CLINICALTRIALS.GOV-ID:	NCT04731298
CLINICAL STUDY PROTOCOL: (CSP)	An open label, single arm, multicentre, proof of concept, phase 2 study to investigate the pharmacokinetics, pharmacodynamics and assess the efficacy and safety to support dose selection of emapalumab in pre-empting graft failure in patients at high risk after allogeneic hematopoietic stem cell transplantation
CSP VERSION & DATE:	Version 3.0; 28 May 2021

Clinical Study Protocol

An open label, single arm, multicentre, proof of concept, phase 2 study to investigate the pharmacokinetics, pharmacodynamics and assess the efficacy and safety to support dose selection of emapalumab in pre-empting graft failure in patients at high risk after allogeneic hematopoietic stem cell transplantation

Study Number:	NI-0501-12
EudraCT Number:	2020-001676-15
Version:	Version 3.0
Date:	28 May 2021

SPONSOR SIGNATURE PAGE

Protocol Number: NI-0501-12

Protocol date and version: 28 May 2021, Version 3.0

Study drug: Emapalumab (NI-0501)

Study title: An open label, single arm, multicentre, proof of concept, phase 2 study to investigate the pharmacokinetics, pharmacodynamics and assess the efficacy and safety to support dose selection of emapalumab in pre-empting graft failure in patients at high risk after allogeneic hematopoietic stem cell transplantation

I approve this protocol.

[redacted] Senior Clinical Scientist	DocuSigned by: [redacted]
[redacted] Senior Clinical Science Leader	DocuSigned by: [redacted]
[redacted] Clinical Study Manager	DocuSigned by: [redacted]
[redacted] Senior Statistical Scientist	DocuSigned by: [redacted]

COORDINATING INVESTIGATOR SIGNATURE PAGE

Protocol Number: NI-0501-12

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I approve this protocol.

[redacted] MD, PhD	DocuSigned by: [redacted]

INVESTIGATOR AGREEMENT

Protocol Number: NI-0501-12

Protocol date and version: 28 May 2021, Version 3.0

Study drug: Emapalumab (NI-0501)

Study title: An open label, single arm, multicentre, proof of concept, phase 2 study to investigate the pharmacokinetics, pharmacodynamics and assess the efficacy and safety to support dose selection of emapalumab in pre-empting graft failure in patients at high risk after allogeneic hematopoietic stem cell transplantation

Investigator endorsement:

I, the undersigned, am responsible for the conduct of this study at this site and agree to conduct the study according to the protocol and any approved protocol amendments, the International Council on Harmonization (ICH) harmonized tripartite guideline E6(R2): Guideline for Good Clinical Practice, and all applicable regulatory authority/government requirements and in accordance with the latest revision of the Ethical Principles for Medical Research Involving Human Subjects (the Declaration of Helsinki).

I will not deviate from the protocol without prior permission from the Sponsor and prior review and written approval from the Institutional Review Board/Independent Ethics Committee, and where applicable, from the Competent Authorities, except where necessary to prevent any immediate danger to a patient. Further, I will not publish results of the study without authorization from the Sponsor.

I have read and understand fully the Investigator's Brochure for emapalumab (NI-0501) and I am familiar with the investigational product and its use according to this protocol.

_____ _____

Investigator's Name Date

_____

Investigator's Signature

SUMMARY OF CHANGES TO THE PREVIOUS PROTOCOL VERSION

The following key changes were done to the previous protocol version 2.0 dated 15 May 2020.

Applicable Sections	Change/Reason
Protocol Synopsis	The synopsis has been updated to reflect the changes reported in this table.
Section 3.1 Overall study design Section 5.4 Dosing Regimen Table 6 Schedule of assessments treatment period (foot note)	These sections/tables have been updated to correct the treatment start criteria. Previous version reported treatment start from CXCL9 value above threshold, whereas treatment should start within 12 hours from CXCL9 (with levels above threshold) sample collection time.
Section 3.2 Study design rationale Section 3.4.5 Follow-up period Table 7 Schedule of assessments follow-up period	These sections have been updated to clarify which data are collected during the survival phone calls in addition to survival data (i.e. occurrence of GvHD, use of defined treatments/procedures to support the graft function post-transplant). Table 7 Schedule of assessments (follow-up period) has been updated to add details of which specific procedures/medications post-HSCT should be collected during the follow-up calls (any HSCT, blood product transfusion, stem cell boost, DLI or haemapoeitic agents received since the previous visit/call).
Section 3.4.1 Screening Period Section 8.3 Clinical assessments	These sections have been updated to allow use of previously performed chest X-rays in case of re-screeening or screening, if chest X-rays were performed within a defined time window. In case of re-screening for patients below 30 kg, previously performed procedures may be used to satisfy screening requirements if re-screening is performed within 21 days from latest results.
Section 4.2 Exclusion criteria	Exclusion criterion 10 has been added in order to exclude patients with current or scheduled administration of therapies known to potentially trigger cytokine release syndrome within 21 days from HSCT. This exclusion criterion has been added given that cytokine release syndrome due to other therapies may interfere with the CXCL9 assessment at inclusion and be a confounding effect for treatment initiation/treatment effect assessment. Exclusion criterion 16 has been updated to allow ongoing participation to interventional trials involving supportive care such as probiotics or antiemetics, graft manipulation, or use of new combinations or new dosing of conventional therapies for conditioning and prophylaxis pre-HSCT. This exclusion criterion has been updated to facilitate recruitment of the target population, as many patients will participate in clinical trials related to new transplant procedures or conventional pre-HSCT treatments which are not expected to affect treatment effect.
Section 6.1 Infection prophylaxis	Herpes Zoster prophylaxis maintenance has been reduced to approximately 2 emapalumab half lives (i.e approximately 44 days) after end of treatment.
Section 6.3 Prohibited treatments	Wording of the prohibited treatments during emapalumab treatment (Methylprednisolone) has been updated for clarity.
Section 7 Study endpoints	This section has been updated to specify in detail the dual component of the main study objective i.e. dose selection and preliminary efficacy of emapalumab in pre-empting graft failure. Wording of the efficacy, safety and immunogenicity endpoints has been updated for clarity and in compliance with the Statisticial Analysis Plan (SAP) wording.

Applicable Sections	Change/Reason
Section 8 Visit schedule and study assessments	Tables 5, 6, 7 (foot notes) have been updated to specify that the inflammatory biomarker sample may also be used to assess baseline values of anti-drug antibodies (ADA). Table 6a has been updated to take off donor chimerism assessment at dose 1 and dose 3. Table 7 Schedule of assessments follow-up period has been updated to add a foot note to specify that during the survival check period (3 years) only Serious Adverse Events (SAEs) related to emapalumab treatment should be collected and reported.
Section 8.4 Laboratory assessments Table 6 Schedule of assessments treatment period (foot note) Table 7 Schedule of assessments follow-up period (foot note)	These sections/tables have been updated to specify that biochemistry is assessed in fasting conditions only "whenever possible".
Section 9.1 Adverse Events	The definition of treatment emergent adverse event (AE) has been updated. Section 9.1.4 Reporting of AEs and 9.2.2 Reporting of SAEs have been re-worded for clarity and reporting procedure of SAE forms has been updated.
Section 9.3 Pregnancy	This section has been updated to clarify the pregnancy reporting process. The patient transition to follow up (for emapalumab treated patients) or to withdrawal visit (for untreated patients) in case of pregnancy has also been clarified.
Section 10.2 Potential Risks	Section 10.2.4 Graft versus tumor effect has been updated to add clarification that the potential effects of emapalumab in patients with hematological or other malignancies undergoing allo HSCT are still unknown. Reference is made to the Investigator's Brochure (IB) for further details.
Section 11.1 Criteria for study treatment interruption/discontinuation	This section has been updated to take off conditions to discontinue treatment (any infection reported as an SAE caused by pathogens favoured by emapalumab treatment and severe infusion related hypersentivity reactions) in line with other emapalumab studies. A general study treatment discontinuation criterion (any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety) has been added.
Section 11.1.4 Non-evaluable patients	This section has been updated to change wording from "replacement" to "non-evaluable" patients and to add conditions for considering a patient non-evaluable for exclusion from the "All evaluable population" analysis. It is also clarified that recruitment for the interim analysis and final analysis will continue until the required number of evaluable patients have been treated.
Section 11.2.1. Temporary study suspension	These sections have been updated to take off one condition for study suspension (occurrence of one systemic infection reported as SAE caused by pathogens favored by emapalumab administration) in line with other emapalumab studies.
Section 12.2 Interim analyses	This section has been updated for clarity and to add details of the additional interim analyses at 10 evaluable patients and at 1 year, 2 years and 3 years post-HSCT.
Section 12.4 Definition of study populations	This section has been updated to add a "Per Protocol" population definition in compliance with the SAP.

PROTOCOL SYNOPSIS

TITLE	An open label, single arm, multicentre, proof of concept, phase 2 study to investigate the pharmacokinetics, pharmacodynamics and assess the efficacy and safety to support dose selection of emapalumab in pre-empting graft failure in patients at high risk after allogeneic hematopoietic stem cell transplantation
SPONSOR	Sobi AG, Switzerland
STUDY DESIGN	Open-label, single arm, sequential dose cohorts, proof of concept, phase 2 study
STUDY OBJECTIVES	The main objective of this proof of concept study is: • To determine the appropriate emapalumab dose regimen neutralizing interferon gamma (IFNγ) activity to pre-empt graft failure (GF) post allogeneic hematopoietic stem cell transplantation (HSCT) in a population with various underlying diseases and at high risk of GF. The following objectives will support the main objective: • To describe the Pharmacokinetic (PK) and Pharmacodynamic (PD) profiles of emapalumab post allogeneic HSCT (allo-HSCT). • To assess the efficacy of emapalumab to pre-empt GF post allo-HSCT. • To assess the safety of emapalumab to pre-empt GF post allo-HSCT. • To assess the immunogenicity of emapalumab post allo-HSCT. Exploratory objectives will be: • To evaluate further data on the correlation between relevant biomarkers including C-X-C motif chemokine ligand 9 (CXCL9) levels and the risk of GF post allo-HSCT in a population with various underlying diseases and at high risk of GF also in the context of development of a diagnostic test.
POPULATION	Children and adults, with malignant and non-malignant underlying diseases, receiving allo-HSCT who are at high risk of GF will be included in the study. Once the appropriate dose has been determined in cohort 1, 2 or 3 and safety assessed by an Independent Data Monitoring Committee (IDMC), children less than 1 year old willbe included in the study. Patients will be included in the study if they meet all the inclusion criteria and none of the exclusion criteria below.
INCLUSION CRITERIA	1. Informed consent form signed by the patient (as required by law) or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as applicable. 2. Recipients of allogeneic HSCT and at high risk of GF based on at least one of the following criteria: • Receiving reduced intensity conditioning (RIC) or non-myeloablative conditioning (NMA) combined with a non-malignant disease or with a graft from Bone Marrow (BM). • *Ex vivo* T cell depleted graft. • Graft from mismatched unrelated or haploidentical donor. • Graft from Umbilical Cord Blood (UCB). 3. Patients requiring allo-HSCT with the following underlying diseases:

	• Malignant disease with high risk of GF, i.e. Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) with primary induction failure, second partial remission or relapse; Chronic Myeloid Leukemia (CML) in blastic phase (circulating blast or blast above 5% in biopsy); Non Hodgkin and Hodgkin Lymphoma and multiple myeloma with primary induction failure, second partial remission or relapse, myelodysplastic syndromes (MDS) and myeloproliferative disorders (MPD) with splenomegaly, myelofibrosis with portal hypertension pre-transplant, MDS/MPD overlap syndromes. • Non-malignant hematological diseases (e.g. autoimmune and metabolic disorders, aplastic anemia, Sickle cell anemia, Fanconi anemia, Diamond-Blackfan anemia, thalassemia, osteopetrosis, Wiskott-Aldrich syndrome, severe combined immunodeficiency, Hemophagocytic lymphohistiocytosis and other immunoregulatory disorders). 4. Male and female patients. 5. Children aged at least 1 year and adults. Once the appropriate dose has been determined in one of the three cohorts and safety has been assessed by the IDMC, children less than 1 year old may be included in the study. 6. Females of child-bearing potential, defined as all women physiologically capable of becoming pregnant, require use of highly effective contraceptive measures from screening until 6 months after the last study drug administration.
EXCLUSION CRITERIA	1. Pregnant (or planning to become pregnant) or lactating female patients. 2. Body weight < 3 kg. 3. Underlying malignant disease with Karnofsky/Lansky performance status equal or less than 40 or an Eastern Cooperative Oncology Group (ECOG) performance status equal or less than 3. 4. Patients presenting CXCL9 levels 10 times above the upper limit of the 95% interval (CI) of the normal range (reported in the CXCL9 assay laboratory manual) within 24 hours prior to HSCT. 5. Clinically manifested infections caused by typical and atypical Mycobacteria, Salmonella, Histoplasma capsulatum and Herpes Zoster on the day of HSCT. 6. Active or clinical suspicion of latent tuberculosis. 7. Concomitant diseases that in the opinion of the Investigator may interfere with the assessment of emapalumab safety or efficacy. 8. Receipt of a Bacille Calmette-Guerin (BCG) vaccine within 3 months prior to HSCT. 9. Receipt of a live or attenuated live (other than BCG) vaccine within 6 weeks prior to HSCT. 10. Current or scheduled administration of therapies known to potentially trigger a cytokine release syndrome within 21 days from HSCT. 11. Patients having received IFNγ during the last 2 weeks prior to HSCT and/or who require treatment with IFNγ. 12. Patients having received emapalumab during the last 6 months prior to HSCT, unless it is known that emapalumab is no longer detectable.

	13. Patients having received kinase inhibitors (Janus kinase inhibitors [JAKi] or bruton tyrosine kinase inhibitors [BTKi]) one week (or 5 half-lives whichever is greater) prior to HSCT. 14. Intolerance to antimicrobial and virus infection prophylaxis. 15. Hypersensitivity to emapalumab or any of the excipients. 16. Ongoing participation in an interventional trial or administration of any investigational drug (within 3 half-lives of the investigational drug) with the exception of interventional trials involving supportive care such as probiotics or antiemetics, graft manipulation, or use of new combinations or new dosing of conventional therapies for conditioning and prophylaxis pre-HSCT.
STUDY PERIODS	**Screening period** Patients enrolled into the study will undergo screening assessments between day -21 and day -8 prior to HSCT. Eligibility is also assessed prior to HSCT (Day 0). Patients will be stratified into two groups at screening to include at least 40% malignant and 40% non-malignant patients. Stratification will allow to explore the appropriate dose inhibiting IFNγ production in a similar number of patients presenting with malignant or non-malignant disease in each cohort. **Allogeneic HSCT** Patients' eligibility is assessed also prior to HSCT and patient's will be considered included in the study if he/she meets all inclusion/exclusion criteria prior to HSCT on day 0. **Monitoring period** The monitoring period will start from the day after the HSCT (day 1) and will last until the absolute neutrophil count (ANC) is above or equal to 500 cells/µL or maximum until monitoring day 42±1, whichever comes first. During the monitoring period, CXCL9 and ANC measurements will be performed daily from day 1 up to day 7, every other day starting from day 9 until day 21 and every 3 days (±1) starting from day 24 until day 42. CXCL9 measurements will be performed by means of a validated assay on a device provided to the sites by Sobi AG. The exact CXCL9 threshold for treatment initiation will be provided in the CXCL9 assay laboratory manual. • If CXCL9 is measured above threshold and ANC is below 500 cells/µL, patients will enter the treatment period. • If CXCL9 is measured below threshold and ANC is below 500 cells/µL, patients will continue the monitoring period until day 42±1 or until a second HSCT is planned. • As soon as the ANC will be ≥500 cells/µL during the monitoring period, patients will move to the extended monitoring period for secondary GF (sGF). **Extended monitoring period** The extended monitoring period will start as soon as the ANC will be ≥500 cells/µL during the monitoring period and will last maximum 98±3 days. During the extended monitoring, CXCL9 and ANC measurements will be performed weekly up to day 98±3 days. In case of signs of sGF outside of the weekly visits, the patient should attend for an unscheduled visit and the assessments foreseen in the extended monitoring period visit should be performed to assess eligibility for treatment.

	• If CXCL9 is measured above threshold and there are signs of sGF (i.e. donor chimerism drop of at least 10% for 2 consecutive measurements and/or ANC below 500 cells/µL and/or thrombocytopenia below 30000/µL not explained by any other reason than potential graft rejection), patients may optionally enter the treatment period, if the investigator will consider pre-emptive treatment with emapalumab the best option for the patient. • If CXCL9 is measured below threshold, patients will continue the extended monitoring period until Day 98±3 days or until a second HSCT is planned. **Criteria not to start treatment during monitoring or extended monitoring** Patients presenting the following conditions at time of initiation of emapalumab treatment will not be eligible to receive emapalumab and will move to the phone-call follow-up period for non-emapalumab treated patients. • Uncontrolled infections (defined as clinically active infection regardless of treatment). • Clinical manifestations of infections representing exclusion criteria (i.e. Atypical mycobacteria, Salmonella, Histoplasma capsulatum, Herpes zoster). • Re-occurrence or progression of the underlying malignant disease based on medical judgment. • Graft versus host disease (GvHD). **Treatment period** • Patients will be monitored for eligibility to treatment during the monitoring and extended monitoring periods. Patients treated for primary or secondary GF will receive emapalumab for maximum 15 infusions or until engraftment is confirmed. • Engraftment is defined as ANC ≥ 500 cells/µL for 3 consecutive measures and donor chimerism above 60% (for primary GF) or ANC ≥ 500 cells/µL for 3 consecutive measures and 2 consecutive measures of donor chimerism above 60% or 7 days of platelets above 20000 cells/µL without transfusion (for secondary GF). • Preferably, ANC recovery should be based upon three consecutive laboratory values (ANC sample drawn 1 or 2 days apart maximum). • Patients must be hospitalized in case of active infections requiring intravenous (IV) antimicrobial therapy during treatment. • If engraftment is confirmed prior to the last dosing day (dose 15) or if the patient discontinues treatment, patients will perform all assessments as per end of treatment visit (EoT) and can be discharged if hospitalized provided that there is no active infections requiring IV antimicrobial therapy. • Patients who take prohibited medications will not be discontinued from emapalumab treatment unless for medical reasons. • Pre-emptive treatment for secondary GF is optional and it is investigator's responsibility to decide whether to start pre-emptive treatment with emapalumab or not.

	Follow-up period (3 years): The follow-up period will last 3 years for both patients who received and who did not receive emapalumab. **Follow-up period (emapalumab treated patients)** All emapalumab treated patients will enter the follow-up period: • Upon completion of treatment or engraftment, whichever comes first. • In case of premature treatment discontinuation for any reason. The follow-up period for patients who received emapalumab will consist of 6 visits: at 1 week ±2 days, 2 weeks ±2 days, 4 weeks ±2 days, 8 weeks ±1 week, 12 weeks ± 1 week and 24 weeks ± 2 weeks after last study drug administration (EoS visit) and 3 phone calls for survival observation at 1, 2 and 3 years after HSCT. During the survival calls defined concomitant medications/procedures and occurrence of GvHD since previous visit/call should be recorded. The first follow-up visit will be 1 week ± 2 days after last study drug administration or 1 week after EoT (in case of treatment discontinuation or engraftment before the last dosing). **Follow-up period (non-emapalumab treated patients)** In case treatment with emapalumab has not been initiated, patients will undergo an EoS visit (within 1 week from the last day in the monitoring periods) and enter the phone calls follow-up. A patient can enter the follow-up period in the following occasions: • At the end of the monitoring (Day 42) or extended monitoring (Day 98). • If they require a second HSCT anytime during the monitoring periods.. • If any prohibited medication is taken during the monitoring periods. • In case of re-occurrence of malignant disease, GvHD diagnosis, uncontrolled infection or clinical manifestations of infections representing exclusion criteria at time of eligibility to treatment. The follow-up period for patients who have entered the monitoring periods and did not receive emapalumab will consist of 4 phone calls at 6 months, 1, 2 and 3 years after HSCT. During the survival calls defined concomitant medications/procedures and occurrence of GvHD since previous visit/call should be recorded. **End of Study (EoS) Visit** • For emapalumab treated patients, the EoS visit corresponds to the last follow-up visit (Follow-up visit 6) at week 24 ±2 days from last study drug administration. • Non-emapalumab treated patients will require to attend the EoS visit within 1 week from the last day in the monitoring periods.
STUDY DRUG ADMINISTRATION, DOSING REGIMEN AND TREATMENT DURATION	Patients entering the monitoring or extended monitoring period and fulfilling the criteria to be pre-emptively treated for primary or secondary graft failure will receive emapalumab as described below: • Emapalumab will be administered by intravenous (IV) infusion over 1 to 2 hours, depending on the volume of the infusion.

