.4 Electrocardiogram

A 12-lead ECG recording will be performed at screening, at the 8 weeks visit, and EOT. The ECG assessments will be performed locally at site and will be reported as “normal” or “abnormal” in the eCRF. Any abnormalities should be specified, and clinical significance assessed. ECGs assessed as abnormal should be assessed by an investigator with experience of assessing ECGs in children at different ages. Abnormalities reported at screening should be recorded as medical history.

Clinically significant abnormal ECG findings should be reported as AEs (see Section 6.5.5.1 for details).

6.5.7 Laboratory safety assessments

Due to the low blood volume in patients foreseen to participate in this study, it will be necessary to reduce sampling. Therefore, WHO recommendations regarding blood sampling are to be followed and if patient care or normal disease monitoring requires prioritization of sampling, this should be adhered to.

Samples will be analyzed at the local laboratory using the local laboratory’s standardized analytical procedures and local procedures for blood collection and processing will be followed. The local laboratory should be accredited or participate in an external quality assurance scheme, e.g. China National Accreditation Service for Conformity Assessment (CNAS). The results from the local laboratory will constitute the primary data of the study to be used for statistical analysis.

Local lab will also be used for patient care and treatment decisions in between study visits.

In the event a study site is unable to analyze any of the protocol required laboratory tests at the local hospital laboratory, such samples can be sent to an external laboratory for analysis, and the results will be accepted in this study. Similarly, test results of the patients performed in other hospitals can be accepted in this study. The test content, test time window, and test result time window and requirements should be consistent with the study protocol.

Clinically significant laboratory values should be reported as AEs (see Section 6.5.5.1.1 for details).

If a sample cannot be performed on the day of the scheduled visit, assessments within ±1 day window from scheduled visit date will be accepted.

6.5.7.1 Pregnancy test

Female of childbearing potential will have a serum pregnancy test taken at screening and Baseline and at EOT and then local urine pregnancy test will be taken monthly (week 4, 8, 12 etc.) until 6 months after the last emapalumab administration.
The outcome of the test will be reported as “positive” or “negative” in the eCRF.

6.5.7.2 Hematology

CBC: white blood cells and differential (including large unstained cells count, whenever performed as routine), red blood cells, hemoglobin, hematocrit, platelets.

6.5.7.3 Chemistry

Glucose, CRP, ferritin, triglycerides, liver (AST, ALT, γGT, LDH, ALP, bilirubin) and renal function (albumin, creatinine, and urea).

6.5.7.4 Coagulation

aPTT (time and/or ratio), PT and/or INR, d-Dimers, fibrinogen.

6.5.7.5 sCD25

sCD25

6.5.7.6 Urinalysis

Glucose, blood, protein and/or albumin, leukocytes, ketones, pH, specific gravity.

6.5.7.7 Genetic confirmation

Sample will be collected during screening if this information is not available in the medical records.

6.5.7.8 CSF

Lumbar puncture for CSF analysis is to be performed in case of suspicion of CNS involvement at Screening providing that coagulation function allows and 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.

6.5.7.9 Tuberculosis (TB)

At screening: IGRA/PPD and PCR; after screening, if clinically indicated (e.g. any clinical signs and symptoms suggestive of TB infection as per investigator discretion), a PCR testing should be performed.

After screening visit TB is to be performed by PCR in any relevant specimen until 44 days after last emapalumab infusion.

6.5.7.10 Infections, other

Infection assessment at Screening should be performed according to the patient's clinical presentation. At a minimum Adenovirus, EBV and CMV viral loads should be assessed together with screen for Histoplasma capsulatum, Leishmania, Salmonella, and atypical mycobacteria.

In case of suspicion of any infection, local testing and treatment guidelines should be followed.

6.5.8 Imaging

6.5.8.1 Abdominal ultrasound

Will be performed every two weeks during the treatment period. Has to include longitudinal measure of the spleen.

6.5.8.2 Chest X-ray

Will be performed if clinically indicated (e.g. in case of clinical suspicion of pulmonary infection or to follow-up a pre-existing infection at screening/baseline). If a CT is performed it will be accepted instead of Chest X-ray.

6.5.8.3 Brain Magnetic Resonance Imaging (MRI)

Only 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.

6.5.9 Post HSCT outcome

Will be assessed in patients who undergo HSCT. Includes engraftment rate, donor chimerism achieved (as available), incidence of acute and chronic graft versus host disease

7 Quality control and quality assurance

This study will be conducted in compliance with this protocol, study specific procedures, contracts, CRO SOPs, the ICH Guideline for GCP [1], and applicable regulatory requirements.

