Clinical Study Protocol

A Phase 2/3, Open-label, Single Arm, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Emapalumab in Adult Patients with Hemophagocytic Lymphohistiocytosis

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INVESTIGATOR AGREEMENT

Protocol Number: NI-0501-10

Protocol Date and Version: 09 March 2020, Version 3.0

Study Drug: emapalumab

Study Title: A Phase 2/3, Open-label, Single Arm, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Emapalumab in Adult Patients with Hemophagocytic Lymphohistiocytosis

Investigator Endorsement:

I, the undersigned, have agreed to serve as a Principal Investigator for this study and to be responsible for the conduct of this study at this site, and I agree to conduct the study according to the protocol and any approved protocol amendments, ICH GCP and all applicable regulatory authority requirements.

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

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

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Name

_____

Site number and address

Please sign this form and make a copy of the form for your site files. The original of the form, reflecting the original signature, will be collected by your monitor and returned to Sobi AG.

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NI-0501-10 SYNOPSIS

Title:	A Phase 2/3, Open-label, Single Arm, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Emapalumab in Adult Patients with Hemophagocytic Lymphohistiocytosis
Sponsor:	Sobi AG, Switzerland
Study Type and Design:	Study NI-0501-10 is an open-label, single arm, multicenter, Phase 2/3 interventional study The study enrolls adult patients with hemophagocytic lymphohistiocytosis (HLH), specifically newly diagnosed patients with malignancy-associated HLH (M-HLH), and newly diagnosed or previously treated patients with non-malignancy-associated HLH The study includes an initial phase enrolling 10 patients. If no untoward significant safety signal attributable to emapalumab treatment (as judged by an iDMC) is identified, enrolment will be broadened and will continue until the target number of patients is reached The patient's participation in the study comprises three parts: screening, treatment period, and follow-up
Study Objectives:	Primary efficacy objective: • To assess the efficacy of emapalumab in adult patients with HLH, as measured by Overall Response Rate Secondary efficacy objectives: • To assess the efficacy of emapalumab as measured by overall survival, time to response, best response on treatment, duration of response • To evaluate the safety and tolerability of emapalumab • To determine the pharmacokinetic (PK) profile of emapalumab • To determine the pharmacodynamic (PD) profile of emapalumab
Study Population:	Eligible patients include male and female patients aged 18 and older at the time of HLH diagnosis, who meet HLH-2004 clinical criteria for the diagnosis of HLH (with or without malignancy), and who have no primary HLH. Patients with M-HLH must be newly diagnosed (i.e. must have received no previous HLH treatments, with the exception of glucocorticoids), while patients with non-malignancy-associated HLH may have previously received HLH therapies (therefore they can be either treatment naïve or treatment experienced)

Inclusion Criteria:

1. Male and female patients aged 18 and older at the time of HLH diagnosis
2. Fulfilment of HLH-2004 clinical criteria, i.e. five of the eight criteria below:
   - Fever
   - Splenomegaly
   - Cytopenias affecting 2 of 3 lineages in the peripheral blood (hemoglobin <90 g/L; platelets <100 x 10^9/L; neutrophils <1 x 10^9/L)
   - Hypertriglyceridemia (fasting triglycerides ≥3 mmol/L or ≥265 mg/dL) and/or hypofibrinogenemia (fibrinogen ≤1.5 g/L)
   - Hemophagocytosis in bone marrow, spleen or lymph nodes
   - Low or absent natural killer (NK)-cell activity
   - Ferritin ≥500 µg/L
   - Soluble CD25 (sCD25, i.e., soluble IL-2 receptor) ≥2400 U/mL *(or equivalent, in case the local lab uses different units)*
3. Patients diagnosed with M-HLH must be treatment naïve; patients diagnosed with HLH driven by any other etiology or idiopathic can be either treatment naïve or treatment experienced
4. Patients with non-malignancy-associated HLH who have already received conventional therapy for HLH must have failed prior treatment as per the treating physician`s judgement. At the time of enrolment, eligible treatment experienced patients may or may not be receiving conventional therapy
5. JAK inhibitors, if administered, must be discontinued before emapalumab initiation
6. Informed consent signed by the patient or by the patient's legally authorized representative(s) (as required by local law)
7. Willing to use highly effective methods of contraception from study drug initiation to 6 months after the last dose of study drug, if female and of childbearing potential

Exclusion Criteria:

1. Primary HLH (documented by the presence of known causative genetic mutations or by the presence of family history)
2. Current (within 60 days from SD0) or scheduled administration of therapies known to trigger the cytokine release syndrome (e.g. chimeric antigen receptor (CAR)-modified T cells, bispecific T cell-engaging antibodies)
3. Current (within 60 days from SD0) or scheduled administration of PD-1/PD-L1/CTLA-4 inhibitors