	• The first infusion must be performed within 12 hours from CXCL9 sample collection time (levels measured above defined threshold). • Treatment will last until maximum dose 15 (up to 56 days) or until evidence of engraftment, whichever comes first. • The first cohort of patients will receive a first infusion of 6 mg/kg at treatment day 0 (TD0), followed by a second infusion at 3 mg/kg after 3 days (TD3). Subsequent infusions of 3 mg/kg will be every 3 or 4 days from previous dose until dose 15 or until engraftment. • A maximum of 2 additional cohorts may be added to allow dosing regimen adaptation based on the PK/PD data observed from the previous cohort(s). Efficacy and safety data will also be considered before adding additional cohorts. • Patients optionally treated for secondary graft failure will receive the same dose of the patients treated for primary graft failure.
TRANSITION BETWEEN COHORTS	• After the last patient of each cohort (cohort 1, 2 or 3) has completed emapalumab treatment for primary GF (4 evaluable patients), patient screening will be put on hold until data will be analyzed. • Patients in monitoring or extended monitoring periods (at the time the Sponsor will communicate that screening is on hold) will proceed to the EoS visit and thereafter transition to the follow-up period (for non-emapalumab treated patients) and receive treatment as per medical practice. • Patients in treatment phase for primary (or secondary) GF will continue to be treated as per protocol. • The Sponsor will communicate to the investigators any decision on the dose regimen to be adopted to the next cohort or if additional patients will be added to the same cohort. • Screening will be resumed once the Sponsor confirms that the study will enroll additional patients in the same dose cohort or if an additional cohort will be initiated with dose regimen adaptations.
INTERIM ANALYSES	Interim analyses (IAs) are planned when the last patient completes pre-emptive treatment for primary GF in a cohort (4 evaluable patients). Once the appropriate dose regimen is determined in cohort 1, 2 or 3, a maximum of 6 additional evaluable patients may be added to the selected cohort. Additional IAs are planned when 7 and 10 evaluable patients have completed treatment with the selected dose, unless the study is stopped for futility or success. A final analysis with all data collected up to EoS will be included in a CSR. IAs will be also performed after 1 and 2 years follow up calls and data collected up to 3 years follow up will be included in an addendum to the CSR.
STUDY COMMITTEES	• An IDMC will be involved during the conduct of the study. The IDMC is composed of relevant experts (external to Sobi AG) and will review the data with the aim to assess the benefit/risk ratio of emapalumab administration and ensure patient safety. • A Dose Decision Committee (DDC) will be responsible for deciding the dose regimen to apply in cohorts 2 and 3 based on a review of PK, PD, efficacy and safety data. The DDC will confirm the appropriate dose and the addition of patients to the last cohort. The DDC is composed of relevant Sobi employees and external experts as necessary.

BACKGROUND THERAPY AND CARE	**INFECTION PROPHYLAXIS** • Patients must receive prophylactic treatment for Herpes Zoster prior to initiation of emapalumab treatment. Prophylaxis should be maintained until approximately 2 emapalumab half lives (i.e. approximately 44 days) after end of treatment. • In case a patient, previously vaccinated for tuberculosis, shows a Purified Protein Derivative (PPD) test result ≥ 5mm and a negative IFNγ-release assay, patients will receive tuberculosis (TB) prophylaxis according to local medical practice. **AUTHORIZED TREATMENTS** The following treatments are allowed during the study: • Prophylaxis and therapy of infections (antibiotics, antifungal and anti-viral) as per local medical practice. • Conditioning (myeloablative conditioning [MAC], RIC or NMA) prior to HSCT as per local medical practice. • GvHD prophylaxis and treatment as per local medical practice. • Steroids during monitoring, extended monitoring and follow up. • During emapalumab treatment only topical steroids are allowed and methylprednisolone up to 2 mg/kg/day (or other equivalent steroid dose) for not more than 2 days. • Hematopoietic growth factors, stem cell boost, donor lymphocyte infusion (DLI). • Intravenous immunoglobulin (IVIG) is only allowed as replacement treatment (i.e. not at doses expected to produce an immunomodulatory effect) based on medical judgement. • Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, IV parenteral nutrition, inotropic support, ultrafiltration or hemodialysis.
	PROHIBITED TREATMENTS The following treatments are not allowed during emapalumab treatment: • Methylprednisolone more than 2 mg/kg/day (or other equivalent steroid dose) for more than 2 days. The following treatments are not allowed during monitoring/extended monitoring and during emapalumab treatment: • All kinase inhibitors. • Interferon gamma-1b. • Biologic drugs (except rituximab used to treat EBV infection or to remove B-cells producing donor specific antibodies). The following treatments are not allowed during the study up to 6 months after the last emapalumab dose or until the end the monitoring period for untreated patients: • Live or attenuated (including BCG) vaccine.
SAMPLE SIZE	In order to treat 4 patients for primary GF per cohort, it is expected to include between 15 to 40 patients to be monitored for primary or secondary GF per cohort. This is based on the assumption that between 10 and 30% of patients will present with a CXCL9 elevation above defined threshold when ANC is below 500 cells/μL during the monitoring period (Sobi AG internal data).

	Considering a maximum of 3 sequential cohorts of 4 evaluable patients, 6 additional evaluable patients to the final cohort with determined dose and potential replacements, it is expected that approximately a maximum of 250 patients will be included in the study to be monitored for graft failure. Given the experience gained with emapalumab in other indications such as hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), a robust PK/PD model has been developed therefore 4 evaluable patients per cohort and a maximum of 3 cohorts are considered sufficient to confirm the PK/PD profile in post-HSCT patients and determine the appropriate dose regimen to pre-emptively treat patients at high risk of GF. Assuming a similar rate of primary and secondary GF, a similar number of patients may optionally start treatment for secondary GF in each cohort. Additional patients may be treated for secondary GF in the final cohort with determined dose.
NON-EVALUABLE PATIENTS	Patients treated for primary GF are considered non-evaluable in case of: • Administration of any prohibited medication during treatment. • Premature treatment withdrawal for reasons other than safety or lack of efficacy. • More than 1 infusion is missed. • Documented delay of treatment initiation by more than 36 hours from CXCL9 sample collection time (levels above threshold). Recruitment will continue until the required number of evaluable patients for each interim analysis and final analysis is met. This definition does not apply for treatment of secondary GF patients.
SITE(S)/COUNTRY(IES)	Approximately 25 sites in around 6-7 countries will participate to the study. Additional sites and countries may be added to ensure recruitment objectives.
STUDY DURATION AND STUDY END DEFINITION	A patient's participation is expected to last approximately 3 years from screening to last phone call Study end is defined as the last patient last call at the end of the follow-up period or at any time before the end of the follow-up period when the last patient completes their last visit.
STUDY ENDPOINTS	The main objective is dual and is composed of: • Dose selection. • Preliminary efficacy of emapalumab treatment pre-empting GF. The endpoints used to assess dose selection are: • Serum concentrations of free emapalumab. • Serum concentration of total IFNγ. • Serum concentration of CXCL9. The main endpoint used to preliminarly assess efficacy of emapalumab in pre-empting GF is: • Occurrence of primary GFs from start of treatment up to end of treatment.

	Efficacy • Occurrence of primary GF from HSCT up to EoS visit. • Occurrence of secondary GF from HSCT up to EoS visit. • Occurrence of primary or secondary GFs from HSCT up to EoS visit. • Occurrence of mixed donor chimerism <10% and <20% (based on unselected leukocytes or sorted T cells) from HSCT up to EoS visit. • Occurrence of received transfusion of blood products due to poor graft function, hematopoietic growth factors, stem cell boost or DLI from HSCT up to 3 years follow up. • Occurrence of receiving an additional allogeneic HSCT from HSCT up to 3 years follow up. • Occurrence of poor graft function from HSCT up to EoS visit. • Occurrence of event free engraftment from HSCT up to 3 years follow up. • Occurrence of GvHD from HSCT up to 3 years follow up. • Occurrence of engraftment syndrome from HSCT up to EoS visit. • Occurrence of endothelial complications from HSCT up to EoS visit. • Overall survival from HSCT up to 3 years follow up. **Safety** • Occurrence of relapse, defined as cumulative incidence of reoccurring malignant underlying disease from HSCT up to EoS visit. • Occurrence of AEs up to EoS visit. • Occurrence of AEs leading to discontinuation of study treatment. • Change from baseline in vital signs, laboratory parameters up to EoS visit. **Immunogenicity** • Occurrence of antibodies against emapalumab (ADA) and Neutralizing antibodies (Nab) from start of treatment up to EoS visit. **Pharmacokinetics** • Serum concentrations of free emapalumab. • PK parameters by non-compartmental analysis (NCA): Cmax (peak serum concentration), Ctrough (concentration just before administration), Cmeantau (mean concentration over a dosing interval), AUCtau (area under curve of a dosing interval), and other parameters as applicable. • Population PK parameters, as applicable. **Pharmacodynamics** • Serum concentrations of free IFNγ (before emapalumab treatment), total IFNγ (free + bound to emapalumab), and CXCL9 (as marker of IFNγ neutralization). • Exploratory inflammatory biomarkers relevant to emapalumab mechanism, condition, underlying disease (e.g. soluble interleukin 2 receptor alpha [sIL2Rα], ferritin, interleukin-6 [IL-6], tumor necrosis factor alpha [TNFα] and soluble CD163 [sCD163]). • Exploratory blood tests measuring cell subsets (e.g. fluorescence-activated cell sorting [FACS] for analysis of specific T-cell and/or macrophage subsets).

	Exploratory endpoints • CXCL9 and other biomarkers relevant to the diagnostic test development measured with different analytical technologies.
STATISTICAL METHODOLOGY	All analyzes are considered exploratory. Efficacy and safety data will be presented by descriptive statistics. Continuous variables will be summarized using the number of patients, the mean, the standard deviation, the median, the minimum value, and the maximum value. Categorical variables will be summarized using frequency counts and percentages. For the appropriate dose cohort the point estimates for the efficacy endpoints will be presented together with the corresponding 95% CI. The relationship between selected covariates (e.g. biomarkers, baseline characteristics) and treatment response will be investigated. The correlation between CXCL9 levels and the risk of GF will be evaluated in the untreated patients. The relationship between selected covariates and the risk of GF will be investigated in the untreated patients.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-drug Antibodies
AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophils Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUCtau	Area Under the Curve of a dosing interval
BCG	Bacillus Calmette-Guérin
BM	Bone Marrow
BTKi	Bruton Tyrosine Kinase inhibitors
CFR	Code of Federal Regulation
CI	Confidence Interval
Cmax	Peak serum concentration
Cmeantau	Mean Concentration over a dosing interval
CML	Chronic Myeloid Leukemia
CMV	Cytomegalovirus
CRA	Clinical Research Associate
CRP	C-reactive Protein
CSR	Clinical Study Report
Ctrough	Concentration just before administration
CU	Compassionate Use
CXCL9	C-X-C Motif Chemokine Ligand 9
eCRF	Electronic Case Report Form
DDC	Dose Decision Committee
DLI	Donor Lymphocyte Infusion
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EoS	End of Study
EoT	End of Treatment
FACS	Fluorescence-activated Cell Sorting

FDA	Food and Drug Administration
FW24	24-week Follow-up
γGT	Gamma-glutamyl Transpeptidase
GCP	Good Clinical Practice
GF	Graft Failure
GvHD	Graft versus Host Disease
HDL	High-density Lipoprotein
HLA	Human Leukocyte Antigen
HLH	Hemophagocytic Lymphohistiocytosis
HSC	Hematopoietic Stem Cell
HSCT	Hematopoietic Stem Cell Transplantation
HZV	Herpes Zoster Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	Intrnational Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethic Committee
IFNγ	Interferon gamma
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IgG1	Immunoglobulin G1
IL-6	Interleukin 6
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRR	Infusion-related Reaction
IV	Intravenous
IVIG	Intravenous Immunoglobulin
JAKi	Janus Kinase inhibitors
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
MAC	Myeloablative Conditioning
MAS	Macrophage Activation Syndrome
MDS	Myelodysplastic Syndromes
MHC	Major Histocompatibility Complex
MPD	Myeloproliferative Disorders
MRD	Minimal Residual Disease
MSD	Meso Scale Discovery

Nab	Neutralizing Antibodies
NaCl	Sodium Chloride
NCA	Non-compartmental Analysis
NK	Natural Killer
NMA	Non-myeloablative
NOAEL	No Observed Adverse Effect Level
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
pGF	Primary Graft Failure
pHLH	Primary hemophagocytic lymphohistiocytosis
PK	Pharmacokinetic
PPD	Purified Protein Derivative
PPV	Positive Predictive Value
PT	Prothrombin Time
RBC	Red Blood Cells
RIC	Reduced Intensity Conditioning
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
sCD163	Soluble CD163
sGF	Secondary Graft Failure
sHLH	Secondary hemophagocytic lymphohistiocytosis
sIL2Rα	Soluble Interleukin 2 Receptor alpha
sJIA	Systemic Juvenile Idiopathic Arthritis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TD	Treatment Day
TEAE	Treatment Emergent Adverse Event
TEN	Toxic Epidermal Necrolysis
TMF	Trial Master File
TNFα	Tumor Necrosis Factor alpha
UCB	Umbilical Cord Blood
WBC	White Blood Cells
WHO	World Health Organization

1 BACKGROUND INFORMATION

1.1 Rationale for targeting Interferon gamma (IFNγ) in graft failure

Hematological stem cell transplant (HSCT) is a potentially life-saving treatment for a number of hematological disorders and malignancies in both adults and in children. However allogeneic HSCT is associated with the risk of graft failure (GF). GF is classified as either primary GF or secondary GF, depending on whether there has been an initial engraftment or not. The diagnosis of GF post HSCT is made on the basis of neutropenia and may be associated with neutropenic fever and infections, including the reactivation of viral infections. Laboratory testing of peripheral blood for chimerism is also established for engraftment monitoring and predicting GF (1).

Immunological mechanisms are thought to be responsible for GF and the surviving T-cells in the recipient are believed to play a major role. Animal studies also indicate that natural killer (NK) cells may be involved (2). The hypothesis is that allogeneic HSCT GF occurs as a result of cell-mediated immune action by residual host immune cells that become activated in the presence of the human leukocyte antigen (HLA) mismatch between the donor and recipient immune cells. Activated cells produce IFNγ inducing immune mediators including C-X-C motif chemokine ligand 9 (CXCL9). Interferon gamma (IFNγ) has been reported to play a deleterious effect on hematological stem cell (HSC) proliferation in many preclinical studies (3, 4, 5).

Emapalumab is a fully human high-affinity anti-IFNγ monoclonal antibody (mAb) that binds to and neutralizes human IFNγ. Emapalumab has been approved by the Food and Drug Administration (FDA) for the treatment of primary hemophagocytic lymphohistiocytosis (HLH).

The following data support the use of emapalumab for GF prevention:

- Nonclinical models of GF.
- Clinical data from:
  1. The Sponsor's studies of emapalumab in HLH patients undergoing HSCT, NI-0501-04 and NI-0501-05, and from compassionate use.
  2. A published study of the role of IFNγ in pediatric patients who underwent HSCT and who experienced GF compared with matching pediatric controls (6).
  3. Patients with kidney transplant rejection.

Based on these initial data, it is hypothesized that elevation of CXCL9 levels predict GF and IFNγ activity could be antagonized post HSCT by administration of emapalumab.

1.1.1 Non-clinical evidence

Studies in mice have indicated an important role for IFNγ in haematopoiesis. De Bruin et al (4) showed in a series of experiments in mice that IFNγ can impair the proliferation of stem cells by negatively modulating their cell cycle via an effect on erythropoietin signaling within the cells. They postulated a role for chronic IFNγ signaling in disorders with impaired stem cell proliferation such as aplastic anemia and graft versus host disease in producing sustained impairment of stem cell renewal.

Using transgenic mice engineered to chronically produce IFNγ (7), they showed that the animals developed a phenotype that resembled human aplastic anemia with loss of bone marrow (BM) cellularity at 3 weeks of age, loss of myeloid cells and pancytopenia at week 6. In this model, there was an inhibition of myeloid progenitor differentiation. Investigations showed no role for T-cell autoimmunity and the authors suggested that aplastic anemia occurs as a result of impaired generation of myeloid progenitors and lineage differentiation rather than an autoimmune mechanism. This report provided consistent negative impact of IFNγ on stem cell proliferation.

Using wild type and IFNγ-receptor deficient mouse strains (8), authors further investigated the role of IFNγ in aplastic anemia with a series of *in vitro* and *in vivo* studies. Treatment with IFNγ produced expanded clones of c-Kit+Sca-1+Lin- cells, with a high proliferative capacity skewed towards myelopoiesis in the BM. These cells engrafted poorly when tested *in vivo* and showed increased Fas expression. When co-cultured with activated T-cells *in vitro*, the cells showed increased apoptosis compared to cells in IFNγ-untreated animals. In models of BM-failure, IFNγ-receptor deficient mice showed attenuated BM destruction and lymphocytes from IFNγ-

deficient strains were less effective in producing BM damage. They concluded that IFNγ enhances apoptotic gene expression in HSC and progenitors and facilitates their destruction in the presence of activated T-cells.

Furthermore, animal studies in IFNγ-receptor deficient mice (9), showed that high serum IFNγ concentration is both necessary and sufficient for graft rejection, inhibiting the development of heterologous, IFNγR1-expressing, hematopoietic cell lineages. The results confirmed that IFNγ is an anti-hematopoietic cytokine *in vivo*. The authors suggested that they paved the way for HSCT management in IFNγR1-deficient patients through IFNγ depletion from the blood. They further raise the possibility that depleting IFNγ may improve engraftment in other settings, such as HSCT from a haplo-identical or unrelated donor.

Using Bacillus Calmette-Guerin (BCG) vaccination in IFN-γR1-deficient mice to create high levels of IFNγ (10), other researchers further investigated the relationship between IFNγ and post-HSCT BM chimerism. Using this model, they first confirmed that successful HSCT chimerism, following a transplant at day 21 correlates with IFNγ levels; the early phase (up to 56 days after BCG) was characterized by high IFNγ and a low proportion of donor cells in the bone marrow, whereas in the later phase, falling IFNγ level was inversely correlated with an increasing proportion of donor cells in the bone marrow.

The suppression of chimerism by the BCG vaccination in the early phase following a transplant at day 21, was abolished by administration of a mouse anti-IFNγ. The cytokine CXCL9 was monitored in the model and the administration of the mouse anti-IFNγ in the early phase following BCG (up to day 56) suppressed CXCL9 plasma levels.

Finally, it was already hypothesized by Murphy in 1987 that HSCT GF occurs via an immunological mechanism relying on surviving recipient T and NK-cells (2). The risk factors for GF are supportive of this hypothesis, particularly the increased incidence when non-myeloablative conditioning (MAC) is used. In addition, animal transplant studies with major histocompatibility complex (MHC)-chimeric animals showed raised levels of IFNγ and rapid loss of chimerism (11).

Preclinical evidence consistently reports the negative impact of IFNγ on stem cell proliferation in a context of activated T-cells, which is likely to work against the engraftment of the donor cells for allogeneic HSCT, even more when non-MAC regimens are used and/or when important HLA mismatches are present.

1.1.2 Clinical evidence

Observational clinical data supporting the rationale to investigate emapalumab in GF are derived from pediatric studies in HLH (NI-0501-04 and NI-0501-05), emapalumab compassionate use cases (data in Sponsor files), and a separate prospective data set of pediatric patients with varying underlying diseases who received HSCT (6).

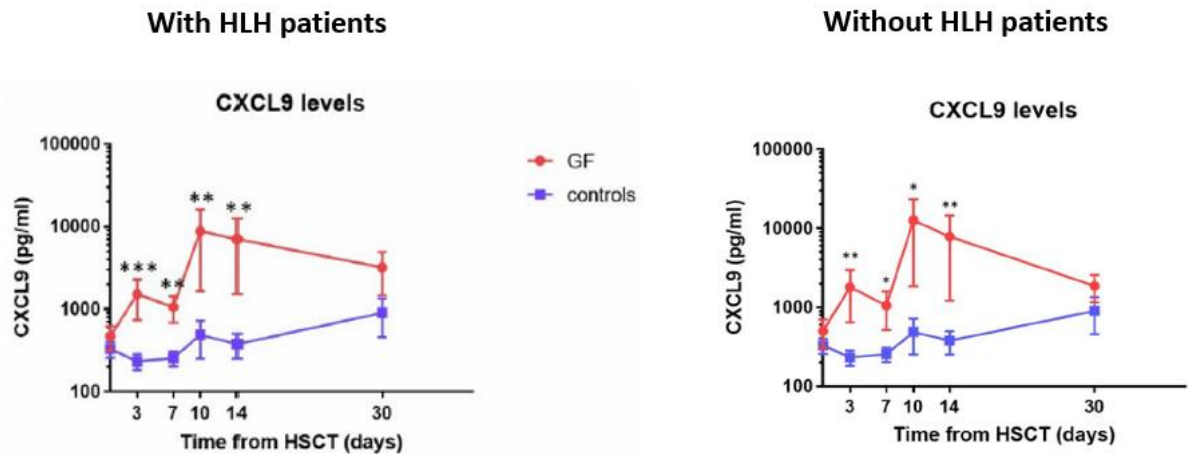
Data from HLH patients undergoing HSCT (n=26) in studies NI-0501-04 and NI-0501-05, and after compassionate use of emapalumab, show a systematic and specific elevation of IFNγ prior to GF (primary and secondary), and in particular an elevation of CXCL9. CXCL9 is almost exclusively produced by activation of the IFNγ receptor and therefore a good surrogate marker of IFNγ activity. An elevation of CXCL9 above 300 pg/mL (value obtained by measuring CXCL9 with Meso Scale Discovery [MSD] assay) was observed several days prior to any other evidence of primary GF and a few days before (or concomitantly) to secondary GF. An elevation of CXCL9 was shown to predict GF with an approximately 86% positive predictive value (PPV) (i.e. risk of GF in patients positive for the marker) and 90% to 100% sensitivity (very low or no false negatives).