The sponsor will systematically review the study quality management to identify, evaluate and control risks to study critical processes and data which would affect patient safety and reliability of study data.

The data collection tool will be a validated Electronic Data Capture (EDC) system. Patient data necessary for analysis and reporting will be entered/transmitted into a validated database or data system.

Data required according to this protocol will be recorded by data entry by the study site personnel. EDC enables the application of software logic to set-up data entry screens and data

checks to ensure the completeness and accuracy of the data entered by the site personnel. Data queries resulting from the application of the software logic are resolved by the site personnel.

The sponsor will identify the data to be collected based on the protocol and prepare EDC system requirement specifications.

The EDC system is a password-protected security system. All study site personnel requiring access must go through a training process before they are granted access. Training records will be maintained.

All personnel with access to EDC system should follow Sponsors requirement for the data entry, the change, and the correction of existing data.

EDC system complies with applicable regulatory requirements and ICH GCP and contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made.

The Sponsor will establish a systematic, prioritized, risk-based approach to monitoring and details will be outlined in the Monitoring Plan

Monitoring visits to the study site will be performed periodically during the study, to help ensure compliance with the protocol, study specific procedures and applicable regulatory requirements. Source documents will be reviewed for verification of agreement with data in eCRFs. All patient informed consent forms will be reviewed. The investigator or institution guarantees access to source documents by Sobi, its representatives, and appropriate regulatory agencies.

The study site may be subject to a quality assurance audit by Sobi or its representatives, as well as inspection by appropriate regulatory agencies.

It is important that the investigator(s) and the relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

8 Statistical plan

A formal statistical analysis plan (SAP) will be written and will provide details of all analyses to be conducted.

8.1 Determination of sample size

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

8.2 Definition of study populations

Safety and efficacy analyses will be conducted on the “All treated analysis set” which will comprise all patients who received at least one infusion of IMP.

8.3 Overall statistical and analytical plan

8.3.1 General statistical issues

The statistical analysis will be described in more detail in the statistical analysis plan (SAP).

All endpoints will be summarized with descriptive statistics. 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 variable) the counts and percentages will be presented.

Suitable tabular and graphical summaries will be prepared for individual data and for appropriate summary statistics, and all data will be listed.

No formal statistical hypothesis testing will be performed.

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

8.3.2 Demographics and baseline characteristics

All demographics and baseline characteristics will be summarized with descriptive statistics.

8.3.3 Analysis related to the primary objective

The primary objective is to collect safety data on emapalumab in treatment-experienced pHLH patients

The primary endpoint is permanent discontinuation of study drug due to emapalumab-related adverse events

The number and percentage of patients who permanently discontinue study drug due to emapalumab-related adverse events will be presented.

8.3.3.1 Secondary endpoints supporting the primary objective

Secondary endpoints supporting the primary objective are:

- Treatment-emergent adverse events (AEs)
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent laboratory abnormalities
- Treatment-emergent vital sign abnormalities

The incidence of treatment-emergent AEs, treatment-emergent SAEs, treatment emergent laboratory abnormalities and treatment-emergent vital sign abnormalities will be summarized in frequency tables by system organ class and preferred term.

8.3.4 Analysis related to the secondary objective

The secondary objective is to collect efficacy data on emapalumab in treatment-experienced pHLH patients

The secondary endpoints supporting the secondary objective are:

- Overall Response, i.e., achievement of either Complete or Partial Response or HLH Improvement, at EOT or week 8 (whichever occurs earlier).
  - Criteria for the definition of Overall Response Rate are reported in Table 5
- Time to first Overall Response, i.e., time from the date of first dose of emapalumab to the first achievement of response (Complete or Partial Response or HLH Improvement)
- Cumulative duration of response, i.e., total time in response from the first achievement of an Overall Response until EOT or week 8 (whichever occurs earlier).
- Ability to reduce glucocorticoids by 50% or more of the baseline dose during emapalumab treatment
- Investigator assessed response
- Survival:
  - To start of HSCT conditioning, i.e., time from the date of first dose of Emapalumab to date of death, with censoring at conditioning for HSCT or at last date of contact for patients who did not undergo conditioning for HSCT
  - After HSCT, i.e., time from HSCT to death, with censoring time at last date of contact for patients with no event. Only patients undergoing HSCT will be included in the analysis

8.3.4.1 Clinical response

Achievement of response and time to first response will be assessed after the database lock via a programmed algorithm. The derivation of the Overall Response is detailed in Table 5.