In conclusion, during the post-transplant period, total IFNγ levels (and even more specifically CXCL9 levels) were elevated in patients experiencing GF. On the contrary, low levels of CXCL9 were observed in patients that didn't experience GF. Given that an elevation of CXCL9 above 300 pg/mL was systematically observed prior to GF post HSCT, CXCL9 can be considered a good predictor of GF.

A separate prospective data set (6), including 15 pediatric patients with various underlying diseases who received HSCT and experienced GF, and 15 matching pediatric controls who did not experience, has shown the same and highly predictive IFNγ signature of GF (Figure 1).

CXCL9 levels by day 3 post-transplant predicted GF with 88.89% sensitivity based on a cutoff of 274.5 pg/mL. Additionally, CXCL9 levels observed prior to GF in patients without HLH were consistent with the levels observed in HLH patients.

Figure 1: CXCL9 Levels Increase from Day 3 Post HSCT in GF patients and similarly for HLH and non-HLH Patients



***: p<0.05; **: p<0.01; ***: p<0.001**

Left figure (with HLH patients): n=30, right figure (without HLH patients): n= 26
Abbreviations: CXCL9, C-X-C Motif Chemokine Ligand 9; GF, graft failure; HLH, hemophagocytic lymphohistiocytosis; HSCT, Hematopoietic stem cell transplantation.
Source: Merli et al., 2019 (6).

In addition, an association of elevated CXCL9 levels with kidney graft rejection has been reported (12). Hricik et al. (13) reported similar predictive values for CXCL9 in acute kidney graft rejection as were observed in HLH patients who underwent HSCT. In this report, CXCL9 predicts the risk for acute kidney graft rejection around 68% and captures nearly all patients at risk (negative predictive value of 92%).

1.1.3 Summary

These data suggest that blocking IFNγ should promote engraftment of donor cells. Given that (i) blocking IFNγ as a treatment approach once GF has occurred would not allow restoration of dead or dying transplanted cells and (ii) a preventive approach would require the treatment of many patients who would not experience GF (between 70 and 80% of the patients who undergo HSCT will not experience GF) it is proposed initiate emapalumab only in high-risk patients (as defined in the inclusion criteria) and once an early elevation of CXCL9 is observed after HSCT in the absence of engraftment.

1.2 Emapalumab

1.2.1 Description and Mode of Action

Emapalumab (previously referred to as NI-0501, trade name Gamifant®) is a fully human immunoglobulin G1 (IgG1) anti-IFNγ monoclonal antibody that binds to and neutralizes IFNγ. Emapalumab binds to both soluble and receptor (IFNγR1)-bound forms of IFNγ.

1.2.2 Preclinical Data

1.2.2.1 Non-clinical Pharmacology

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

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

1.2.2.2 Toxicology

Binding and functional data demonstrated that Rhesus and Cynomolgus monkeys were relevant species for evaluating the safety of emapalumab. No off-target toxicity was attributed to emapalumab when it was 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 the expected pharmacological effect of emapalumab (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.

While it was not possible to establish the No Observed Adverse Effect Level (NOAEL) in the 13-week toxicity study, the NOAEL in the 8-week study was assumed to be the highest dose tested, i.e. 30 mg/kg/week.

Embryo-fetal development, as well as fertility and early embryonic development studies, were performed in mice, testing therapeutic and multiple doses of the rat anti-mouse IFNγ surrogate antibody XMG 1.2. No effects on embryo-fetal development (i.e., embryo-fetal survival, fetal weight, sex ratio or morphology) were observed. No effects were observed on estrous cycling in treated females, mating or fertility in treated male or treated female mice, male reproductive organ weights, or any ovarian, uterine, or litter parameter related to treatment of male or female mice. The NOAEL for emapalumab in these studies was therefore determined to be the highest dose-level tested of 150 mg/kg.

More details are available in the current Investigator's Brochure (IB).

1.2.3 Clinical Data

1.2.3.1 Phase 1 experience

Emapalumab has been evaluated in a randomized, double-blinded, placebo-controlled, single ascending dose Phase 1 study (protocol NI-0501-03) in 20 healthy adult subjects. Six subjects received placebo and 14 received emapalumab IV at single ascending doses of 0.01, 0.1, 1 and 3 mg/kg.

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

The infusions of emapalumab were well tolerated. The monitoring after drug infusion did not reveal any serious or unexpected off–target safety or immunogenicity concerns. A Herpes Zoster infection was reported as a serious adverse reaction in the highest dose group (3 mg/kg), which resolved with conventional treatment. This serious adverse reaction can be considered as a consequence of the expected pharmacological effect of emapalumab.

More details are available in the current IB.

1.2.3.2 Phase 2/3 experience

An open-label, single arm, international, multicenter Phase 2/3 study evaluated the efficacy, safety and PK/pharmacodynamic (PD) profiles of multiple intravenous (IV) administrations of emapalumab in pediatric patients with primary HLH (pHLH) (study NI-0501-04).

The primary efficacy endpoint was Overall Response at the End of the Treatment (EoT) in the study NI-0501-04 defined as achievement of either a complete or partial response or HLH improvement based on pre-specified objective criteria. Overall Response Rate at EoT was 64.7% (95% CI: 44%, 78%) in all patients, and 63% (95% CI: 42%, 81%) in second-line patients. In both groups, the lower limit of the 95% CI was higher than the pre-defined null hypothesis of 40% (p=0.0031 and p=0.0134, respectively).

Overall, 70.6% of all treated patients were alive at last observation, with a median follow-up time of 13.6 months (interquartile range: 4.5 to 15.3 months). Among the patients who underwent HSCT, 91% of all treated patients were alive at last observation (up to 1-year post-HSCT).

The median duration of treatment was 8.4 weeks (range from 4 days to 30 weeks). Doses of 1-10 mg/kg have been administered. The great majority of infusions were well tolerated.

In line with the risks due to the immune deficiency status of pHLH patients, the most commonly reported AEs were infections, which were reported in 19 patients. In 11 patients, infections were reported as a SAE. Only 2 SAEs (both infections) were assessed as possibly related to emapalumab, one disseminated histoplasmosis (leading to treatment discontinuation) and one necrotizing fasciitis (assessed by the Investigator as possibly related based on the temporal relationship). Both events resolved upon administration of appropriate antibiotics. At study entry, 13 patients had ongoing infections, which did not preclude initiation of emapalumab.

An open-label, single arm, multicenter Phase 2 study (Study NI-0501-06) is ongoing to evaluate the efficacy and safety of emapalumab in systemic juvenile idiopathic arthritis (sJIA) patients developing active macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis (sHLH) who have shown inadequate response to standard of care. The dosing regimen foresees emapalumab administration at an initial dose of 6 mg/kg and continuation at a dose of 3 mg/kg every 3 days until study day 15 and twice-a-week thereafter.

Study NI-0501-05 is ongoing to enable the long-term surveillance and collect outcome data for patients who have received at least one infusion of emapalumab in either NI-0501-04, NI0501-06 or compassionate use (CU) patients. The protocol includes a follow-up period of 1 year after HSCT or 1 year after last emapalumab infusion for patients not undergoing HSCT. No safety concern has emerged from the long-term safety surveillance.

An open-label, single arm, multicenter study (Study NI-0501-09) is ongoing to provide wider access to emapalumab to pHLH patients who have failed or are intolerant to conventional HLH therapies or who are treatment naïve. Emapalumab is administered at a starting dose of 3 mg/kg with the option to increase the dose to 6 mg/kg or 10 mg/kg. Infusions will be performed twice weekly, except for the second infusion which must be administered on day 3. The duration of treatment is minimum 4 weeks and maximum 6 months.

Additional studies are ongoing for secondary forms of HLH. For more details on the clinical experience, please refer to the current IB.

1.2.3.3 Conclusion

Emapalumab is in development for the treatment of primary and secondary forms of HLH. The benefit expected from the targeted neutralization of IFNγ by emapalumab has been validated by the recent FDA approval of emapalumab (Gamifant®) for the treatment of patients with pHLH who have refractory, recurrent or progressive disease or intolerance with conventional HLH therapy. The safety profile of emapalumab has been assessed as acceptable, and no post-marketing commitments have been requested by the FDA with regard to safety.

Based on the analyses conducted to date, no sign of any off-target effect of emapalumab has been detected.

Multiple medications have been administered concomitantly with emapalumab and no evidence of drug-drug interactions has been reported to date.

2 OBJECTIVES

The main objective of this proof of concept study is:

- To determine the appropriate emapalumab dose regimen neutralizing IFNγ activity to pre-empt graft failure post allogeneic HSCT in a population with various underlying diseases and at high risk of GF.

The following objectives will support the main objective:

- To describe the PK and PD profiles of emapalumab post allo-HSCT.
- To assess the efficacy of emapalumab to pre-empt GF post allo-HSCT.
- To assess the safety of emapalumab to pre-empt GF post allo-HSCT.
- To assess the immunogenicity of emapalumab post allo-HSCT.

Exploratory objectives will be:

- To evaluate further data on the correlation between relevant biomarkers including C-X-C motif chemokine ligand 9 (CXCL9) levels and the risk of GF post allo-HSCT in a population with various underlying diseases and at high risk of GF also in the context of development of a diagnostic test.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Overall study design

This study is an open-label, single arm, sequential dose cohorts, proof of concept phase 2 study and it enrolls children and adults receiving allogeneic HSCT who are at high risk of graft failure. Children less than 1 year old will be included only after the appropriate dose regimen has been determined in one of the three cohorts and safety assessed by an Independent Data Monitoring Committee (IDMC).

The study is comprised of the following study periods: screening (Day -21 to Day -8), allogeneic HSCT Day 0, monitoring period for primary GF (Day 1 up to Day 42), extended monitoring for secondary GF (up to Day 98), treatment period (up to 56 days) and follow-up period of 3 years after HSCT. The overall study design is shown in Table 1.

Patients presenting CXCL9 levels above a defined threshold and an ANC below 500 cells/µL will be eligible to receive emapalumab during the monitoring period (Day 1 to Day 42).

Patients presenting CXCL9 levels above thresholds and signs of secondary GF (i.e. donor chimerism drop of at least 10% for 2 consecutive measurements and/or absolute neutrophil count [ANC] below 500 cells/µL and/or thrombocytopenia below 30000/µL not explained by any other reason than potential graft rejection) during the extended monitoring period (up to Day 98) will also be eligible to receive emapalumab. Pre-emptive treatment for secondary GF is optional.

A maximum of 3 cohorts is foreseen to determine the appropriate dose to pre-emptively treat primary GF. Data will be analyzed after the last patient completes emapalumab treatment in each cohort. After each cohort, the Sponsor will decide whether to stop the study or to add an additional cohort with dosing regimen adaptation based on observed PK/PD profile and benefit risk profile.

Once the appropriate dose has been determined a maximum of 6 evaluable additional patients may be added to the corresponding cohort to explore the potential benefit of emapalumab in preventing primary GF.

Patients will be stratified at screening in order to include at least 40% malignant and 40% non-malignant (by means of an interactive response technology).

Table 1: Overall study design for cohort 1, 2 or 3

SCREENING	HSCT	MONITORING (Primary GF)	EXTENDED MONITORING (Secondary GF)	FOLLOW-UP (for emapalumab treated[2] and non-emapalumab treated patients[3])
Day -21 to Day-8	**Day 0**	**Day 1 to Day 42**	**Up to Day 98[1]**	**3 years from HSCT**
		Criteria to start emapalumab treatment for prevention of primary GF: **ANC < 500/µL + CXCL9 above threshold**	Criteria to start emapalumab treatment for prevention of secondary GF: **Signs of secondary GF[4] + CXCL9 above threshold**	
		↓ ↓ ↓ ↓ Treatment must start within 12 hours from CXCL9 sample collection time **TREATMENT PERIOD** (Up to engraftment[5] or **maximum 15 doses**)	↓ ↓ ↓ ↓ Treatment must start within 12 hours from CXCL9 sample collection time **TREATMENT PERIOD (optional)** (Up to engraftment[5] or **maximum 15 doses**)	

[1]Extended monitoring for secondary GF (sGF) starts as soon as ANC equal or above 500 cells/µL during the monitoring period.

[2]For patients treated with emapalumab: the follow-up period starts one week after last study drug administration (or EoT) and consists of 6 visits and 3 phone calls at 1, 2 and 3 years after HSCT.

[3]For patients who have not received emapalumab: the follow-up period will start one week after the last day in the monitoring or extended monitoring periods and will last 3 years from HSCT and will consist of phone calls at 6 months, 1, 2 and 3 years after HSCT.

[4]Donor chimerism drop of at least 10% for 2 consecutive measurements and/or ANC below 500 cells/µL and/or thrombocytopenia below 30000/µL not explained by any other reason than potential graft rejection.

[5]Engraftment for primary GF is defined as ANC ≥ 500 cells/µL for 3 consecutive measures and donor chimerism above 60%. Engraftment for secondary GF is defined as ANC ≥ 500 cells/µL for 3 consecutive measures and 2 consecutive measures of donor chimerism above 60% or 7 days of platelets above 20000 cells/µL without transfusion.

3.2 Study design rationale

This study is designed as an open-label, single arm, proof of concept study in order to determine the appropriate emapalumab dosing regimen neutralizing IFNγ in patients at risk of GF prior to initiating a pivotal study.

An open label, single arm design is considered appropriate given the life-threatening condition of the patient population and due to the early stage of development of emapalumab in this indication. The proposed treatment strategy is not an alternative to current treatments, therefore patients will receive the same standard of care as if they were not enrolled in the study.

Patients receiving HSCT at high risk of GF will be included in the study to ensure patients with highest unmet need are included. Only patients presenting CXCL9 levels above a defined threshold and an ANC below 500 cells/µL will be eligible to receive emapalumab treatment for primary GF. Patients with CXCL9 above threshold will also be eligible to receive emapalumab based on treating physician's decision in case of signs of secondary graft failure (i.e. donor chimerism drop of at least 10% for 2 consecutive measurements and/or ANC below 500

cells/μL and/or thrombocytopenia below 30000/μL not explained by any other reason than potential graft rejection) during the extended monitoring period.

CXCL9 elevation is observed several days prior to any clinical signs of primary GF and provides the opportunity of a biomarker driven pre-emptive treatment approach and to initiate early treatment to inhibit the deleterious activity of IFNγ on the graft. In case of secondary GF, preliminary observations have shown an elevation of CXCL9, a few days before GF or concomitantly (see section 1.1.2 and IB). This preliminarily observed difference of CXCL9 elevation time prior to GF justifies the need to consider pre-emptive treatment of secondary GF as optional based on medical judgment.

For the above mentioned reasons, each study cohort completion is based on the recruitment of the required number of evaluable patients treated for primary GF (see sample size section 12.1). Given that similar PK/PD profile of emapalumab is expected in patients treated to pre-empt primary and secondary GF, data obtained in the secondary GF patients may be used to inform dose decision for the subsequent cohorts.

Patients with CXCL9 levels below threshold will be monitored and will enter follow up for non-emapalumab treated patients at the end of the monitoring periods. This additional group of patients will allow to confirm the frequency of GF when CXCL9 levels are below threshold.

In clinical practice, GF is usually not confirmed until at least day 21 and up to 42 days following HSCT, therefore the monitoring period for primary GF will last up to 42 days. As soon as an ANC is ≥500 cells/μL, patients will enter the extended monitoring period for secondary GF which will last up to 98 days. ANC increase can occur within 10 days after HSCT, but may take up to 30-40 days, mostly depending on the source of stem cells. Secondary GF, which may occur after initial engraftment, is usually observed within the first few months after transplant, therefore the extended monitoring will last up to 98 days.

To achieve rapid IFNγ neutralization, an initial dose of 6 mg/kg emapalumab will be administered. To maintain further IFNγ neutralization covering the duration of engraftment, emapalumab administration will be continued at a dose of 3 mg/kg after 3 days (second infusion) and every 3 or 4 days thereafter until stable engraftment has been achieved or until a maximum of 15 doses. This definition of treatment duration will guarantee that patients are treated until the graft has clearly engrafted but not beyond. Further details on the dose regimen rationale can be found in section 5.3.

Patients treated pre-emptively for secondary graft failure will receive the same dose regimen as patients treated pre-emptively for primary graft failure in the 3 cohorts.

Patients will be followed up until 3 years post HSCT in order to collect survival data, occurrence of GvHD and use of defined treatments or procedures to support the graft function post-transplant.

Patients will be stratified at screening into two groups in order to include at least 40% malignant and 40% non-malignant. Stratification will allow to explore the appropriate dose inhibiting IFNγ production in a similar number of patients presenting malignant or non-malignant disease in each cohort. Patients below 1 year are considered more vulnerable and will therefore not be included in the study until the safety has been confirmed in patients 1 year or older.

3.3 Transition between cohorts

- After the last patient of each cohort (cohort 1, 2 or 3) has completed emapalumab treatment for primary GF (4 evaluable patients), patient screening will be put on hold until data will be analyzed.
- Patients in monitoring or extended monitoring periods (at the time the Sponsor will communicate that screening is on hold) will proceed to the EoS visit and thereafter transition to the follow-up period (for non-emapalumab treated patients) and receive treatment as per medical practice.
- Patients in treatment phase for primary or secondary GF will continue to be treated as per protocol.
- The Sponsor will communicate to the investigators any decision on the dose regimen to be adopted to the next cohort or if additional patients will be added to the same cohort (rules described in section 12.2).
- Screening will be resumed once the Sponsor confirms that the study will enroll additional patients in the same dose cohort or if an additional cohort will be initiated with dose regimen adaptations.

3.4 Study periods

3.4.1 Screening Period

Screening starts with the signature of the informed consent by the patient or by the patient's legally authorized representative prior to any study-related procedures. It is the responsibility of the investigator/delegate to obtain written informed consent from each subject or legally authorized representative(s) after adequate face-to-face explanation of the objectives, methods, and potential hazards of the study.

It is permitted to re-screen patients once if the reason for non-eligibility was transient (e.g. abnormal laboratory test, insufficient wash-out period of a forbidden medication). All screening assessments must be repeated at the time of re-screening, except chest X-ray which should be repeated if older than 21 days. For patients below 30 kg, procedures performed during the screening period may be used to satisfy screening requirements if re-screening is performed within 21 days from the latest results.

Chest X-rays performed as part of medical practise prior to screening may be used to satisfy screening requirements if they are performed within the screening window of 21 days before HSCT.

Patients who have given written informed consent will undergo screening assessments between Day -21 and Day -8 prior to HSCT and will be assessed for eligibility to enter the study. Eligibility is also assessed prior to HSCT (Day 0). Patients will be stratified in order to include at least 40% of the patients with malignant and 40% with non-malignant disease (by means of an interactive response technology). Stratification will allow to explore the appropriate dose inhibiting IFNγ production in a similar number of patients presenting with malignant or non-malignant disease in each cohort. Assessments to be performed during screening are presented in the schedule of assessment (Table 5a and Table 5b).

A patient screening log will be maintained by the investigator for all eligible and non-eligible patients, with specification of reasons for non-eligibility, if applicable.

3.4.2 Allogeneic HSCT

Assessments to be performed on the day of HSCT are presented in the schedule of assessment (Table 5a and Table 5b) Patient's eligibility is assessed by checking inclusion/exclusion criteria prior to HSCT on Day 0. A patient is considered included in the study if he/she meets all inclusion/exclusion criteria prior to HSCT.

3.4.3 Monitoring and extended monitoring periods

Assessments to be performed during the monitoring periods are presented in the schedule of assessment (Table 5a and Table 5b).

See Table 2 and Table 3 for details on the transition from monitoring to extended monitoring, treatment and follow up in case of ANC < 500/µL (Table 2) and ≥500 cells/µL (Table 3) during the monitoring period.

CXCL9 measurements will be performed by means of a validated assay on a device provided to the sites by Sobi AG. The exact CXCL9 threshold for treatment initiation will be provided in the CXCL9 assay laboratory manual.

Monitoring period

The monitoring period will start from the day after the HSCT (day 1) and will last until ANC is ≥500 cells/µL or maximum until monitoring day 42±1, whichever comes first. During the monitoring period, CXCL9 and ANC measurements will be performed daily from day 1 up to day 7, every other day starting from day 9 until day 21 and every 3 days (±1) starting from day 24 until day 42.

- If CXCL9 is measured above threshold and ANC is below 500 cells/µL, patients will enter the treatment period.
- If CXCL9 is measured below threshold and ANC is below 500 cells/µL, patients will continue the monitoring period until day 42±1 or until a second HSCT is planned.
- As soon as the ANC will be ≥500 cells/µL during the monitoring period, patients will move to the extended monitoring period for secondary GF (sGF).

Extended monitoring period

The extended monitoring period will start as soon as the ANC will be equal or above 500 cells/µL during the monitoring period and will last maximum 98±3 days.

During the extended monitoring, CXCL9 and ANC measurements will be performed weekly up to day 98±3 days. In case of signs of sGF outside of the weekly visits, the patient should attend for an unscheduled visit and the assessments foreseen in the extended monitoring period visit should be performed to assess eligibility for treatment.

- If CXCL9 is measured above threshold and there are signs of sGF (i.e. donor chimerism drop of at least 10% for 2 consecutive measurements and/or ANC below 500 cells/µL and/or thrombocytopenia below 30000/µL not explained by any other reason than potential graft rejection), patients may optionally enter the treatment period, if the investigator will consider pre-emptive treatment with emapalumab the best option for the patient.
- If CXCL9 is measured below threshold, patients will continue the extended monitoring period until Day 98±3 days or until a second HSCT is planned.

Criteria not to start treatment during monitoring or extended monitoring

Patients presenting the following conditions at time of initiation of emapalumab treatment will not be eligible to receive emapalumab and will move to the phone-call follow-up period for non-emapalumab treated patients (see section 3.4.5).

- Uncontrolled infections (defined as clinically active infection regardless of treatment).
- Clinical manifestations of infections representing exclusion criteria (i.e. Atypical mycobacteria, Salmonella, Histoplasma capsulatum, Herpes zoster).
- Re-occurrence or progression of the underlying malignant disease based on medical judgment.
- GvHD.

3.4.4 Treatment Period

Assessments to be performed during the treatment period are detailed in the Schedule of Assessments (Table 6a and Table 6b).

Criteria to enter treatment during the monitoring and extended monitoring period, and not to start treatment, are defined in section 3.4.3.

- Patients treated for primary or secondary GF will receive emapalumab for maximum 15 infusions or until engraftment is confirmed.
- Engraftment is defined as ANC ≥ 500 cells/µL for 3 consecutive measures and donor chimerism above 60% (for primary GF) or ANC ≥ 500 cells/µL for 3 consecutive measures and 2 consecutive measures of donor chimerism above 60% or 7 days of platelets above 20000 cells/µL without transfusion (for secondary GF).
- Preferably, ANC recovery should be based upon three consecutive laboratory values (ANC sample drawn 1 or 2 days apart maximum).
- Patients must be hospitalized in case of active infections requiring IV antimicrobial therapy during treatment.
- If engraftment is confirmed prior to the last dosing day (dose 15) or if patients discontinue treatment, patients will perform all assessments as per end of treatment visit (EoT) and can be discharged if hospitalized provided that there is no active infections requiring IV antimicrobial therapy.
- Patients who take prohibited medications will not be discontinued from emapalumab treatment unless for medical reasons.
- Pre-emptive treatment for secondary GF is optional and it is investigator's responsibility to decide whether to start pre-emptive treatment with emapalumab or not.

End of Treatment (EoT) visit

Assessments to be performed during the EoT visit are detailed in the Schedule of Assessments (Table 6a and Table 6b).

Patients who discontinue treatment or engraft before the last dosing day (dose 15) will attend the EoT visit. Patients who complete treatment until dose 15 will not be required to undergo an EoT visit.

3.4.5 Follow-Up Period

Assessments to be performed during the follow-up period are detailed in the Schedule of Assessments (Table 7a and Table 7b). The follow-up period will last 3 years from the HSCT date for both patients who received and those who did not receive emapalumab, as detailed below.

Follow-up period: emapalumab treated patients

All emapalumab treated patients will enter the follow-up period:

(i) Upon completion of treatment or engraftment, whichever comes first

(ii) In case of premature treatment discontinuation for any reason

The follow-up period for patients who received emapalumab will consist of 6 visits: at 1 week ±2 days, 2 weeks ±2 days, 4 weeks ±2 days, 8 weeks ±1 week, 12 weeks ± 1 week and 24 weeks ± 2 weeks after last study drug administration (EoS visit) and 3 phone calls for survival observation at 1, 2 and 3 years after HSCT.

During the survival calls defined concomitant medications/procedures (i.e. any HSCT, blood product transfusion, stem cell boost, DLI or hematopoietic agents) and occurrence of GvHD since previous visit/call should be recorded.

The first follow-up visit will be 1 week ± 2 days after last study drug administration or 1 week after EoT (in case of treatment discontinuation or engraftment before the last dosing day).

Follow-up period: non-emapalumab treated patients

In case treatment with emapalumab has not been initiated, patients will undergo an EoS visit (within 1 week from the last day in the monitoring periods) and enter the phone calls follow-up.

A patient can enter follow-up in the following occasions:

(i) At the end of the monitoring (Day 42) or extended monitoring (Day 98).

(ii) If they require a second HSCT anytime during the monitoring periods.

(iii) If any prohibited medication is taken during the monitoring periods.

(iv) In case of re-occurrence of malignant disease, GvHD diagnosis, uncontrolled infection or clinical manifestations of infections representing exclusion criteria at time of eligibility to treatment.

The follow-up period for non-emapalumab treated patients will consist of 4 phone calls at 6 months, 1, 2 and 3 years after HSCT. During the survival calls defined concomitant medications/procedures (i.e. any HSCT, blood product transfusion, stem cell boost, DLI or hematopoietic agents) and occurrence of GvHD since previous visit/call should be recorded.

End of Study Visit

Assessments to be performed during the EoS visit are detailed in the Schedule of Assessments (Table 7a and Table 7b).

- For emapalumab treated patients, the EoS visit correspond to the last follow-up visit (Follow-up visit 6) at week 24 ±2 days from last study drug administration.
- Non-emapalumab treated patients will require to attend the EoS visit within 1 week from the last day in the monitoring periods.

Table 2 Transition between periods in case of ANC < 500 cells/µL during the monitoring period

Monitoring	**Treatment**	**Follow-up** For emapalumab treated patients	**Follow-up** For non-emapalumab treated patients
CXCL9 **above threshold** + ANC <500 cells/µL ➡	Enter treatment period	Enter follow-up period: ✓ Upon completion of treatment or engraftment during treatment, whichever comes first ✓ Upon premature treatment discontinuation for any reason	Perform EoS visit and enter phone-calls follow-up period: ✓ At the end of monitoring or ext monitoring period ✓ In case of re-occurrence of malignant disease, GvHD diagnosis, uncontrolled infection or clinical manifestations of infections representing exclusion criteria at time of treatment ✓ If a second HSCT is required ✓ If any prohibited med is taken during the monitoring periods
CXCL9 **below threshold** + ANC <500 cells/µL ⬇ Continue monitoring ✓ Unless a second HSCT is required ✓ As soon as ANC ≥ 500, transition to extended monitoring Table 3			

Table 3 Transition between periods in case of ANC ≥ 500 cells/µL during the monitoring period

Monitoring	**Extended Monitoring**	**Treatment**	**Follow-up** For emapalumab treated patients	**Follow-up** For non-emapalumab treated patients
As soon as ANC ≥ 500 cells/µL during monitoring, enter extended monitoring	CXCL9 **above threshold** + Signs of sGF ➡	Enter treatment period	Enter follow-up period: ✓ Upon completion of treatment or engraftment during treatment, whichever comes first ✓ Upon premature treatment discontinuation for any reason	Perform EoS visit and enter phone-calls follow-up period: ✓ At the end of monitoring or ext monitoring period ✓ In case of re-occurrence of malignant disease, GvHD diagnosis, uncontrolled infection or clinical manifestations of infections representing exclusion criteria at time of treatment ✓ If a second HSCT is required ✓ If any prohibited med is taken during the monitoring periods
	If CXCL9 **below threshold** Continue extended monitoring unless a second HSCT is required			

3.4.6 Unscheduled visit

Assessments to be performed during the unscheduled visit are detailed in the Schedule of Assessments (Table 7a and Table 7b). Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit, appropriate assessments will be performed based on medical judgment. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

3.4.7 Withdrawal visit

Assessments to be performed during the withdrawal visit are detailed in the Schedule of Assessments (Table 7a and Table 7b). In case of premature withdrawal from the study for any reason (except informed consent withdrawal), patients should undergo a withdrawal visit within 1 week from the date of withdrawal.

3.5 Study duration and study end

The study will start with the act of signing the informed consent form and ends with the last phone call or last patient visit. The study is expected to last approximately 3 years from screening to the last phone call for each patient.

Study end is defined as the last patient last call at the end of the follow-up period (3 years) or at any time before the end of the follow-up period when the last patient completes their last visit.

3.6 Study committees

3.6.1 Independent Data Monitoring Committee

An IDMC has responsibility for safeguarding the interests of subjects by monitoring relevant data obtained in the study and making appropriate recommendations based on the reported data.

The IDMC will be fully operational prior to enrolment of the first subject into the study. The IDMC is composed of relevant experts (external to Sobi AG) and will review the data with the aim to assess the benefit/risk ratio of emapalumab administration and ensure patient safety.

The composition, frequency of meetings and operation of the IDMC is described in the IDMC charter.

3.6.2 Dose Decision Committee

A Dose Decision Committee (DDC) will be responsible for deciding the dose regimen to apply in cohorts 2 and 3 based on a review of PK, PD, efficacy and safety data. The DDC will confirm the appropriate dose and the addition of patients to the last cohort. The DDC is composed of relevant Sobi employees and external experts as necessary.

The composition, frequency of meetings and operation of the DDC is described in the DDC charter.

4 STUDY POPULATION

Children and adults, with malignant and non-malignant underlying diseases, receiving allo-HSCT, who are at high risk of GF, will be included in the study. Children less than 1 year old will be included in the study once the appropriate dose regimen has been determined in cohort 1, 2 or 3 and safety has been assessed by the IDMC. Patients will be included in the study if they meet all the inclusion criteria and none of the exclusion criteria below.

4.1 Inclusion criteria

1. Informed consent form signed by the patient (as required by law) or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as applicable.
2. Recipients of allogeneic HSCT and at high risk of GF, based on at least one of the following criteria:
   - Receiving reduced intensity conditioning (RIC) or non-myeloablative (NMA) conditioning, combined with a non-malignant disease or with a graft from Bone Marrow (BM).
   - *Ex vivo* T cell depleted graft.
   - Graft from mismatched unrelated or haploidentical donor.
   - Graft from Umbilical Cord Blood (UCB).
3. Patients requiring allo-HSCT with the following underlying diseases:
   - Malignant disease with high risk of GF, i.e. Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL), with primary induction failure, second partial remission or relapse; Chronic Myeloid Leukemia (CML) in blastic phase (circulating blast or blast above 5% in biopsy); Non Hodgkin and Hodgkin Lymphoma and multiple myeloma with primary induction failure, second partial remission or relapse; myelodysplastic syndromes (MDS) and myeloproliferative disorders (MPD) with splenomegaly; myelofibrosis with portal hypertension pre-transplant; MDS/MPD overlap syndromes.
   - Non-malignant hematological diseases (e.g. autoimmune and metabolic disorders, aplastic anemia, Sickle cell anemia, Fanconi anemia, Diamond-Blackfan anemia, thalassemia, osteopetrosis, Wiskott-Aldrich syndrome, severe combined immunodeficiency, Hemophagocytic lymphohistiocytosis and other immunoregulatory disorders).
4. Male and female patients.
5. Children aged at least 1 year and adults. Once the appropriate dose has been determined in one of the three cohorts and safety has been assessed by the IDMC, children less than 1 year old may be included in the study.
6. Females of child-bearing potential, defined as all women physiologically capable of becoming pregnant, require the use of highly effective contraceptive measures from screening until 6 months after the last study drug administration.

4.2 Exclusion criteria

1. Pregnant (or planning to become pregnant) or lactating, female patients.
2. Body weight < 3 kg.
3. Underlying malignant disease with Karnofsky/Lansky performance status equal or less than 40 or an ECOG performance status equal or less than 3.
4. Patients presenting CXCL9 levels 10 times above the upper limit of the 95% CI of the normal range (reported in the CXCL9 assay laboratory manual) within 24 hours prior to HSCT.
5. Clinically manifested infections caused by typical and atypical Mycobacteria, Salmonella, Histoplasma capsulatum and Herpes Zoster on the day of HSCT.
6. Active or clinical suspicion of latent tuberculosis.
7. Concomitant diseases that, in the opinion of the Investigator, may interfere with the assessment of emapalumab safety or efficacy.

8. Receipt of a Bacille Calmette-Guerin (BCG) vaccine within 3 months prior to HSCT.
9. Receipt of a live or attenuated live (other than BCG) vaccine within 6 weeks prior to HSCT.
10. Current or scheduled administration of therapies known to potentially trigger a cytokine release syndrome within 21 days from HSCT.
11. Patients having received IFNγ during the last 2 weeks prior to HSCT and/or who require treatment with IFNγ.
12. Patients having received emapalumab during the last 6 months prior to HSCT, unless it is known that emapalumab is no longer detectable.
13. Patients having received kinase inhibitors (Janus kinase inhibitors [JAKi] or bruton tyrosine kinase inhibitors [BTKi]) one week (or 5 half-lives whichever is greater) prior to HSCT.
14. Intolerance to antimicrobial and viral infection prophylaxis.
15. Hypersensitivity to emapalumab or any of the excipients.
16. Ongoing participation in an interventional trial or administration of any investigational drug (within 3 half-lives of the investigational drug) with the exception of interventional trials involving supportive care such as probiotics or antiemetics, graft manipulation, or use of new combinations or new dosing of conventional therapies for conditioning and prophylaxis pre-HSCT.

4.3 Criteria for women of childbearing potential

4.3.1 Acceptable methods of contraception

To ensure compliance, the study personnel must remind women of childbearing potential at each visit to use the methods of contraception defined for this study.

Females of child-bearing potential require the use of highly effective contraceptive measures (failure rate of less than 1% per year), from screening up to 6 months after the last study drug administration:

Highly effective contraceptive measures include:

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

The methods of birth control used (including non-pharmacological methods) must be recorded in the electronic Case Report Form (eCRF).

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Description of Investigational Medicinal Product

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

Emapalumab is manufactured by a third-party manufacturing facility duly qualified by Sobi AG and is supplied as described in the IMP Manual. Vials are filled single-use glass vials which require a 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 or 25 mg
L-Histidine	1.55 mg
L-Histidine monohydrochloride, monohydrate	3.14 mg
Sodium chloride (NaCl)	7.31 mg
Polysorbate 80	0.05 mg
pH	6.0 ± 0.2

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

5.2 Investigational Medicinal Product Handling

5.2.1 Packaging and Labeling

Emapalumab will be supplied to study sites in glass vials containing 10 mL or 20 mL solution at a concentration of 5 mg/mL or 25 mg/mL. Labeling and packaging will be prepared to meet local regulatory requirements. The Investigational Medicinal Product (IMP) Manual provides further details.

5.2.2 Investigational Medicinal Product Supply

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

5.2.3 Receipt, storage, preparation and administration

Emapalumab receipt, storage, preparation, administration will be described in details in the IMP manual.

5.2.3.1 Receipt and storage

The emapalumab vials will be transported with temperature monitoring device, in order to ensure consistent temperatures during transit. When the study drug is received at the site, the Investigator or Pharmacist will check for accurate delivery and absence of temperature deviation alarms.

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

Documentation of the storage conditions of the study drug must be maintained over the timeframe the study drug is stored at the site, until such time as it is used, disposed of, or returned to Sobi AG or designee.

Regular inspections of the emapalumab vials are required, as detailed in the IMP manual. For guidance on the Preparation and Administration of Individual Doses of Study Drug emapalumab refer to the IMP manual.

5.2.3.2 Preparation

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

The specific dose to be administered for an individual infusion is determined as detailed in section 5.4. As emapalumab is dosed in mg/kg, the weight of the patient must be taken within 24 hours of the preparation of the study drug for administration.

Full instructions for the preparation, including dilution steps, and method for administration of emapalumab are available in the IMP Manual that will be provided to all investigational sites.

5.2.3.3 Administration

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

It is recommended that an IV central line remains in place to ensure venous access during the treatment period. This will improve patient's comfort and ensure a reliable drug administration. However, peripheral infusions have been successfully performed in some patients.

Since no data are available on the compatibility of emapalumab with other IV substances or additives, other medications/substances should not be added to the infusion material or infused simultaneously through the same IV line. If the same IV line is used for subsequent infusions of other drugs, the line should be flushed appropriately with saline before and after infusion of emapalumab.

The infusion of emapalumab will be performed under the direct supervision of the Investigator (or delegate), preferably in the morning and preferably at the same time for each infusion, in an environment with access to emergency equipment and trained medical personnel.

Details of the infusion must be recorded in the patient's Medical Notes or other source documents and have to include:

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

In the event that a patient experiences an infusion-related reaction (IRR), the infusion may be halted (as per Investigator's judgment) and symptomatic treatment may be administered.

The decision to restart the infusion will be based on the evolution of the patient's status and on the physician's own medical judgment. The infusion will be restarted at half of the rate being used at the time of onset of the IRR.

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

5.2.4 IMP Accountability and Destruction

5.2.4.1 Accountability

When the study drug is received at the site, the Investigator or Pharmacist (or appropriate designee) should acknowledge its receipt by signing (or initialing) and dating the documentation. Documentation should be returned to Sponsor (or designee) and a copy retained in the Investigator's file.

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

Drug accountability records shall include:

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

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

Unused study drug must not be discarded or used for any purpose not authorized by the Sponsor.

5.2.4.2 Destruction, Return and Disposal

Periodically during the study and at the conclusion of participation of the study by the site, the CRA will monitor and collect the Drug Accountability Forms, before making arrangements for study drug return or authorization of destruction by the study site.

5.3 Rationale for Dosing Regimen

The PK and PD of emapalumab have been studied in primary HLH patients. It has been shown that emapalumab significantly decreased the concentrations of CXCL9. The PK and PD of emapalumab are influenced by IFNγ production. The higher the IFNγ production, the higher the clearance and the concentration of emapalumab required to reach the same level of CXCL9. In primary HLH patients, total IFNγ concentrations varied markedly (from 10^2 to 10^6 pg/mL) between subjects and within subjects as a function of time, indicating a sustained and variable IFNγ production. This required administration of emapalumab twice-a-week until HSCT and adaptation of the dose between 1 and 10 mg/kg.

In addition to the IFNγ production, population PK analyses of data obtained in HLH patients identified body weight (highly correlated to age) as the main factor influencing emapalumab PK. As emapalumab doses are administered in mg/kg, no additional dose adaptation is required in adults as compared to young children.

In an ongoing study (NI-0501-06) in sJIA in patients developing MAS, emapalumab is administered intravenously at an initial dose of 6 mg/kg and continued at 3 mg/kg for up to 4 weeks. Initial results suggest that in sJIA patients developing MAS, emapalumab administration not only neutralizes IFNγ activity, as indicated by normalization of CXCL9, and leads to a decrease in IFNγ production.

Given the pathophysiology of GF, it is likely that IFNγ production is acute and not sustained. However, the exact levels of IFNγ production in patients with various underlying diseases experiencing GF may vary within and between patients and it is unknown at this time if pre-emptive treatment with emapalumab may affect IFNγ

production and profile over time in this context. In addition, various degrees of chimerism can be expected prior to GF and varied IFNγ production may be observed. Because of the known impact of IFNγ production on emapalumab PK and PD, the Sponsor intends to characterize the level and evolution of IFNγ production in this study to define the appropriate emapalumab dosing regimen for prevention of allogenic HSCT GF.

To determine the emapalumab dosing regimen for the first cohort, the following elements have been taken into consideration:

- The initial dose of emapalumab should be high enough to limit loss of donor cells and to allow rapid reversal of the GF process which is likely to have already started upon elevation of CXCL9 in the patients at risk
- IFNγ activity should be neutralized during the entire engraftment period (ranging from 2 to 6 weeks, depending on the stem cell source)
- Prolonged administration should be limited to allow full graft-versus-tumor activity (for patients transplanted for hematological malignancies) and anti-infectious activity of the graft after successful HSCT.

To achieve rapid IFNγ neutralization, an initial dose of 6 mg/kg emapalumab will be administered. To maintain further IFNγ neutralization covering the duration of engraftment, emapalumab administration will be continued at a dose of 3 mg/kg after 3 days (second infusion) and every 3 or 4 days thereafter until stable engraftment has been achieved or until a maximum of 15 doses. This definition of treatment duration will guarantee that patients are treated until the graft has clearly engrafted but not beyond.

A similar dosing regimen consisting of a loading dose of 6 mg/kg and maintenance doses of 3 mg/kg for up to 4 weeks is currently being investigated in MAS/sJIA patients (study NI-0501-06).

To further support the proposed dosing regimen, simulations were performed based on the currently available PK and PK/PD models assuming either a sustained or a decreasing IFNγ production, as observed in primary HLH patients or MAS/sJIA patients, respectively.

Simulations were performed with a dosing duration of 2 weeks (Figure 3) and of 6 weeks (Figure 4). The upper graphs in the figures show the simulations in the case of a sustained IFNγ production. The graphs at the bottom show the simulations performed assuming a decrease in IFNγ production over time.