The number and percentage of patients achieving Overall Response at EOT or week 8 (whichever occurs earlier), i.e., Complete Response or Partial Response or HLH improvement, as well as No Response will be provided.

The number and percentage of patients achieving each component of Overall Response will also be provided.

Time to first Overall Response is defined as time from the date of first dose of emapalumab to the first achievement of response (Complete or Partial Response or HLH Improvement). Patients without a response will be censored at the EOT visit date or last assessment.

Time to first response prior to HSCT will be presented by Kaplan-Meier curve with median calculated if available. Associated two-sided 95% confidence intervals will be calculated for the median.

Cumulative duration of response is defined as total time in response from the first achievement of an Overall Response until EOT or week 8 (whichever occurs earlier). Cumulative duration of response will be analyzed descriptively using summary statistics.

In addition to the programmed algorithm of response, investigator's assessment of clinical response up to HSCT will be presented descriptively.

8.3.4.2 Reduced glucocorticoids compared to baseline

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

8.3.4.3 Survival

Survival to start of HSCT conditioning is defined as time from first dose of IMP to date of death from any cause. Patients with no event will be censored at start of conditioning for HSCT or at the date of last contact for patients who did not undergo HSCT.

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

Survival to start of HSCT conditioning and Survival after HSCT will be estimated applying Kaplan-Meier methodology. Survival rates and associated two-sided 95% confidence intervals will be obtained at key time points. Median survival time, 75th and 25th percentiles will be calculated where available with associated two-sided 95% confidence intervals.

8.3.5 Exploratory endpoint supporting the secondary objective

[redacted]

8.3.6 Analysis of safety and tolerability data

8.3.6.1 Adverse events

Reported AEs during the study will be coded using MedDRA.

8.3.7 Interim analysis

No formal interim analysis is planned.

8.3.8 Multiple comparison/multiplicity

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

8.3.9 Handling of missing data

Methods for handling missing data will be described in the SAP.

9 Data collection, handling and record keeping

9.1 Data standards

Collection of data should be performed in the CDASH format, according to the CDISC. The standards should be used to the extent possible and/or required for the specific study/project. The minimum requirement of the CDISC standard is to collect all core variables specified as 'Required' in the Study Data Tabulation Model format.

9.2 Case report form

A CRF is required and should be completed for each enrolled patient. In this study a web based, validated electronic data capture (EDC) software tool will be used to collect and process the study data. The management of the EDC system will be based on the model of outsourcing.

The data should be entered by site users into the EDC system on an ongoing basis. In principle, it is recommended to perform data entry within 5 working days from the visit date unless otherwise specified by the site Clinical Trial Agreement. To ensure data quality within EDC, automated edit checks will be built into the EDC system and triggered to correct or verify the input data. Any data changes or modifications within EDC will be automatically tracked by an audit trail detailing date, time and name of the user performing corrections.

Clinical data management will be conducted in accordance with regulatory standards. This applies to data recorded directly in eCRF and to data from other sources stored at secure servers (e.g. IXRS). Additional details regarding data collection and validation procedures will be detailed in a Data Management Plan.

Access to the EDC system is granted and revoked in accordance with regulatory requirements. Only authorized personnel will have access to the electronic data capture system upon completion of the user training.

The investigator will review and approve the eCRF entries for each patient with an electronic signature. The signatures serve to attest that the information contained on the eCRFs is correct. At all times, the investigator has final responsibility for the accuracy and authenticity of all data entered on the CRFs.

The completed original eCRFs are the sole property of Sobi and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities, without written permission from Sobi.

At the end of the study, a final copy of the database will be stored at the Sponsor. Sobi will ensure that an eCRF copy of trial's final and locked data is provided to the Investigator in a form of a write protected PDF files and that the eCRF copies are an exact copy of the data maintained in the database.

9.3 Source data

Patient source documents are the physician's patient records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart. In those cases, the information collected on the eCRFs must match those charts. In some cases, a portion of the source documents for a given patient may be the eCRF.

A separate source document location agreement will be completed and signed by the principal investigator and the monitor before study start.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g. via an audit trail).

9.4 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of patients. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study patients.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

When a deviation from the protocol is identified, the investigator or designee must ensure the CRO is notified. The CRO will follow up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and / or efficacy of the patient to determine patient continuation in the study.