- On the left-hand side graphs, the total IFNγ concentrations are given as a function of time for initial total IFNγ concentrations of 10,000 pg/mL (orange lines), 50,000 pg/mL (blue lines) and 250,000 pg/mL (green lines).
- On the graphs in the middle, the emapalumab concentrations are given as a function of time for a body weight of 5 kg (dashed lines) and 70 kg (solid lines) and initial total IFNγ concentrations of 10,000 pg/mL (orange lines), 50,000 pg/mL (blue lines) and 250,000 pg/mL (green lines). The grey area indicates the mean of the individual three highest peak and trough concentrations observed in Studies NI-0501-04 and NI-0501-05 and in CU patients (cut-off date 20 July 2017).
- On the right-hand side graphs, the CXCL9 concentrations are given as a function of time for a body weight of 5 kg (dashed lines) and 70 kg (solid lines) and initial total IFNγ concentrations of 10,000 pg/mL (orange lines), 50,000 pg/mL (blue lines) and 250,000 pg/mL (green lines). The black dashed line indicates a CXCL9 level of 300 pg/mL.

Figure 3: PK and PD simulations assuming a sustained IFNγ production (upper panel) or decreasing IFNγ production (lower panel) for an emapalumab dosing duration of 2 weeks

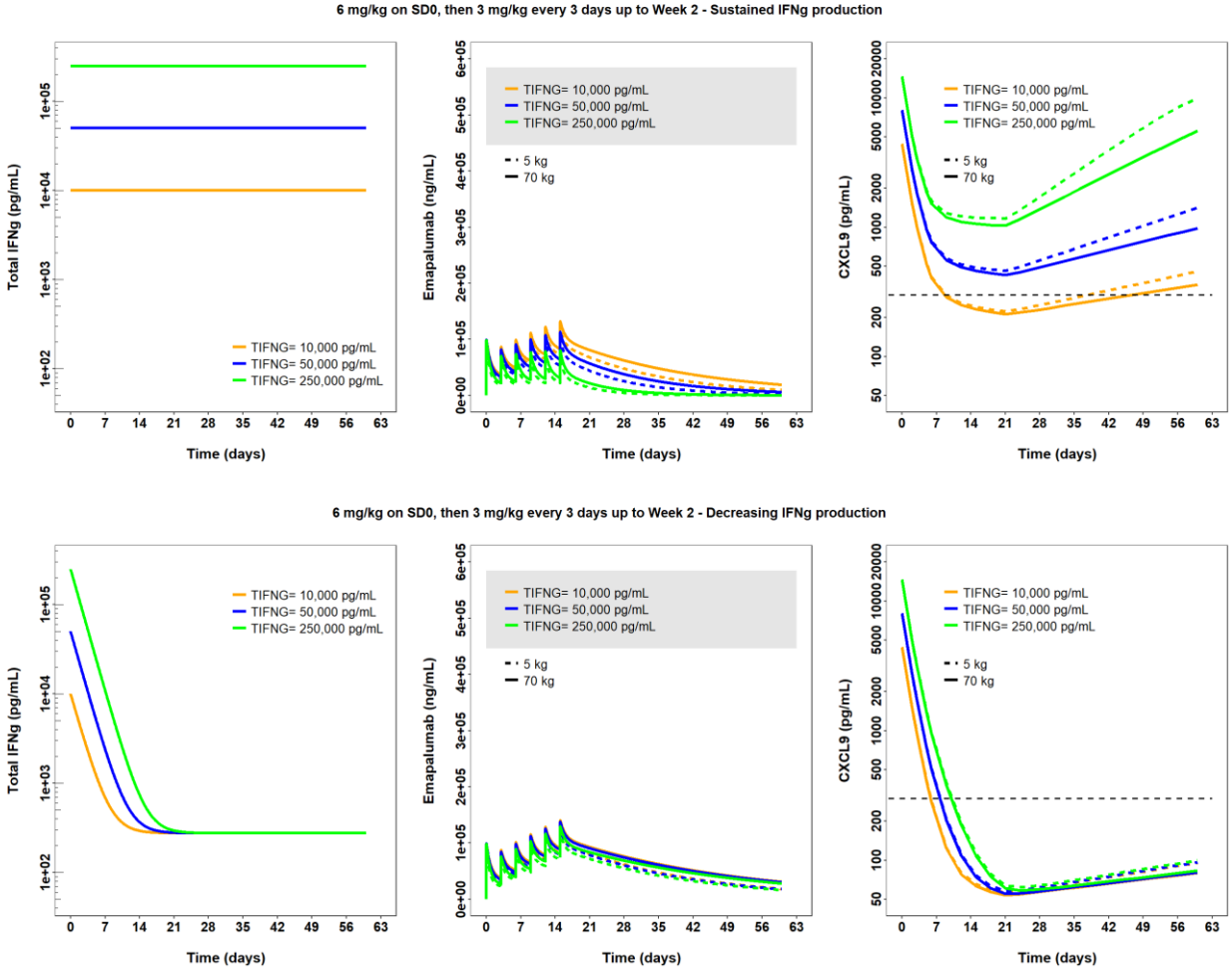
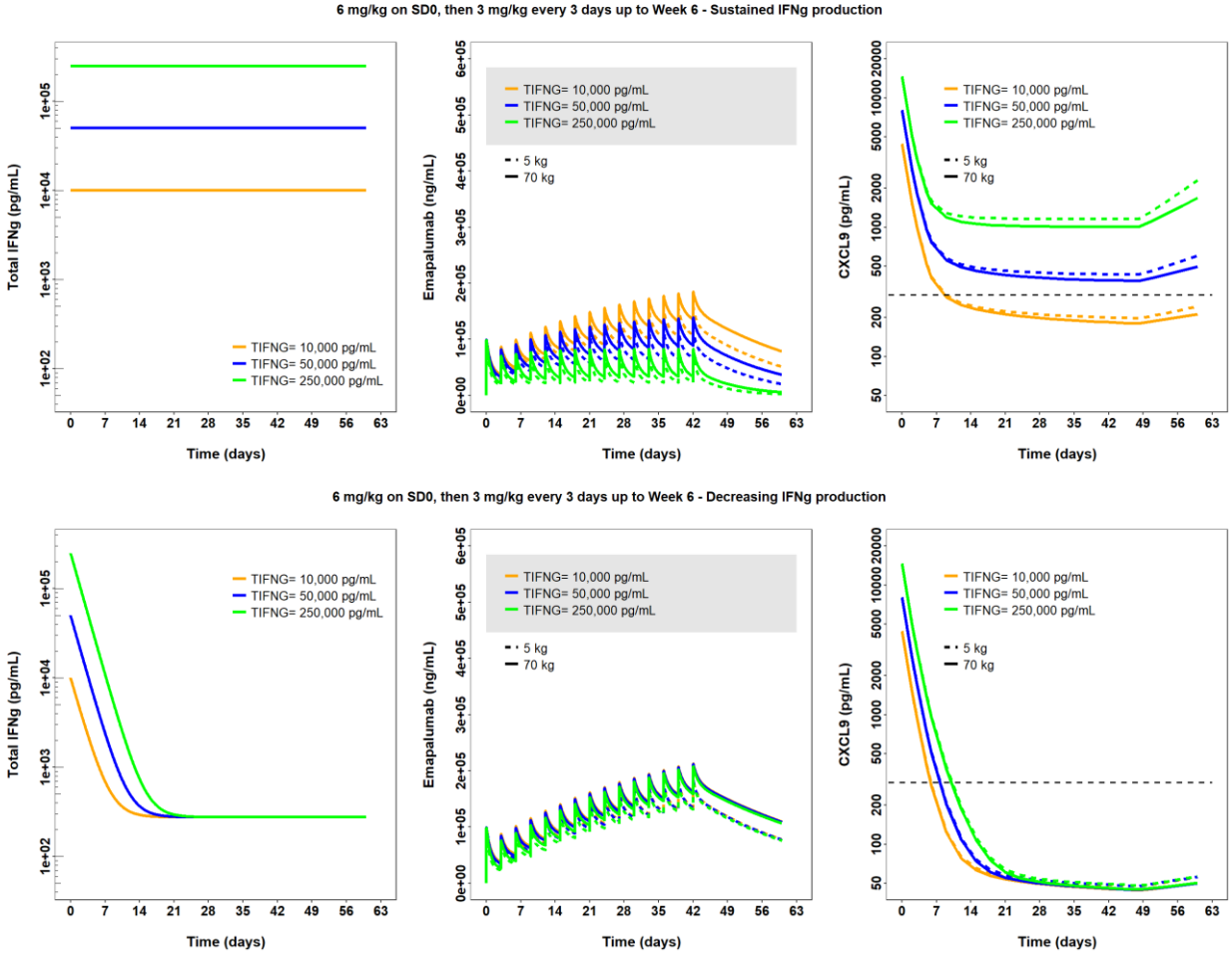


Figure 4: PK and PD simulations assuming a sustained IFNγ production (upper panel) or decreasing IFNγ production (lower panel) for an emapalumab dosing duration of 6 weeks



The results of the simulations indicate the following:

- In patients with a sustained IFNγ production, emapalumab treatment initiation leads to a rapid decrease in CXCL9. Subsequently CXCL9 remains at a stable level, which is determined by the magnitude of the underlying IFNγ production. Upon dosing discontinuation, emapalumab levels decrease and CXCL9 levels start increasing again. Emapalumab clearance and the concomitant increase in CXCL9 are more pronounced in patients with a high IFNγ production.
- In patients with a decreasing IFNγ production, the contribution of the target-mediated clearance to the overall clearance of emapalumab is limited. Emapalumab treatment initiation leads to a rapid decrease in CXCL9. However, in these patients the decrease in CXCL9 is more pronounced as compared to patients with a sustained IFNγ production, because it is driven by the emapalumab-induced neutralization of free IFNγ as well as the decrease in IFNγ production. Upon treatment discontinuation, emapalumab clearance is slow, reaching normal linear clearance, while CXCL9 levels remain low.

The simulations performed demonstrate the importance of the evolution of the IFNγ production on the selection of the appropriate dosing regimen in emapalumab-treated patients. Based on these simulations, emapalumab treatment for up to 6 weeks will be needed in order to neutralize IFNγ during the entire engraftment period in patients with sustained IFNγ production. An initial emapalumab dose of 6 mg/kg followed by 3 mg/kg is predicted to neutralize IFNγ in patients with total IFNγ levels of 10,000 pg/mL, which is considered a reasonable rationale for selecting this dose regimen for Cohort 1.

Since higher dose levels of emapalumab will be required to neutralize IFNγ in patients who would present higher IFNγ levels (e.g. up to 250,000 pg/mL), the proposed dose regimens to be used in Cohort 2 and 3 are higher than in Cohort 1. The dose levels could be increased in 2 different ways. The initial dose 6 mg/kg may be given for a longer period (either for 3, 6, 9 or 15 doses) before decreasing to a lower maintenance dose of 3 mg/kg. Or, as an alternative, both the initial dose level and the maintenance dose level may be increased to 10 mg/kg for 3 doses followed by a maintenance dose of 6 mg/kg (Table 4).

The highest potential dose level is 10 mg/kg for 3 doses followed by 6 mg/kg up to no more than 15 doses. As described in the current version of the IB, a dose up to 10 mg/kg daily have been administered with no reported safety concern so far.

5.4 Dosing Regimen

Patients entering the monitoring or extended monitoring period and fulfilling the criteria to be pre-emptively treated for primary or secondary graft failure (as outlined in section 3.4.3) will receive emapalumab as described below:

- Emapalumab will be administered by IV infusion over 1 to 2 hours depending on the volume of the infusion.
- The first infusion must be performed within 12 hours from CXCL9 sample collection time (with levels above defined threshold).
- Treatment will last until maximum dose 15 (up to 56 days) or until evidence of engraftment, whichever comes first.
- The first cohort of patients will receive a first infusion of 6 mg/kg at treatment day 0 (TD0), followed by a second infusion at 3 mg/kg after 3 days (TD3). Subsequent infusions of 3 mg/kg will be every 3 or 4 days (from previous dose) until dose 15 or until engraftment.
- A maximum of 2 additional cohorts may be added to allow dosing regimen adaptation based on the PK/PD observed from the previous cohort(s). Efficacy and safety data will also be considered before adding additional cohorts.
- The dose regimen options for cohort 2 or cohort 3 are presented in Table 4.
- Patients optionally treated for secondary graft failure will receive the same dose as the patients treated for primary graft failure.

Table 4: dose regimen options in cohort 2 or 3

Cohort 2 or Cohort 3	**Option 1** 6 mg/kg for 3 doses followed by 3 mg/kg from dose 4 until dose 15 or until engraftment
	Option 2 6 mg/kg for 6 doses followed by 3 mg/kg from dose 7 until dose 15 or until engraftment
	Option 3 6 mg/kg for 9 doses followed by 3 mg/kg from dose 10 until dose 15 or until engraftment
	Option 4 6 mg/kg for 15 doses or until engraftment
	Option 5 10 mg/kg for 3 doses followed by 6 mg/kg from dose 4 until dose 15 or until engraftment

6 BACKGROUND THERAPY AND CARE

6.1 Infection prophylaxis

- Patients must receive prophylactic treatment for Herpes Zoster prior to initiation of emapalumab treatment. Prophylaxis should be maintained until approximately 2 emapalumab half lives (i.e. approximately 44 days) after end of treatment
- In case a patient, previously vaccinated for tuberculosis, shows a Purified Protein Derivative (PPD) test result ≥ 5 mm and a negative IFNγ-release assay, patients will receive TB prophylaxis according to local medical practice.

6.2 Authorized treatments

The following treatments are allowed during the study:

- Prophylaxis and therapy of infections (antibiotics, antifungal and anti-viral) as per local medical practice.
- Conditioning (myeloablative conditioning [MAC], RIC or NMA) prior to HSCT as per local medical practice.
- GvHD prophylaxis and treatment as per local medical practice..
- Steroids during monitoring, extended monitoring and follow up.
- During emapalumab treatment only topical steroids are allowed and methylprednisolone up to 2 mg/kg/day (or other equivalent steroid dose) for not more than 2 days.
- Hematopoietic growth factors, stem cell boost, donor lymphocyte infusion (DLI).
- Intravenous immunoglobulin (IVIG) is only allowed as replacement treatment (i.e. not at doses expected to produce an immunomodulatory effect) based on medical judgment.
- Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, IV parenteral nutrition, inotropic support, ultrafiltration or hemodialysis.

6.3 Prohibited treatments

The following treatments are not allowed **during emapalumab treatment**:

- Methylprednisolone more than 2 mg/kg/day (or other equivalent steroid dose) for more than 2 days.

The following treatments are not allowed during **monitoring/extended monitoring and during emapalumab treatment**:

- All kinase inhibitors.
- Interferon gamma-1b.
- Biologic drugs (except rituximab used to treat EBV infection or to remove B-cells producing donor specific antibodies).

The following treatments are not allowed **during the study up to 6 months after the last emapalumab dose or until the end the monitoring period for untreated patients:**

- Live or attenuated (including BCG) vaccine.

7 STUDY END POINTS

The main objective is dual and is composed of:

- Dose selection.
- Preliminary efficacy of emapalumab treatment pre-empting GF.

The endpoints used to assess dose selection are:

- Serum concentrations of free emapalumab.
- Serum concentration of total IFNγ.
- Serum concentration of CXCL9.

The main endpoint used to preliminarly assess efficacy of emapalumab in pre-empting GF is:

- Occurrence of primary GFs from start of treatment up to end of treatment.

7.1 Efficacy

- Occurrence of primary GF from HSCT up to EoS visit.
- Occurrence of secondary GF from HSCT up to EoS visit.
- Occurrence of primary or secondary GFs from HSCT up to EoS visit.
- Occurrence of mixed donor chimerism <10% and <20% (based on unselected leukocytes or sorted T cells) from HSCT up to EoS visit.
- Occurrence of received transfusion of blood products due to poor graft function, hematopoietic growth factors, stem cell boost or DLI from HSCT up to 3 years follow up.
- Occurrence of receiving an additional allogeneic HSCT from HSCT up to 3 years follow up.
- Occurrence of poor graft function from HSCT up to EoS visit.
- Occurrence of event free engraftment from HSCT up to 3 years follow up.
- Occurrence of GvHD from HSCT up to 3 years follow up.
- Occurrence of engraftment syndrome from HSCT up to EoS visit.
- Occurrence of endothelial complications from HSCT up to EoS visit.
- Overall survival from HSCT up to 3 years follow up.

7.2 Safety

- Occurrence of relapse, defined as cumulative incidence of reoccurring malignant underlying disease from HSCT up to EoS visit.
- Occurrence of AEs up to EoS visit.
- Occurrence of AEs leading to discontinuation of study treatment.
- Change from baseline in vital signs, laboratory parameters up to EoS visit.

7.3 Immunogenicity

- Occurrence of antibodies against emapalumab (ADA) and Nab from start of treatment up to EoS visit.

7.4 Pharmacokinetic

- Serum concentrations of free emapalumab.
- PK parameters by non-compartmental analysis (NCA): Cmax (peak serum concentration), Ctrough (concentration just before administration), Cmeantau (mean concentration over a dosing interval), AUCtau (area under curve of a dosing interval), and other parameters as applicable.
- Population PK parameters, as applicable.

7.5 Pharmacodynamics

- Serum concentrations of free IFNγ (before emapalumab treatment), total IFNγ (free + bound to emapalumab), CXCL9 (as marker of IFNγ neutralization).
- Exploratory inflammatory biomarkers relevant to emapalumab mechanism, condition, underlying disease (e.g. soluble interleukin 2 receptor alpha [sIL2Rα], ferritin, interleukin-6 [IL-6], tumor necrosis factor alpha [TNFα] and soluble CD163 [sCD163]).
- Exploratory blood tests measuring cell subsets (e.g. fluorescence-activated cell sorting [FACS] for analysis of specific T cell and/or macrophage subsets).

7.6 Exploratory endpoints

- CXCL9 and other biomarkers relevant to the diagnostic test development measured with different analytical technologies.

8 VISIT SCHEDULE AND STUDY ASSESSMENTS

The visit schedule and the study assessments for patients of **weight ≥30 kg** are described in Table 5a (Screening, HSCT, monitoring and extended monitoring periods), Table 6a (Treatment period), Table 7a (Follow-up period, unscheduled visit and withdrawal visit).

The visit schedule and the study assessments for patients of **weight < 30 kg** are described in Table 5b (Screening, HSCT, monitoring and extended monitoring periods), Table 6b (Treatment period), Table 7b (Follow-up period, unscheduled visit and withdrawal visit). Some assessments are not performed in patients of **weight <15 kg** and these are indicated with an (*) in the assessment schedule.

Visits must occur on the designated day with allowed window as indicated. The same assessment schedule is foreseen for Cohort 1, 2 and 3.

The assessments that are mandatory during a visit are marked with an X. Optional assessment to be performed based on medical judgment are marked with an (X).

Table 5a: Schedule of assessments for Screening, HSCT, monitoring and extended monitoring (cohort 1, 2 and 3) – Patients ≥ 30 kg

PERIOD (Duration)		**SCREENING (Up to 13 days)**	**HSCT[1] (1 day)**	**MONITORING (Up to 42 ±1 days)**	**EXTENDED MONITORING (Up to 98 ±3 days)**
VISITS Days ± visit window		**SD -21 to SD-8**	**D0**	**MD1, MD2, MD3, MD4, MD5, MD6, MD7 MD9, MD11, MD13, MD15, MD17, MD19, MD21, MD24±1, MD27±1, MD30±1, MD33±1, MD36±1, MD39±1, MD42 ±1**	**Visits every 7±1 days** First EM visit is 7±1 days from the last day in the monitoring period (patient transition to EM period as soon as ANC ≥500 in the monitoring)
Demographics and baseline characteristics	Informed Consent	X			
	Demographics	X			
	Relevant medical history and previous treatments	X			
	Donor and graft characteristics		X		
	Stratification by underlying disease (malignant/non-malignant)	X			
Clinical Assessments	Review of inclusion/exclusion criteria[2]	X	X		
	Assess eligibility to emapalumab treatment			X	
	Height	X			
	Weight	X	X		
	Vital Signs (BP, HR, body temperature)	X	X	X	
	Chest X-Ray	X	Anytime a pulmonary infection is suspected		
	12-Lead ECG	X			
	Physical Examination	X	X	As clinically indicated	
	Occurrence of GvHD and/or engraftment syndrome, graft failure, graft rejection			X	
Laboratory procedures	Search for infections[3]		X[3]	Anytime an infection is suspected	
	TB testing[2]	X		Anytime an infection is suspected	
	Serum pregnancy test	X			
	Urine pregnancy test		X	MD30	Every 4 weeks (from last pregnancy test)
	Urinalysis	X			
	Coagulation	X			
	Biochemistry[4]	X			
	Hematology including differential hematology[4]	X			X
	Absolute Neutrophil Count (ANC)		X[5]	X	
	Donor chimerism[6]			MD1, MD7, MD15, MD21, MD27, MD33, MD39	X
	HLA antibodies against donor cells		X		
	CXCL9[8]		X[5]	X	
	Inflammatory biomarkers[7]	X	X	X	
AEs & Concomitant medications		X	X	X	

Table 5a foot notes
Abbreviations: SD: Screening Day; MD: Monitoring Day; D: Day; EM: Extended Monitoring; BP: Blood Pressure; HR: Heart Rate; TB: Tuberculosis; ANC: Absolute Neutrophil Count; HLA: Human Leukocyte Antigen; CXCL9: C-X-C Motif Chemokine Ligand 9; AEs: Adverse Events
1: All assessments/procedures must be performed pre HSCT, unless otherwise specified
2: TB results from the screening (IFNγ-release assay/PPD test) must be available at the latest prior to HSCT for eligibility assessment.
3: Atypical mycobacteria, salmonella, histoplasma capsulatum, herpes zoster, HHV6, CMV, EBV, adenovirus, parvovirus.
4: Biochemistry: Glucose, C-reactive protein (CRP), Sodium, Potassium, Chloride, Calcium, Magnesium and Phosphate, AST, ALT, γGT, ALP, LDH, bilirubin (total, direct and indirect), triglycerides, cholesterol (total and HDL), Albumin, creatinine, urea (fast conditions whenever possible), Ferritin. Hematology: hematocrit, hemoglobin, platelets, RBC, WBC. Hematology differential: lymphocytes, monocytes, neutrophils.
5: Pre HSCT
6: Donor chimerism must be assessed at the monitoring visits as indicated unless the patient transitioned to extended monitoring period or treatment
7: Free IFNγ, CXCL9 and other inflammatory biomarkers in serum (e.g. IL-6, TNFα, sCD163 and sIL2Rα). These samples may also be used to assess baseline values of ADA.
8: The CXCL9 sample is analysed locally with a device provided by the Sponsor.

Table 5b: Schedule of assessments for Screening, HSCT, monitoring and extended monitoring (cohort 1, 2 and 3) – Patient weight < 30 kg

PERIOD (Duration)		**SCREENING (Up to 13 days)**	**HSCT[1] (1 day)**	**MONITORING (Up to 42 ±1 days)**	**EXTENDED MONITORING (Up to 98 ±3 days)**
VISITS Days ± visit window		**SD -21 to SD-8**	**D0**	**MD1, MD2, MD3, MD4, MD5, MD6, MD7 MD9, MD11, MD13, MD15, MD17, MD19, MD21, MD24±1, MD27±1, MD30±1, MD33±1, MD36±1, MD39±1, MD42 ±1**	**Visits every 7±1 days** First EM visit is 7±1 days from the last day in the monitoring period (patient transition to EM period as soon as ANC ≥500 in the monitoring)
Demographics and baseline characteristics	Informed Consent	X			
	Demographics	X			
	Relevant medical history and previous treatments	X			
	Donor and graft characteristics		X		
	Stratification by underlying disease (malignant/non-malignant)	X			
Clinical Assessments	Review of inclusion/exclusion criteria[2]	X	X		
	Assess eligibility to emapalumab treatment			X	
	Height	X			
	Weight	X	X		
	Vital Signs (BP, HR, body temperature)	X	X	X	
	Chest X-Ray	X	Anytime a pulmonary infection is suspected		
	12-Lead ECG	X			
	Physical Examination	X	X	As clinically indicated	
	Occurrence of GvHD and/or engraftment syndrome, graft failure, graft rejection			X	
Laboratory procedures	Search for infections[3]		X	Anytime an infection is suspected	
	TB testing[2]	X		Anytime an infection is suspected	
	Urinalysis	X			
	Coagulation	X			
	Biochemistry[4]	X			
	Hematology including differential hematology[4]	X			X
	Absolute Neutrophil Count (ANC)		X[5]	X (except at MD6 for patients below 15 kg)	
	Donor chimerism			As clinically indicated	
	HLA antibodies against donor cells		X		
	CXCL9[7]		X[5]	X (except at MD6 for patients below 15 kg)	
	Inflammatory biomarkers[6]	X	X	X (except at MD6 for patients below 15 kg)	
AEs & Concomitant medications		X	X	X	

Table 5b foot notes

Abbreviations: SD: Screening Day; MD: Monitoring Day; D: Day; EM: Extended Monitoring; BP: Blood Pressure; HR: Heart Rate; ECG: Electrocardiogram; GvHD: Graft versus Host Disease; TB: Tuberculosis; ANC: Absolute Neutrophil Count; HLA: Human Leukocyte Antigen; CXCL9: C-X-C Motif Chemokine Ligand 9; AEs: Adverse Events

1: All assessments/procedures must be performed pre HSCT, unless otherwise specified.
2: TB results from the screening (IFNγ-release assay/PPD test) must be available at the latest prior to HSCT for eligibility assessment.
3: Atypical mycobacteria, salmonella, histoplasma capsulatum, herpes zoster, HHV6, CMV, EBV, adenovirus, parvovirus.
4: Biochemistry: Glucose, C-reactive protein (CRP), Sodium, Potassium, Chloride, Calcium, Magnesium and Phosphate, AST, ALT, γGT, ALP, LDH, bilirubin (total, direct and indirect), triglycerides, cholesterol (total and HDL), Albumin, creatinine, urea (fast conditions whenever possible), Ferritin. Hematology: hematocrit, hemoglobin, platelets, RBC, WBC. Hematology differential: lymphocytes, monocytes, neutrophils.
5: Pre HSCT.
6: Free IFNγ, CXCL9 and other inflammatory biomarkers in serum (e.g. IL-6, TNFα, sCD163 and sIL2Rα). These samples may also be used to assess baseline values of ADA.
7: The CXCL9 sample is analysed locally with a device provided by the Sponsor.

Table 6a: Schedule of assessments for Treatment period (Cohort 1, 2 and 3) – Patients weight ≥ 30 kg

PERIOD (Duration)		**TREATMENT[1] (Up to 56 days)**															**EoT**
VISITS		**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**	**Dose 6**	**Dose 7**	**Dose 8**	**Dose 9**	**Dose 10**	**Dose 11**	**Dose 12**	**Dose 13**	**Dose 14**	**Dose 15**	Only for patients that discontinue treatment or engraft before dose 15
Days ± visit window		**TD 0**	**TD 3**	**3 or 4 days from previous dose**													**3 days from engraftment (if before dose 15) or treatment discontinuation**
Study drug administration		X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Anti-viral prophylaxis[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Assessments	Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	12-lead ECG	X														X	X
	Chest X-Ray	Only in case of clinical suspicion of pulmonary infection														X	X
	Physical Examination	X	As medically required													X	X
	Weight[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Record GvHD, engraftment syndrome, GF, graft rejection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures All sampling pre-dose unless otherwise specified	Biochemistry and hematology including differential hematology[6]	X		X		X		X		X		X		X		X	X
	ANC		X		X		X		X		X		X		X		
	Coagulation															X	X
	MRD[7]	X										X					X[8]
	Urine pregnancy test	X							X							X	X
	Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Atypical Mycobacteria, Salmonella, Histoplasma, HZ	if an infection is suspected														X	X
	HHV6, CMV, EBV, Adenovirus, Parvovirus	X	Repeat at dose 5 and dose 10 (only in patients positive to these infections prior to treatment) at all other visits only if an infection is suspected													X	X
	TB testing	X[9]	if an infection is suspected													X	X
	Cells subsets	X		X[11]		X[11]		X[11]		X[11]		X[11]		X[11]		X[11]	X[11]
	Donor chimerism					X		X		X		X		X		X	X
	Inflammatory biomarkers[10]	Pre/post	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	HLA antibodies against donor cells								X							X	X
	PK	Pre/	Pre/	Pre/	Pre/	Pre/		Pre/		Pre/		Pre/		Pre/		Pre/	X

PERIOD (Duration)		**TREATMENT[1] (Up to 56 days)**														**EoT**
VISITS		**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**	**Dose 6**	**Dose 7**	**Dose 8**	**Dose 9**	**Dose 10**	**Dose 11**	**Dose 12**	**Dose 13**	**Dose 14**	**Dose 15**	Only for patients that discontinue treatment or engraft before dose 15
Days ± visit window		**TD 0**	**TD 3**	**3 or 4 days from previous dose**													**3 days from engraftment (if before dose 15) or treatment discontinuation**
		post	post	post	post	post		post		post		post		post		post	
	Antibodies against emapalumab	X						X								X	X
AEs & Concomitant medications		X															

Table 6a Foot Notes
Abbreviations: TD: Treatment Day; ECG: Electrocardiogram; MRD: Minimal Residual Disease; HZ: Herpes zoster; HHV: Human Herpes Virus; CMV: Cytomegalovirus; EBV: Epstein-Barr Virus; GF: Graft Failure; GvHD: Graft versus Host Disease; PK: pharmacokinetics; AEs: Adverse Events
1: It is recommended that all assessments/procedures are performed pre dose, unless otherwise specified
2: First infusion should be done within 12 hours from CXCL9 sample collection time (levels above threshold)
3: Prophylaxis against HZ virus infection must be in place prior to treatment and must be maintained until approximately 2 emapalumab half lives (i.e. approximately 44 days) after end of treatment
4: Vital signs include body temperature, heart rate, blood pressure. Heart rate/blood pressure must be measured pre-dose, within 30 minutes from start of infusion and at 1 and 2 hours post-infusion. Temperature only pre-dose. More frequent measurements will be done in case is medically indicated.
5: Within 24 hours of the planned infusion
6: Biochemistry: Glucose, C-reactive protein (CRP), Sodium, Potassium, Chloride, Calcium, Magnesium and Phosphate, AST, ALT, γGT, ALP, LDH, bilirubin (total, direct and indirect), triglycerides, cholesterol (total and HDL), Albumin, creatinine, urea (fasting conditions whenever possible), Ferritin. Hematology: hematocrit, hemoglobin, platelets, RBC, WBC. Hematology differential: lymphocytes, monocytes, neutrophils.
7: MRD is performed in malignant patients only (in order to monitor re-occurrence or progression of the malignant disease).
8: MRD should be done at EoT only if EoT occurs prior to dose 11.
9: TB test prior to treatment must be repeated only if the test performed at screening occurred more than 30 days before treatment or if there is clinical suspicion of TB. Availability of the results of the TB test (if repeated prior to emapalumab administration) is not required provided that (i) results from the test performed at screening are available (ii) the microbiological analysis of the sample collected prior to treatment is ongoing and (iii) the patient clinical condition is not indicative of the presence of an active infection.
10: Free IFNg (pre-dose only before dose 1) and total IFNγ, CXCL9 and other inflammatory biomarkers in serum (e.g. IL-6, TNFα, sCD163 and sIL2Rα).
11: The cell subsets sample will be collected only if the lymphocyte counts from the previous visit are above a certain threshold (defined in the laboratory manual)

Table 6b: Schedule of assessments - Treatment period (Cohort 1, 2 and 3) – Patient weight < 30 kg

PERIOD (Duration)		**TREATMENT[1] (Up to 56 days)**															**EoT**
VISITS		**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**	**Dose 6**	**Dose 7**	**Dose 8**	**Dose 9**	**Dose 10**	**Dose 11**	**Dose 12**	**Dose 13**	**Dose 14**	**Dose 15**	Only for patients that discontinue treatment or engraft before dose 15
Days ± visit window		**TD 0**	**TD 3**	**3 or 4 days from previous dose**													**3 days from engraftment (if before dose 15) or treatment discontinuation**
Study drug administration		X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Anti-viral prophylaxis[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Assessments	Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	12-lead ECG	X														X	X
	Chest X-Ray	Only in case of clinical suspicion of pulmonary infection														X	X
	Physical Examination	X	As medically required													X	X
	Weight[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Record GvHD, engraftment syndrome, GF, graft rejection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures All sampling pre-dose unless otherwise specified	Biochemistry and hematology including differential hematology[6]	X		X		X		X		X		X		X		X	X
	ANC		X*		X*		X*		X		X		X		X		
	Coagulation															X	X
	MRD[7]	X*										X*					X[8]*
	Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Atypical Mycobacteria, Salmonella, Histoplasma, HZ	if an infection is suspected														X*	X*
	HHV6, CMV, EBV, Adenovirus, Parvovirus		if an infection is suspected														
	TB testing	X[9]	if an infection is suspected													X	X
	Donor chimerism	As clinically indicated														X*	X*
	Inflammatory biomarkers[10]	Pre/post	X*	X	X*	X	X*	X	X	X	X	X	X	X	X	X	X
	HLA antibodies against donor cells															X	X
	PK	Pre/ post	Pre/ post	Pre/ post	Pre/ post	Pre/ post		Pre/ post		Pre/ post		Pre/ post		Pre/ post		Pre/ post	X

PERIOD (Duration)		**TREATMENT[1] (Up to 56 days)**														**EoT** Only for patients that discontinue treatment or engraft before dose 15
VISITS		**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**	**Dose 6**	**Dose 7**	**Dose 8**	**Dose 9**	**Dose 10**	**Dose 11**	**Dose 12**	**Dose 13**	**Dose 14**	**Dose 15**	
Days ± visit window		**TD 0**	**TD 3**	**3 or 4 days from previous dose**													**3 days from engraftment (if before dose 15) or treatment discontinuation**
	Antibodies against emapalumab	X						X								X	X
AEs & Concomitant medications		X															

Table 6b Foot Notes
Abbreviations : EoT : End of Treatment ; TD : Treatment Day ; ECG : Electrocardiogram ; MRD : Minimal Residual Disease; HZ: Herpes zoster; HHV: Human Herspes Virus; CMV: Cytomegalovirus; EBV: Epstein-Barr Virus; GF: Graft Failure; GvHD: Graft versus Host Disease; HLA: Human Leukocyte Antigen; PK: pharmacokinetics; AEs: Adverse Events
***This sample is not collected for patients < 15 kg and will be performed as clinically indicated**
1: It is recommended that all assessments/procedures are performed pre dose, unless otherwise specified
2: First infusion should be done within 12 hours from CXCL9 sample collection time (levels above threshold)
3: Prophylaxis against HZ virus infection must be in place prior to treatment and must be maintained until approximately 2 emapalumab half lives (i.e. approximately 44 days) after end of treatment
4: Vital signs include body temperature, heart rate, blood pressure. Heart rate/blood pressure must be measured pre-dose, within 30 minutes from start of infusion and at 1 and 2 hours post-infusion. Temperature only pre-dose. More frequent measurements will be done in case is medically indicated.
5: Within 24 hours of the planned infusion
6: Biochemistry: Glucose, C-reactive protein (CRP), Sodium, Potassium, Chloride, Calcium, Magnesium and Phosphate, AST, ALT, Γgt, ALP, LDH, bilirubin (total, direct and indirect), triglycerides, cholesterol (total and HDL), Albumin, creatinine, urea (fasting conditions whenever possible), Ferritin. Hematology: hematocrit, hemoglobin, platelets, RBC, WBC. Hematology differential: lymphocytes, monocytes, neutrophils.
7: MRD is performed in malignant patients only (in order to monitor re-occurrence or progression of the malignant disease).
8: MRD should be done at EoT only if EoT occurs prior to dose 11.
9: TB test prior to treatment must be repeated only if the test performed at screening occurred more than 30 days before treatment or if there is clinical suspicion of TB. Availability of the results of the TB test (if repeated prior to emapalumab administration) is not required provided that (i) results from the test performed at screening are available (ii) the microbiological analysis of the sample collected prior to treatment is ongoing and (iii) the patient clinical condition is not indicative of the presence of an active infection.
10: Free IFNg (pre-dose only before dose 1) and total IFNγ, CXCL9 and other inflammatory biomarkers in serum (e.g. IL-6, TNFα, Scd163 and Sil2Rα).

Table 7a: Schedule of assessments - Follow-up period, withdrawal visit, EoS and unscheduled visit (Cohort 1, 2 and 3) - Patients weight ≥ 30 kg

PERIOD (Duration)		**FOLLOW UP[1] (3 years)**										
VISITS		**FU 1[1]**	**FU 2[1]**	**FU 3[1]**	**FU 4[1]**	**FU 5[1]**	**FU6[1] or EoS visit[1,2] or Withdrawal visit[3]**	**Phone calls**				**Unscheduled Visit[4]**
Days ± window		**Week 1 ±2 days**	**Week 2 ±2 days**	**Week 4 ±2 days**	**Week 8 ±1 week**	**Week 12 ±1 week**	**Week 24 ±2 Weeks**	**6 months ±2 weeks from HSCT[2]**	**1 year ±4 week from HSCT[1,2]**	**2 year ±4 weeks from HSCT[1,2]**	**3 year ±4 Weeks from HSCT[1,2]**	
Clinical Assessments	Vital Signs (BP, HR, body temperature)	X	X	X	X	X	X					X
	12-lead ECG											(X)
	Chest X-ray	Only in case of clinical suspicion of pulmonary infection					X					(X)
	Physical Examination	As medically required					X					X
	Weight	X	X	X	X	X	X					X
	Record engraftment syndrome			X	X	X	X					(X)
	Record GvHD, GF, graft rejection	X	X	X	X	X	X					(X)
Laboratory Procedures	Biochemistry and hematology including differential haematology[5]	X		X	X	X	X					(X)
	Re-occurrence or progression of underlying malignant disease (MRD)			X	X	X	X					(X)
	Urine Pregnancy Test (if applicable)			X	X	X	X					(X)
	Urinalysis	X	X	X	X	X	X					(X)
	Search for infections[6]	If an infection is suspected										(X)
	TB testing						X					(X)
	Cells subsets			X		X	X[8]					(X)
	Donor chimerism			X	X	X	X					(X)
	Inflammatory biomarkers[7]	X	X	X	X	X	X					(X)
	HLA antibodies against donor cells						X					(X)
	PK			X	X	X	X[8]					(X)
	Antibodies against emapalumab			X		X	X[8]					(X)
Survival check and GvHD occurrence recording								X				(X)
Relevant concomitant medications/procedures[9]		X						X				X
AEs		X						Only SAEs related to emapalumab				X

Table 7a Foot Notes
Abbreviations: FU: Follow Up; EoS: End of Study visit; BP: Blood Pressure; HR; Heart Rate; ECG: Electrocardiogram; MRD: Minimal Residual Disease; GF: Graft Failure; GvHD: Graft versus Host Disease; HLA: Human Leukocyte Antigen PK: pharmacokinetics; AEs: Adverse Events
1: This visit is foreseen for emapalumab treated patients. FU week 1 to be scheduled 1 week ±2 days from last study drug administration or 1 week after EoT (in case of treatment discontinuation or engraftment before the last dosing 15).
2: This visit is foreseen for non-emapalumab treated patients. The EoS visit for non-emapalumab treated patients must be scheduled within 1 week from the last day in the monitoring periods.
3: In case of premature withdrawal from the study for any reason (except informed consent withdrawal), patients should undergo a withdrawal visit within 1 week from the date of withdrawal.
4: Assessments marked as (X) will be done if considered medically relevant
5: Biochemistry: Glucose, C-reactive protein (CRP), Sodium, Potassium, Chloride, Calcium, Magnesium and Phosphate, AST, ALT, γGT, ALP, LDH, bilirubin (total, direct and indirect), triglycerides, cholesterol (total and HDL), Albumin, creatinine, urea (fasting conditions whenever possible), Ferritin. Hematology: hematocrit, hemoglobin, platelets, RBC, WBC. Hematology differential: lymphocytes, monocytes, neutrophils.
6: Atypical mycobacteria, salmonella, histoplasma capsulatum, herpes zoster, HHV6, CMV, EBV, adenovirus, parvovirus.
7: Total IFNg, CXCL9 and other inflammatory biomarkers in serum (e.g. IL-6, TNFα, sCD163 and sIL2Rα)
8: this sample is collected for emapalumab treated patients only
9: Relevant procedures /medications are defined as any HSCT, blood product transfusion, stem cell boost, DLI or hematopoietic agents received since the previous visit/call.