The investigator and CRO must contact Sobi immediately if a deviation is discovered that significantly affects or has the potential to significantly affect human patient protection or the reliability of study results.

The investigator will also assure that deviations are reported and documented in accordance with IEC and applicable regulatory requirements.

9.5 Database closure

Prior to database closure, all tasks or criteria defined in the data management plan must be completed and documented. The study database must be locked before generation of any results. The database lock will be approved by relevant study personnel and all edit accesses will be removed. The study database can only be unlocked in case critical errors, affecting the main conclusions of the study, are discovered.

9.6 Record retention

The investigator or head of the study site (medical institution) should maintain a record of the location(s) of investigator's essential documents as defined in the ICH GCP Guideline [1] including source documents and should have control of and continuous access to all essential documents and records generated by the investigator/institution before, during, and after the study.

All documents and data relating to the study will be kept securely by the investigator in a secure file and/or electronically. The storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval. The data will be available for evaluation and/or audits from Health Authorities, Sobi or Sobi's representatives.

When a copy is used to replace an original document (e.g. source documents, eCRF), the copy should fulfill the requirements for certified copy as defined in ICH GCP Guideline [1].

The records should be retained by the Investigator as specified in the Clinical Trial Agreement and in accordance with local regulations.

If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator or another institution. Archiving on behalf of the investigator can also be delegated to Sobi.

10 End of study

The end of study at a patient level is either the EOS visit or the withdrawal visit.

The end of this study at the study level is defined as date of the last patient out, i.e. the last patient's last visit.

11 Sponsor's discontinuation criteria

11.1 At patient level

11.1.1 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 investigator 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 investigator'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.

11.1.2 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.

11.1.3 Decision to Discontinue Treatment

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. There are no predefined rules for permanent study drug discontinuation based on the current safety profile of the drug. The Investigator may request expert advice or a discussion with the Sponsor, if relevant prior to taking a decision; however, the ultimate decision remains the Investigator`s responsibility. The reason for premature treatment discontinuation should be documented in the patient's chart and the eCRF. After treatment discontinuation (for any reason), it is recommended that the patient will continue in the study for a long-term follow-up.

11.2 At site level

Significant violation of ICH GCP and all applicable laws, regulations and protocol procedure that compromises the ability to achieve the primary study objectives or compromises patient safety may lead to the affected site to be discontinued from study participation by to Sponsor.

11.3 At the study level

Sponsor reserves the right to temporarily suspend and to discontinue the study prior to inclusion of the intended number of patients but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating patients as soon as possible. Patients already enrolled in the study should continue in the study as per protocol unless judged otherwise by Investigator.

All study materials must be collected and all the eCRFs completed to the greatest extent possible.

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.
After re-evaluation of benefit/risk, the sponsor 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;
- to discontinue the study.

12 Dissemination and publication of results

Sobi will register the study by posting study information and post study results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations, e.g., on http://www.chictr.org.cn/, http://www.chinadrugtrials.org.cn/ and www.clinicaltrials.gov. The results of this study will be published within 12 months of the end of study.

Sobi is committed to publishing study results in a complete, accurate, balanced, transparent, and timely manner. Sobi follows the principles of the International Committee of Medical Journal Editors (ICMJE) recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals including criteria for authorship [38].

The data from this study will be considered for reporting at a scientific meeting or for publication in a scientific journal. The sponsor will be responsible for these activities and will work with the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues. The results of the study, or any part thereof, shall not be published without the prior written consent and approval of Sobi, such consent and approval not to be unreasonably withheld.

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Appendix 1 Additional Protocol Signatures

Sponsor's Clinical Study Manager

[redacted]

Signature

Date

Sponsor's Statistician

[redacted]

Signature

Date

Appendix 2 Study Administrative Structure

All sites and investigator will be listed with names and their curricula vitae (CVs) in the TMF

Monitoring:	[redacted]
SAE reporting:	Swedish Orphan Biovitrum AB (**Sobi**) SE-112 76 Stockholm, Sweden
Data management: Statistics: Investigational products (production): Investigational products (packaging and labeling):	[redacted]
Clinical laboratory:	Local laboratories to be used
Central laboratory:	[redacted]

Commented [BP1]: Should this be redacted? I'm not too familiar with doing redactions but could the lab information be important to redact if not for the rest?

Commented [BP2R1]: I think have Tigermed in here should be redacted as I think the CRO information should be kept separate?

Commented [PH3R1]: I think you are right about this. Will be redacted