Table 7b: Schedule of assessments – Follow-up period, withdrawal visit, unscheduled visit (Cohort 1, 2 and 3) - Patient weight < 30 kg

PERIOD (Duration)		**FOLLOW UP (3 years)**										
VISITS		**FU 1[1]**	**FU 2[1]**	**FU 3[1]**	**FU 4[1]**	**FU 5[1]**	**FU6[1] or EoS visit[1,2] or Withdrawal[3]**	**Phone calls**				**Unscheduled Visit[4]**
Days ± window		**Week 1 ±2 days**	**Week 2 ±2 days**	**Week 4 ±2 days**	**Week 8 ±1 week**	**Week 12 ±1 week**	**Week 24 ±2 Weeks**	**6 months ±2 weeks from HSCT[2]**	**1 year ±4 week from HSCT[1,2]**	**2 year ±4 weeks from HSCT [1,2]**	**3 year ±4 Weeks from HSCT [1,2]**	
Clinical Assessments	Vital Signs (BP, HR, body temperature)	X	X	X	X	X	X					X
	12-lead ECG											(X)
	Chest X-ray	Only in case of clinical suspicion of pulmonary infection					X					(X)
	Physical Examination	As medically required					X					X
	Weight	X	X	X	X	X	X					X
	Record engraftment syndrome			X	X	X	X					(X)
	Record GvHD, GF, graft rejection	X	X	X	X	X	X					(X)
Laboratory Procedures	Biochemistry and hematology including differential haematology[5]	X		X	X	X	X					(X)
	Re-occurrence or progression of underlying malignant disease (MRD)			X*	X*	X*	X					(X)
	Urinalysis	X	X	X	X	X	X					(X)
	Search for infections[6]	If an infection is suspected										(X)
	TB testing						X					(X)
	Donor chimerism						X*					(X)
	Inflammatory biomarkers[7]	X	X	X	X	X	X					(X)
	HLA antibodies against donor cells						X*					(X)
	PK			X	X	X	X[8]					(X)
	Antibodies against emapalumab			X		X	X[8]					(X)
Survival check and GvHD occurrence recording								X				(X)
Relevant concomitant medications/procedures[9]		X						X				X
AEs		X						Only SAEs related to emapalumab				X

Table 7b: Foot Notes
Abbreviations: FU: Follow Up; EoS: End of Study visit; BP: Blood Pressure; HR; Heart Rate; ECG: Electrocardiogram; MRD: Minimal Residual Disease; HZ: Herpes zoster; GF: Graft Failure; GvHD: Graft versus Host Disease; HLA: Human Leukocyte Antigen; PK: pharmacokinetics; AEs: Adverse Events
***This sample is not collected for patients < 15 kg and will be performed as clinically indicated**
1: This visit is foreseen for emapalumab treated patients. FU week 1 to be scheduled 1 week ±2 days from last study drug administration or 1 week after EoT (in case of treatment discontinuation or engraftment before the last dosing 15).
2: This visit is foreseen for non-emapalumab treated patients. The EoS visit for non-emapalumab treated patients must be scheduled within 1 week from the last day in the monitoring periods.
3: In case of premature withdrawal from the study for any reason (except informed consent withdrawal), patients should undergo a withdrawal visit within 1 week from the date of withdrawal.
4: Assessments marked as (X) will be done if considered medically relevant
5: Biochemistry: Glucose, C-reactive protein (CRP), Sodium, Potassium, Chloride, Calcium, Magnesium and Phosphate, AST, ALT, γGT, ALP, LDH, bilirubin (total, direct and indirect), triglycerides, cholesterol (total and HDL), Albumin, creatinine, urea (fasting conditions whenever possible), Ferritin. Hematology: hematocrit, hemoglobin, platelets, RBC, WBC. Hematology differential: lymphocytes, monocytes, neutrophils.
6: Atypical mycobacteria, salmonella, histoplasma capsulatum, herpes zoster, HHV6, CMV, EBV, adenovirus, parvovirus.
7: Total IFNg, CXCL9 and other inflammatory biomarkers in serum (e.g. IL-6, TNFα, sCD163 and sIL2Rα)
8: This sample is collected for emapalumab treated patients only
9: Relevant procedures /medications are defined as any HSCT, blood product transfusion, stem cell boost, DLI or hematopoietic agents received since the previous visit/call

8.1 .Demographics, medical history and baseline characteristics

Demographics and medical history:

- Demographics: date of birth and/or age, sex, race and ethnicity (if allowed by local regulations).
- Relevant medical history (where possible diagnosis not symptoms must be recorded). Any new medical condition from informed consent signature must be reported as an AE.

Baseline characteristics:

- Underlying disease history including initial diagnosis and date of disease onset.
- Eastern Cooperative Oncology Group (ECOG) performance status for malignant diseases.
- Donor/graft characteristics: Donor type, HLA/gender match, source and number of stem cells, ABO compatibility, GvHD prophylaxis and type of graft manipulation.
- Infection positivity prior to HSCT.
- Type of conditioning (NMA, RIC, MAC).
- Vaccination history.

Reason for screening failure must be collected in the eCRF.

8.2 Prior and concomitant medications

Prior and concomitant medications (ongoing at screening) including previous medications/procedures used to treat the underlying disease and infection prophylaxis, type of conditions and vaccination history must be collected in the eCRF.

8.3 Clinical assessments

8.3.1 Vital signs

Vital signs will be measured at the visits as indicated in the assessments schedule (from Table 5a to Table 7b). Vital signs include body temperature, heart rate, systolic and diastolic blood pressure.

During the treatment period, heart rate and blood pressure must be measured pre-infusion (within 30 minutes from start of infusion) and at 1 and 2 hours post-infusion. Temperature can be measured pre-infusion only. More frequent measurements will be done in case this is medically indicated.

Any clinically relevant change in vital signs following signature of the informed consent form (ICF) should be collected as AE.

8.3.2 Height and weight

Height and body weight will be measured at the visits as indicated in the assessments schedule (from Table 5a to Table 7b).

Height will be measured at screening only. During treatment body weight must be measured within 24 hours prior to the planned infusion.

8.3.3 Physical examination

Physical examination will be performed as indicated in the assessments schedule (From Table 5a to Table 7b). A complete physical examination will be performed at screening, prior to HSCT, prior to treatment, at the last dosing day (dose 15) or EoT and at the follow-up visit 6 (week 24). During all other visits, the physical examination will be performed if medically indicated, based on medical history and symptoms or to follow up any abnormalities previously recorded as well as occurrence of new signs and symptoms. Physical examination must be documented in the relevant eCRF page.

Clinically relevant finding (other than the underlying disease) that are present prior to signing the informed consent must be recorded on the medical history page of the eCRF. Physical examination findings made after signing of informed consent, which meet the definition of an AE, must be recorded on the AE page of the eCRF.

8.3.4 Post-HSCT clinical assessments

Several clinical assessments are performed post-HSCT during monitoring, treatment and follow up. These assessments are reported in the assessment schedule under clinical assessments from Table 5a to Table 7b.

- Monitoring of occurrence of GvHD and/or engraftment syndrome, graft failure and graft rejection will be assessed during the monitoring, extended monitoring, treatment and follow-up period. Information on the severity and clinical characteristics of GvHD, engraftment syndrome, graft failure and graft rejection (in case of occurrence) will be collected in the eCRF.
- Re-occurrence or progression of the underlying malignant diseases will be monitored prior to treatment initiation, during treatment and follow-up period as indicated in the assessment schedule. Re-occurrence or progression of the disease will be assessed by measuring the minimal residual disease (MRD) in patients with malignant underlying disease.

8.3.5 Chest X-ray

A chest X-ray will be performed as a measure for detection of pulmonary infections and will be performed at screening, EoT and follow-up visit 6 (week 24). A chest X-ray should be done any time there is a clinical suspicion of pulmonary infection based on medical judgment.

Refer to Section 3.4.1 Screening period for acceptance criteria of previously performed chest X-rays for screening or re-screening.

8.3.6 ECG

A 12-lead electrocardiogram (ECG) will be performed at screening, prior to treatment and EoT. The ECG will be interpreted locally by the investigator or delegate.

Clinically relevant ECG findings that are present prior to informed consent signature must be recorded in the medical history section of the eCRF. Clinically relevant findings found after informed consent signature must be reported as an AE.

8.4 Laboratory assessments

In accordance with current regulations (ICH E11, 20 July 2000), blood sampling in infants and children must be done by using micro-sampling techniques in order to minimize as much as possible the blood drawn and/or the number of venipunctures.

The amount of blood foreseen to be drawn during the study remains below the limits recommended by existing guidelines for blood sample volume limits (WHO | Blood Sample Volumes in Child Health Research: Review of Safe Limits). The amount of blood has been estimated by assuming the scenario of a patient remaining in each study period for the maximum duration of each period i.e. up to 42 days in monitoring period, up to 98 days extended monitoring and dosed every 3 or 4 days for up to 15 infusions and completing the follow-up period of 24 weeks. It is expected that patients will remain in each period less than the maximum duration.

Laboratory assessments have been minimized in infants and children according to body weight. Laboratory parameters will be assessed during the study at the time points detailed in Table 5a, 6a, 7a for patient of weight ≥30 kg and in Table 5b, 6b, 7b for patients of weight <30 kg. Some assessments are not performed in patients of weight <15 kg and these are indicated with an (*) in the assessment schedule.

The laboratory parameters to be assessed during the study are listed below. Details on which parameters will be performed locally will be provided in a laboratory manual.

- Hematology: hematocrit, hemoglobin, platelets, red blood cells (RBC), white blood cells (WBC).
- Hematology differential: lymphocytes, monocytes, neutrophils.
- Biochemistry: ferritin, glucose, C-reactive protein (CRP), sodium, potassium, chloride, calcium, magnesium and phosphate, aspartate aminotrtansferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH),

bilirubin (total, direct and indirect), triglycerides, cholesterol (total and high-density lipoprotein [HDL]), albumin, creatinine, urea (fasting conditions whenever possible).

- Coagulation tests: activated partial thromboplastin (aPTT), prothrombin time (PT).
- Urinalysis: glucose, blood, protein, leucocytes, ketones, pH and specific gravity.
- Serum pregnancy test (if applicable).
- Urine pregnancy test (if applicable).
- Donor chimerism.
- HLA antibodies against donor cells.
- MRD (in malignant patients only).

Any clinically relevant change in laboratory assessment following signature of the ICF should be collected as an AE. Details on sample preparation and handling will be described in a laboratory manual.

8.4.1 Search for infections

Infection search will be performed during the study at the time points as detailed in the assessments schedule (Table 5a, Table 6a and Table 7a for patient of weight ≥30 kg and in Table 5b, Table 6b and Table 7b for patients of weight <30 kg). Some assessments are not performed in patients of weight <15 kg and these are indicated with an (*) in the assessment schedule.

Search for infections include the following pathogens:

- **Atypical mycobacteria, Salmonella, Histoplasma capsulatum, Herpes zoster**

  Patients with clinical manifestations of any of these infections prior to HSCT are not eligible. Patients presenting with clinical manifestations of these infections prior to treatment (TD0) **must not be treated**.

- **Mycobacterium tuberculosis**
  - **At screening**

    TB testing at screening will be performed via IFNγ-release assay or PPD test. In the case of a patient having received BCG vaccination, a PPD test must be performed and combined with IFNγ-release assay if the PPD result ≥5 mm.

    Results of the TB testing performed at screening must be available prior to HSCT for eligibility assessment. Patients presenting active or clinical suspicion of latent TB are not eligible to enter the study.

    In addition, a baseline sample via polymerase chain reaction [PCR] in any relevant specimen (e.g., urine or blood, if sputum is not easily obtained) has to be obtained, as this test will be used starting from emapalumab treatment initiation to perform regular TB monitoring.

  - **Prior to treatment**

    TB testing is repeated prior to treatment only in the case the test at screening is older than 30 days or if there is clinical suspicion on TB.

    The TB test prior to treatment should be performed with PCR only.

    Availability of the results of the TB test (if repeated prior to emapalumab administration) is not required provided that (i) results from the test performed at screening are available (ii) the microbiological analysis of the sample collected prior to treatment is ongoing and (iii) the patient clinical condition is not indicative of the presence of an active infection.

    Patients with clinical manifestations of TB prior to treatment **must not be treated**.

  - **At all the other visits**

    At all other visits TB testing is performed with PCR only.

- **Human Herpes virus 6 (HHV6), cytomegalovirus (CMV), Epstein-Barr virus (EBV), adenovirus and parvovirus**

  These infections will be monitored during the study in order to collect information to interpret potential influence on the HSCT outcome and to monitor any infection re-activation due to the interferon gamma inhibition.

Details on sample preparation and handling for search for infections will be described in a laboratory manual.

8.4.2 CXCL9 assay

The time points for assessment of CXCL9 are indicated in the assessment schedule Table 5a for patient of weight ≥30 kg and in Table 5b for patients of weight <30 kg. Some assessments are not performed in patients of weight <15 kg and these are indicated with an (*) in the assessment schedule.

CXCL9 in serum will be measured locally with a validated assay. A device to perform the CXCL9 measurements will be provided to the sites by Sobi AG.

CXCL9 is the primary predictive biomarker used for treatment decision in combination to other clinical laboratory assessments for both primary and secondary graft failure. The exact CXCL9 threshold for treatment initiation and instructions for use of the technology will be provided in the CXCL9 assay laboratory manual.

- Pre-HSCT - Patients presenting CXCL9 levels 10 times above the upper limit of the 95% CI of the normal range (please refer to CXCL9 assay laboratory manual) within 24 hours prior to HSCT are not eligible.
- Post-HSCT - Starting from day 1 during the monitoring and extended monitoring, CXCL9 will be measured to assess eligibility to treatment.

Leftover of the CXCL9 sample will be shipped to Sobi AG (Switzerland) for further exploratory analyses as defined in the exploratory endpoints section 7.6. Further details on the sample to be collected, volume and processing will be provided in a laboratory manual for the CXCL9 assay.

8.4.3 Pharmacokinetic, pharmacodynamics, immunogenicity and other exploratory assessments

PK, PD and immunogenicity will be performed during the study at the time points as detailed in the assessments schedule (Table 5a, Table 6a and Table 7a for patient of weight ≥30 kg and in Table 5b, Table 6b and Table 7b for patients of weight < 30 kg). Some assessments are not performed in patients of weight <15 kg and these are indicated with an (*) in the assessment schedule.

Details of which parameters will be assessed are reported in section 7.3 (immunogenicity), section 7.4 (pharmacokinetics), section 7.5 (pharmacodynamics) and section 7.6 (exploratory endpoints).

Details on sample preparation and handling will be described in a laboratory manual.

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An Adverse Event (AE) is any adverse change i.e. any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease that occurs in a subject during the course of the study (after signing of the informed consent), whether or not considered by the investigator as related to study treatment.

A treatment-emergent AE is any AE temporally associated with the use of study treatment whether or not considered by the investigator as related to the study treatment.

AEs include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the start of the study.
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

AEs diagnosis *versus* signs/symptoms

For any AE, a diagnosis should be recorded rather than individual signs and symptoms. However, if at the time of AE reporting, a diagnosis is not available, each individual sign/symptom should be recorded. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be removed and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Persistent and recurrent AEs

A persistent AE is such an event that extends without resolution over period of time. Such events should only be recorded once. A recurrent AE is such an event that recurs at intervals with resolution after individual recurrences. Each recurrence of an AE should be recorded as a separate event.

AEs should be recorded in the appropriate section of the eCRF.

9.1.2 Intensity of Adverse Events

The intensity of clinical AEs is graded on a three-point scale (mild, moderate and severe).

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

For AEs not listed in the World Health Organization (WHO) toxicity scale, the three categories of intensity are defined as follows:

- Mild: The event may be noticeable to the subject. It does not influence daily activities, and usually does not require intervention.
- Moderate: The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- Severe: The event may cause noticeable discomfort, and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious (see section 9.2.1 for definition of SAE). Medical judgment should be used on a case-by-case basis.

Seriousness, rather than severity assessment, determines the regulatory reporting obligations.

9.1.3 Relationship to study treatment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment and reported as either related or unrelated. The determination of the likelihood that the study drug caused the AE will be provided by an investigator who is a qualified physician.

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug.
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable).
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.

9.1.4 Reporting of adverse event

For both treated and untreated patients, AEs must be collected until EoS visit. All AEs occurring after study start (i.e., signing of informed consent) must be recorded in the AE pages of the eCRF.

All AEs should be followed until the event has resolved. AEs still ongoing at EoS visit should be followed until they are no longer considered clinically relevant for both treated and untreated patients.

9.2 Serious adverse event (SAEs)

9.2.1 Definitions of SAEs

A serious adverse event is any AE that meets any of the following criteria (as per ICH guidelines):

- Is fatal.
- Is life-threatening (note: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).
- Requires in-patient hospitalization or prolongs an existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are exempted from being reported:

- Hospitalization for social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen.

However, complications that occur during hospitalization are AEs or SAEs (for example if a complication prolongs hospitalization or is medically significant as defined above).

9.2.2 Reporting of SAEs

For both treated and untreated patients, all SAEs occurring after study start (i.e., signing of informed consent) must be recorded in the AE pages of the eCRF. Collection of SAEs is required until EoS visit for both treated and untreated patients.

For emapalumab treated patients, new SAEs occurring after the EoS (during the 3 years survival check) must be reported to the Sponsor within 24 hours of the investigator's knowledge of the event, **only** if considered causally related to previous exposure to the study treatment by the investigator.

SAEs still ongoing at EoS visit must be followed up until resolution or stabilization, or until the event outcome is provided, e.g., death.

Reporting procedures

All SAEs must be reported by the investigator to the Sponsor within 24 hours of the investigator's first knowledge of the event.

All SAEs must be recorded on an SAE form, irrespective of the study treatment received by the subject, and whether or not this event is considered by the investigator to be related to study treatment.

The SAE forms must be emailed to the Sobi Global Pharmacovigilance & Patient Safety department (contact details are provided on the SAE form). The investigator must complete the SAE form in English and must assess the causal relationship of the event to study treatment.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Sponsor may contact the investigator to obtain further information.

If the subject 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.

The reference safety document to assess expectedness of a suspect serious adverse reaction and reported by the sponsor to Health Authorities, Independent Ethic Committes (IECs)/Institutional Review Boards (IRBs) and investigators is the reference safety information section of the current version of the IB.

9.3 Pregnancy

Emapalumab treatment must be permanently discontinued in case of pregnancy. The investigator must counsel the subject and discuss the risks of continuing pregnancy and the possible effects on the fetus.

In case of pregnancy, emapalumab treated patients will move to follow-up period. Non-emapalumab treated patients will be withdrawn after perfoming the EoS/withdrawal visit.

9.3.1 Reporting of pregnancy

Irrespective of whether emapalumab treatment was received or not, any pregnancy up to EoS visit must be reported.

All pregnancies should be reported using the Sobi Pregnancy Notification Form, which must be sent to the Sponsor (email contact details provided on the Pregnancy Notification Form) within 24 hours of the investigator's knowledge of the pregnancy.

9.3.2 Follow-up of pregnancy

Additional information on the pregnancy and its outcome will be collected using the Sobi Pregnancy Notification Form and reported to the Sponsor.

Any AE associated with the pregnancy must be reported in the AE pages of the eCRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in section 9.2.2.

9.4 Study safety monitoring

Clinical study safety information (e.g. AEs, SAEs, infection AEs, infusion related reactions, laboratory values, ECGs and vital signs) is monitored and reviewed on a continuous basis by the Sponsor's Clinical team (in charge of ensuring subjects' safety as well as data quality) by periodically monitoring clinical

studies activities from protocol conception to database closure. In addition, an IDMC is monitoring safety data (see section 3.6.1).

10 BENEFIT/RISK MANAGEMENT

10.1 Potential benefits

Data collected to date in HLH patients undergoing HSCT (Studies NI-0501-04/05 and compassionate use) and published data (6) from patients with various underlying diseases receiving HSCT, support the potential use of emapalumab to preempt GF by neutralizing IFNγ production and consequently prevent the loss of the graft.

Currently, once GF is confirmed, the only treatment is a second transplant.

Based upon the rates of overall survival, GF following HSCT is a life-threatening condition. The one year overall survival after GF has been reported between 45 to 60%, regardless of the procedure performed after GF is confirmed. Although loss of the graft itself leads to death only in a minority of cases (less than 5%) (14, 15), the risk of death in the absence of a second HSCT is almost certain, mostly due to infections in the context of extended neutropenia (16). The chances of survival depend on the quality of the graft, the initial successful engraftment, the mismatch between the donor and recipient and on the conditioning regimen. Nevertheless, even after a second transplant, survival remains low with approximately 1 out of 2 patients alive after one year, for the most optimistic reports.

There is significant unmet medical need for the prevention and/or treatment of GF. The availability of a therapeutic option which would lower the risk of GF in high risk patients would:

- Reduce the number of patients who would require a potential second HSCT.
- Provide an opportunity to lower GvHD occurrence by allowing an increased use of T-cell depleted grafts or stronger immunosuppression in a context where anti- IFNγ would promote engraftment.
- Improve the chance of success in fragile patients due to disease or age with less toxic conditioning regimens.
- Ultimately, reduce the mortality post-HSCT.

Patients that will not receive emapalumab and included in the study, will benefit from medical monitoring of their post-transplant clinical intercourse for up to 3 years. These patients will also contribute to further assess the relevance of CXCL9 as a potential biomarker to predict the risk of GF.

10.2 Potential risks

Due to the nature of emapalumab chemical structure and mechanisms of action and based on current experience with emapalumab, the following potential risks have been identified: infections caused by pathogens likely favoured by the lack of IFNγ biological activity, IRRs, and occurrence of anti-emapalumab antibodies.

In addition, based on literature evidence and mechanisms of action of emapalumab, IFNγ neutralization may adversely affect graft-versus-tumor activity after allo-HSCT.

10.2.1 Infections

The impact on the immune defense caused by the neutralization of IFNγ is known from patients with inborn errors of the IL 12/23-IFN-γ circuit, particularly patients with complete or partial IFNγ receptor 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 (17, 18). The mean age of the first environmental mycobacterial infection is 3.1 and 13.4 years in patients with complete and partial deficiency, respectively (19).

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

Individuals with anti-IFNγ auto-antibodies are also susceptible to develop mycobacterial infections (for the vast majority atypical mycobacterial infections), but also opportunistic infections (e.g., caused by Histoplasma Capsulatum, Salmonella, Herpes Zoster virus) (20).

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

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

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

For more information regarding the risk of infections in completed and ongoing clinical trials with emapalumab, refer to the latest version of the IB.

10.2.2 Infusion-related reactions

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

From the clinical experience to date, the risk of IRRs associated with emapalumab treatment seems to be very low.

After more than 1000 infusions administered to HLH patients up to the dose of 10 mg/kg, no anaphylactic/anaphylactoid or other significant reactions were observed with emapalumab. IRRs were mainly transient skin reactions observed during and shortly after emapalumab infusions (corresponding to less than 2% of the infusions performed). They resolved spontaneously and did not lead to emapalumab permanent discontinuation.

For more information regarding occurrence of IRRs in completed and ongoing clinical trials with emapalumab, please, refer to the current IB.

10.2.3 Anti-drug antibodies

Occurrence of ADAs inactivating therapeutic effects of the treatment and, in rare cases, inducing adverse reactions, is a potential risk associated with the administration of mAbs. Treatment-emergent ADAs were detected in:

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

No adverse events, including decreased efficacy, attributable to antibodies have occurred in these patients.

For more information regarding occurrence of ADAs in completed and ongoing clinical trials with emapalumab, please, refer to the current IB.

10.2.4 Graft versus tumor effect

IFNγ plays a complex role in induction of graft versus tumor effect in recipients of allogeneic hematopoietic stem cell transplantation (21).

The potential effects of emapalumab in patients with hematological or other malignancies undergoing allo HSCT are still unknown. Based on literature evidence, neutralization of IFNγ may adversely affect graft-versus-tumor activity. Therefore, risk minimization measures have been put in place (see Section 10.2.5 below).

For more information regarding malignancy patients treated with emapalumab and ongoing clinical trials with emapalumab, please, refer to the current IB.

10.2.5 Risk minimization measures

In order to ensure safe use of emapalumab in this patient population, the following risk minimization measures will be implemented: stringent exclusion criteria, specific prophylactic treatments, ongoing search for infections caused by relevant pathogens, monitoring for specific AEs, IDMC oversight of patient's safety and comprehensive stopping rules.

All risks mentioned above are considered to be manageable in this patient population, providing that adequate risk mitigation measures are applied to help ensure positive benefit-risk ratio. Risk minimization measures are described below.

10.2.5.1 Measures prior to study enrollment

Prior to enrollment into the study, the following patients will be excluded from participation in the study:

- < 1 year of age (until appropriate dose has been determined).
- With clinically manifested infections caused by Mycobacteria, Salmonella, Histoplasma Capsulatum and HZV prior to HSCT.
- With clinical suspicion of latent tuberculosis.
- Who received BCG vaccine within 3 months prior to HSCT.
- Who received live or attenuated live (other than BCG) vaccine within 6 weeks prior to HSCT.
- With hypersensitivity to emapalumab or any of the excipients.
- With concurrent diseases which may significantly affect the assessment of emapalumab safety or efficacy.
- Pregnant (or planning to become pregnant) or lactating female patients.

10.2.5.2 Measures during the study

The following measures are applied during the monitoring period and treatment with emapalumab:

- Prophylactic use of antivirals for herpes zoster virus.
- Search for pathogens during the study in case of clinical suspicion of infections caused by typical and atypical mycobacteria, salmonella, Histoplasma capsulatum and herpes zoster virus.
- Search for TB at pre-defined time-points..
- Monitoring of re-occurrence of malignant disease by MRD
- Antibodies against emapalumab.
- Pregnancy test for early detection of pregnancy.

- Involvement of IDMC, a group of individuals external to and independent from Sobi AG, investigators and study personnel. An IDMC will review the safety data with the aim to ensure that patients are not exposed to unnecessary risks.
- Appropriate study treatment interruption/discontinuation (see section 11.1) and study stopping rules (see section 11.2).

10.2.6 Benefit-risk evaluation

Based on experience from clinical studies with emapalumab in healthy volunteers and patients with primary and secondary forms of HLH and considering the anticipated benefit and risk minimization measures in place in this protocol, the benefit-risk profile of emapalumab appears to be favorable for its use in patients who are at risk of GF after HSCT.

11 STUDY STOPPING RULES

11.1 Criteria for study treatment interruption/discontinuation

11.1.1 Emapalumab infusion rate decrease /interruption

In case of clinically relevant changes in patient status during emapalumab infusion, the rate of infusion may be decreased or the infusion temporarily interrupted, if deemed necessary by the Investigator and later restarted if patient's situation allows for continuation of the infusion.

11.1.2 Emapalumab permanent discontinuation

Study drug must be permanently discontinued in the following situations:

- Any treatment emergent adverse reaction (i.e. assessed as related), which is considered as life-threatening.
- Any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety.
- Re-occurrence of malignant disease as judged by the investigator based on clinical assessment including MRD monitoring.

In the situations described above, IDMC will be promptly informed and involved in evaluation of the patient's data.

Other situations that must lead to treatment permanent discontinuation are:

- Pregnancy.
- If a re-transplant is needed based on medical judgment.
- Graft failure.

The reason for study treatment discontinuation should be documented as appropriate in the eCRF.

The Investigator can decide at any time during the study to discontinue the treatment in a patient based on medical judgment, taking into account the benefit/risk ratio for continuing the treatment.

Decision to discontinue treatment will have no impact on the patient's care. All patients who discontinue treatment will be treated according to local medical practice. A subject who prematurely discontinues study treatment is NOT considered as withdrawn from the study. All assessments relevant to EoT visit must be performed and the patient will enter the follow-up period.

11.1.3 Premature withdrawal from the study

Patients (or their legal representative) have the right to voluntarily withdraw consent to participate in the study at any time for any reason. In addition, the Investigator has the right to withdraw a patient from the study at any time, if considered in the best interest of the patient based on medical judgment. Patients should be informed of circumstances under which their participation may be terminated by the Investigator without the patient's consent. Any administrative or other reasons for withdrawal must be explained to the patient.

The reason for study withdrawal should be documented in the eCRF and patient's chart.

In any case, the decision to withdraw or be withdrawn from the study will have no impact on the patient's care and on further treatments administered after withdrawal. Patients who are withdrawn from the study will receive alternative treatments according to the standard of care.

11.1.4 Non-evaluable patients

The following cases represent non-evaluable patients when treated for primary GF:

- Administration of any prohibited medication during treatment.
- Premature treatment withdrawal for reasons other than safety or lack of efficacy.
- More than 1 infusion missed.

- Documented delay of treatment initiation by more than 36 hours after CXCL9 sample collection time and levels above threshold.

Recruitment of patients treated for primary GF will continue until the required number of evaluable patients for each interim analysis and final analysis is met.

This definition of non-evaluable patients does not apply for patients treated for secondary GF.

11.2 Criteria for study suspension/termination

11.2.1 Temporary study suspension

The study may be temporarily suspended in the following situations:

- Occurrence of one (1) SAE which is life-threatening or fatal and that is both unexpected and assessed as related to the use of emapalumab.
- At the IDMC own request as an outcome of their regular or ad hoc study data review.

Enrolment of any new patient will be suspended until further notice. Patients already enrolled in the study should continue receiving emapalumab per protocol unless decided otherwise by the Investigator.

In the case of study suspension, the IDMC will be promptly informed to allow for analysis of the data that were already generated and to provide recommendations which will also include further management of patients already enrolled in the study.

After evaluation of benefit/risk profile based on available data, the IDMC may recommend any of the following:

- Resume the study without any change in the conduct of the study.
- Resume the study with the amendment of the protocol to address any new safety concerns.
- Permanent study termination.

11.2.2 Study Termination for safety reasons

Termination of the study must be considered in the case of occurrence of two (2) deaths due to any reasons suggesting a reasonable possibility that the deaths are related to the use of emapalumab. This process will involve the IDMC, Sponsor and the Investigator. The management of patients already enrolled in the study will also be part of the IDMC recommendations.

11.2.3 Study Termination for efficacy reasons

The decision to terminate the study due to absence of a demonstrated benefit can be made by the Sponsor.

In case of study termination, the management of the patients already enrolled in the study will also be part of the IDMC recommendations.

12 STATISTICAL METHODS

12.1 Sample Size

In order to treat 4 patients for primary GF per cohort, it is expected to include between 15 to 40 patients to be monitored for primary or secondary GF per cohort. This is based on the assumption that between 10 and 30% of patients will present with a CXCL9 elevation above defined threshold when ANC is below 500 cells/µL during the monitoring period (Sobi AG internal data).

Considering a maximum of 3 sequential cohorts of 4 evaluable patients and 6 additional evaluable patients to the final cohort with determined dose and potential non-evaluable patients, it is expected that approximately a maximum of 250 patients will be included in the study to be monitored for GF.

Given the experience gained with emapalumab in other indications such as hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), a robust PK/PD model has been developed, therefore 4 evaluable patients per cohort and a maximum of 3 cohorts are considered sufficient to confirm the PK/PD profile in post-HSCT patients and determine the appropriate dose regimen to pre-emptively treat patients at high risk of GF.

Assuming a similar rate of primary and secondary GF, a similar number of patients may optionally start treatment for secondary GF in each cohort. Additional patients may be treated for secondary GF in the final cohort with determined dose.

12.2 Interim analyses

Interim analyses (IAs) are planned when the last patient completes pre-emptive treatment for primary GF in a cohort (4 evaluable patients). Total IFNγ levels, CXCL9 levels and PK/PD data will be assessed for inclusion of additional dose cohorts. The benefit risk of emapalumab will be assessed by IDMC and sponsor before transitioning to the next dose regimen in cohort 2 or 3.

Once the appropriate dose regimen is determined in cohort 1, 2 or 3, a maximum of 6 additional evaluable patients may be added to the selected cohort. Additional IAs are planned when 7 and 10 evaluable patients have completed treatment with the selected dose, unless the study is stopped for futility or success. A final analysis with all data collected up to EoS will be included in a CSR.

IAs will be also performed after 1 and 2 years follow up calls and data collected up to 3 years follow up will be included in an addendum to the CSR.

Given that similar PK/PD profile of emapalumab is expected in patients treated to pre-empt primary and secondary GF, data obtained in the secondary GF patients may also be used.

The following guidance will be followed for inclusion of additional patients to the same cohort (once the appropriate dose has been selected) or to stop the study for futility or success.

After 4 evaluable patients have completed treatment for primary GF in a cohort with selected dose:

- 3 or more patients experienced GF, the study will be stopped for futility.
- 0 to 2 patients experienced GF, 3 additional patients may be added.

After 7 evaluable patients have completed treatment for primary GF:

- 5 or more patients experienced GF, the study will be stopped for futility.
- 2 to 4 patients experienced GF, 3 additional patients may be added.

0 to 1 of the patients experienced GF, the study can be stopped for success.

12.3 Patients stratification

Patients will be stratified into two groups at screening (at least 40% malignant and 40% non-malignant) by means of an interactive response technology. Stratification will allow to explore the appropriate dose inhibiting IFNɣ production in a similar number of patients presenting with malignant or non-malignant disease in each cohort.

12.4 Definition of study populations

The following analysis sets/populations will be used:

- All included population: This population will comprise all patients included in the study whether they are treated or not and will be used for presenting safety endpoints.
- All treated population: This population will comprise all patients who received at least one dose of investigational product and will be used for presenting efficacy endpoints.
- All evaluable population: This population will comprise all patients treated for primary GF who have:
    - No administration of any prohibited medication during treatment.
    - No premature treatment withdrawal for reasons other than safety or lack of efficacy.
    - Not more than 1 infusion missed.
    - No delay of treatment initiation (more than 36 hours from CXCL9 sample collection time with levels above threshold).

  This population is the primary analysis population for determination of the appropriate dose regimen and to assess efficacy of emapalumab in pre-empting primary graft failure.
- Per protocol population: This population includes all evaluable patients without major protocol deviations. A major protocol deviation is here defined as a deviation that has been classified as major based on that it might influence the primary efficacy endpoint (pre-emption of GF). The per protocol population will be used to assess the appropriate dose regimen and efficacy of emapalumab in pre-empting primary GF.
- PK/PD population: This population will comprise all patients included in the study treated with emapalumab and with at least one post-dose PK sample. The PK/PD population will be used for presenting PK/PD endpoints.

12.5 Overall statistical and analytical plan

Full details of all statistical considerations and planned statistical analyses will be specified in the SAP, which will be finalized before the first interim analysis which takes place when the last patient in the first dose cohort completes his/her treatment period. This section contains an overview of the planned methods of analysis.

All analyses are considered exploratory. Data will be presented by emapalumab dose regimen, total emapalumab group and untreated group. The emapalumab groups will also be divided by treatment for primary graft failure (pGF) and secondary graft failure (sGF) and by malignant and non-malignant where applicable.

Continuous variables will be summarized using the number of patients, the mean, the standard deviation, the median, the minimum value, and the maximum value. Categorical variables will be summarized using frequency counts and percentages.

Statistical analysis will be performed using Statistical Analysis Software (SAS) software Version 4 or later (SAS Institute, Inc, Cary, North Carolina, United States).

12.5.1 Demographics and baseline characteristics

Demographic data and baseline characteristics will be presented using summary statistics.

12.5.2 Efficacy Data

Efficacy data will be summarized using descriptive statistics.

Point estimates for the efficacy endpoints will be presented together with the corresponding 95% confidence intervals (CI) in the appropriate dose cohort.

The relationship between selected covariates (e.g. biomarkers, baseline characteristics) and treatment response will be investigated.

The relationship between selected covariates and the risk of GF will be investigated in the untreated patients.

12.5.3 Safety Data

Safety data will be listed and summarized using descriptive statistics.

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

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

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

12.5.4 Pharmacokinetic and Pharmacodynamic Data

Pharmacokinetic and pharmacodynamic calculations

The serum concentration of free emapalumab will be measured as a function of time to determine the PK of emapalumab in this patient population. PK parameters will be calculated and used to support determination of the appropriate dose regimen of emapalumab.

NCA will be used to calculate the following PK parameters after each cohort: Cmax (peak serum concentration), Ctrough (concentration just before administration), Cmeantau (mean concentration over a dosing interval) and AUCtau (area under curve of a dosing interval). Other PK parameters may be calculated as appropriate.

In addition, at the end of the study individual emapalumab concentration-time data will be subject to population PK analysis using non-linear mixed effects modeling. The anticipated covariate effects of body weight and time-varying total IFNγ will be included in the model. Additional covariate effects might be investigated. A specific PK modeling analysis plan will be prepared.

An exploratory PK/PD analysis using non-linear mixed effects modeling will be conducted. The main PD biomarker investigated will be CXCL9. Additional PD biomarkers may also be evaluated. The anticipated covariate effect of time-varying total IFNγ will be included in the CXCL9 model. Additional covariate effects might be investigated.

The population PK and PK/PD analyses may be reported separately.

All PK and PD data will be summarized using descriptive statistics.

12.5.5 Exploratory analyses

The correlation between relevant biomarkers including CXCL9 levels and the risk of GF post allo HSCT will be evaluated in the untreated patients.

Specific exploratory analyses evaluating the impact of study endpoints when CXCL9 and other relevant biomarkers are measured with different analytical methods will be defined in a SAP.

12.5.6 Handling of missing data

Due to the exploratory nature of the study no imputation of missing data will be performed, all analyses will be based on observed data.

13 ETHICAL AND LEGAL ASPECTS

13.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Sobi AG, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in the International Conference on Harmonization (ICH) Guideline E6-R2 and in accordance with the general ethical principles grounded in the Declaration of Helsinki. The study will receive approval from an IRB/IEC prior to commencement and where applicable by law also from National Competent Authorities. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2 Investigator's Responsibilities

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

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

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

13.3 Coordinating investigator

The coordinating investigator of the trial is responsible for contributing to the study design in the context of the multi-center trial and will review and sign the CSR.

13.4 Informed Consent

Before being enrolled in this clinical study, the patient (or its legally authorized representative) must consent to participate, after the nature, scope, and possible consequences of the study have been explained in a form understandable to him or her. An informed consent document that includes both information about the study and the consent form will be prepared and given to the patient. This document will contain all ICH, GCP, and locally required regulatory elements (whichever is more stringent). The document will be in a language understandable to the patient (or its legally authorized representative) and will specify who obtained informed consent from the patient, and when the informed consent was obtained. The patient (or its legally authorized representative) must be informed about their right to withdraw from the study at any time. The written informed consent form must not be changed without prior discussion with the sponsor. Before any revisions are implemented, the revised written informed consent form must be approved by the IEC/IRB.

Information for patients will be split into a Patient Information Sheet that provides detailed information about the trial and its benefits and risks, and the Informed Consent Form that summarizes the content of the Patient Information Sheet and is used to obtain the dated signature from the patient (or its legally authorized representative) as evidence of the patient's agreement to participate in the study. The Investigator acknowledges that consent is a process that begins with explaining the study and obtaining signature on the consent document, and continues throughout the patient's participation in the study. The Investigator will remain responsible for ensuring adequate consent is obtained and documented.

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

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

13.5 Confidentiality and data privacy

Sobi AG shall respect patients' rights to protect their personal data in compliance with ICH, relevant national legislation, and international data protection regulations (whichever is the most stringent). All records and copies thereof used for conducting the study, for regulatory purposes or sent to Sobi AG shall be anonymized in accordance with relevant national legislation and international data protection laws.

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

13.6 Protocol amendments

Substantial amendments will be submitted to the IRB/IEC for approval, and where applicable to National Competent Authorities. Approval must be obtained before implementation of the amended version occurs.

13.7 Approval of clinical study protocol and amendments

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

Sobi AG can only supply study drug to an Investigator after Sobi AG or their authorized representative has received documentation on all ethical and legal requirements for starting the study. This documentation must also include a list of the members of the IRB/IEC and their occupation and qualifications. If the IRB/IEC will not disclose the names of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. Formal approval by the IRB/IEC should mention the study title, study code, study site, and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member (chairman or secretary of the IRB/IEC). Before the first patient is enrolled in the study, all ethical and legal requirements must be met.

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

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

All documents handed over to patients or their legal representative prior to use must first be reviewed and approved by Sobi AG, and upon approval by Sobi AG submitted to and reviewed and approved by the competent IRB/IEC.

13.8 Ongoing information for IRB/IEC

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

- Information on SAEs or suspected unexpected serious adverse reactions (SUSARs) as per local applicable rules and timelines.
- Periodic reports on the progress of the study.
- Deviations from the protocol or anything that may involve added risk to patients.

13.9 Closure of the study

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

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

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

13.10 Record Retention

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

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

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

13.11 Liability and insurance

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

13.12 Financial disclosure

Investigators and study site staff directly involved in the treatment or evaluation of the patients are required to provide financial disclosure information at the start of the study, every 2 years during the conduct of the study, and at the end of the study, in order for Sobi AG to be able to submit complete and accurate certification or disclosure statements in accordance with applicable national and local regulations, including FDA 21 Code of Federal Regulation (CFR) Part 54 requirements. In addition, Investigators must provide Sobi AG with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

13.13 Disclosure of protocol and study results and publication policy

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 www.clinicaltrials.gov and EudraCT. The results of this study will be published within 12 months of the end of study.

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

Sobi AG will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Sobi AG will support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements. Any formal publication of the study in which contributors exceeded that of conventional monitoring and/or data acquisition will be considered as a joint publication by the Investigator and the appropriate Sobi AG personnel.

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

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

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

14 MONITORING AND AUDITING

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

14.1 Study monitoring and source data verification

As part of the responsibilities commensurate with participating in the study, the Investigator agrees to maintain and have available for monitoring adequate case records (accurate source documents and eCRFs) for the patients treated under this protocol. In addition, the Investigator agrees to maintain all administrative documents (e.g., IRB/IEC correspondence, investigational product and supplies shipment manifests, monitoring logs, or correspondence with Sobi AG and with any of its representatives for this study). When a copy is used to replace an original document, the copy should fulfill the requirements for certified copies. The Investigator agrees to cooperate with the monitor(s) to ensure that any issue detected in the course of the monitoring visits is resolved.

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

14.2 On-site audits

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

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

14.3 Serious GCP breaches

Sobi AG is required to report a serious GCP Breach within 7 days to applicable health authorities.

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

Therefore, should an Investigator become aware of a possible serious GCP breach (e.g. non-reporting of critical safety information that has the potential of jeopardizing patients' safety), Sobi AG must be notified within 24 hours.

15 DOCUMENTATION AND USE OF STUDY FINDINGS

15.1 Documentation of study results

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

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

Sobi AG will ensure that the Investigator has control of and continuous access to the eCRF data reported to the Sponsor until data base lock.

The eCRF pages must be reviewed and electronically signed by the Investigator named in the study protocol or by a designated sub-investigator. At the end of the study, Sobi AG will ensure that a readable image of the eCRF is provided to the Investigator, to be maintained in his/her records. Sobi AG will ensure that the eCRF copies left with the Investigator (print-outs and/or pdf exports) are an exact copy of the data maintained in the database.

15.2 Use of computerized systems at the clinical trial center

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

The system must allow the Sponsor, clinical research associate, auditors or inspectors to verify source data without infringing privacy rights of other patients, e.g., access must be restricted to records pertaining to the study patients and access to other patients must not be possible. This should include access to the audit trail. If the electronic Health System does not comply with these requirements, the Sponsor reserves the right to be provided with paper print outs from the System containing the same information as the electronic original records.

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