	4. Life-expectancy associated with the underlying disease (triggering HLH) < 3 months 5. Ongoing participation in an investigational trial, or administration of any investigational treatment within 30 days from Screening 6. History of hypersensitivity or allergy to any components of emapalumab 7. Active mycobacteria*, Histoplasma capsulatum,* or *Leishmania* infections 8. Evidence of latent tuberculosis 9. Infection with HIV (HIV ELISA or PCR positive), hepatitis B (HBsAg positive), Hepatitis C (anti-HCV positive) unless the viral load by PCR is negative 10. Concomitant diseases that in the opinion of the Investigator may significantly affect the likelihood of a response to treatment and/or the assessment of emapalumab safety and/or efficacy 11. Receipt of a bacille Calmette-Guerin (BCG) vaccine within 12 weeks prior to Screening 12. Receipt of a live or attenuated live (other than BCG) vaccine within 6 weeks prior to Screening 13. Pregnancy or lactation (female patients)
Study Drug:	Emapalumab (previously referred to as NI-0501) is a fully human high-affinity monoclonal antibody that binds to and neutralizes IFNγ
Dosing Regimen & Frequency of Administration:	Emapalumab will be administered by intravenous (IV) infusion over a period of 1 to 2 hours depending on the volume to be infused, at an initial dose of 6 mg/kg Emapalumab treatment will be continued at the dose of 3 mg/kg, every 3 days until SD15, and then twice-a-week If the treating physician deems appropriate, the dose of emapalumab may be increased (back to 6 mg/kg, and up to 10 mg/kg), guided by clinical and laboratory response. During the initial phase of the study, PK/PD data may also be considered
Treatment Duration:	It is not expected that treatment duration will be the same across the study population Treatment shall continue until a clinically satisfactory response is achieved. Shall the duration of treatment exceed 12 weeks, an assessment of a favorable benefit/risk profile must be provided and confirmed by the iDMC If HSCT is planned, treatment can be administered until HSCT In all cases, treatment can be stopped upon achievement of complete clinical response, if at least two infusions of emapalumab at the dose of 3 mg/kg have been administered

	Patients will undergo a Week 4 Assessment Visit 3 days after the last emapalumab infusion administered in Week 4 Treatment may be shorter, and in such instance an End of Treatment (EoT) visit shall be performed 3 days after the last administration of emapalumab Whenever a patient receives treatment beyond Week 4, both a Week 4 Assessment Visit and an End of Treatment (EoT) visit shall be performed After treatment discontinuation (for any reason), patients will continue in the study for long-term follow-up until 1 year after last emapalumab administration (or after HSCT, if performed) If HLH recurs or reactivates during the off-drug follow-up, treatment with emapalumab can be reinstated
Background Therapy & Concomitant Medications:	In all patients, emapalumab will be initiated on a background of glucocorticoids. Therapy with dexamethasone at a dose of 10 mg/m^2 daily will be initiated in any patient not receiving glucocorticoids at the time of emapalumab start. If a patient is already receiving glucocorticoids, he/she will continue at their current dose, as long as it corresponds to at least 5 mg/m^2 daily dexamethasone (unless intolerance is documented) In case of M-HLH, emapalumab can be administered with standard malignancy-directed therapy, as deemed appropriate by the Investigator, with the exception of the therapies listed as exclusion criteria Administration of advanced therapies known to trigger the cytokine release syndrome (e.g., chimeric antigen receptor (CAR)-modified T cells, bispecific T cell-engaging antibodies, PD-1 inhibitors) and the administration of JAK inhibitors are prohibited Calcineurin inhibitors can be continued if they are being administered at the time of screening. Calcineurin inhibitors can be withdrawn at any time at the discretion of the Investigator IV immunoglobulins are only allowed as replacement treatment During emapalumab treatment, intrathecal (IT) therapy (e.g. methotrexate and glucocorticoids) can be continued or started de novo, if clinically indicated The administration of additional HLH therapies, concomitantly with emapalumab, will be allowed in the case of documented unsatisfactory HLH control after at least 3 doses of emapalumab. Unless a patient has been previously vaccinated, prophylaxis for herpes zoster must be in place on study day minus 1 (or, at the latest, before initiation of emapalumab treatment) and must be maintained for 2 half-lives (approximately 44 days) after last emapalumab administration

	Patients may receive additional prophylactic antimicrobial treatments according to local standards of care Analgesic therapies, blood product transfusions, electrolyte and glucose infusions, antibiotics, anti-fungal treatments, anti-viral treatments, and general supportive care are allowed Vaccination with a live or live-attenuated (including BCG) vaccine must be avoided for 2 half-lives after last emapalumab administration
Sample Size:	According to the adaptive design of this study, the initial sample size planned for each etiology (i.e. M-HLH and non-malignancy-associated HLH) is 10 patients. The sample size for each of the two etiologies (i.e. M-HLH and non-malignancy-associated HLH) will be reviewed in an ongoing way. Recruitment to particular etiologies may be stopped for futility while recruitment to other etiologies may be expanded up to a sample size of 25 patients for a particular etiology
Number of Sites:	Initially approximately 5. The number may be increased depending on the observed recruitment rate
Study Duration and Study End Definition:	After emapalumab discontinuation (for any reason), patients will continue in the study for long-term follow-up until 1 year after last emapalumab administration (or after HSCT, if performed) The analysis of the primary efficacy endpoint will be performed once the last enrolled patient underwent the Week 4 Assessment Visit (or EoT Visit in case of earlier treatment discontinuation) The end of the study is defined as last patient last visit (LPLV) at 1 year after last emapalumab infusion or HSCT (as applicable)
Study Surveillance, Safety Reporting and Stopping Rules:	The study includes an initial phase enrolling 10 patients. If no untoward significant safety signal attributable to emapalumab treatment (as judged by an iDMC) is identified, enrolment will be broadened; subsequently, the iDMC will meet every time data for an additional 10 patients in total are available (or earlier, should any untoward event occur), to confirm that the safety profile of emapalumab remains favorable. In addition, the Sponsor will review the data on an ongoing basis, to monitor for the emergence of any safety signals Emapalumab infusions should be performed under medical supervision, in an environment with access to emergency equipment and trained medical personnel, and monitored as per local standard of care based on the patient's clinical condition Adverse events (AEs) will be recorded from the date of the ICF signature until the end of the study, as follows: - Signs and symptoms of HLH will not be reported as adverse events; however, sustained worsening or reactivation of HLH during or after emapalumab treatment will be reported as an AE

	- SAEs must be communicated by the Investigator to Sobi AG by fax or e-mail within 24 hours of awareness - After the Day+60 Visit (i.e. once at least 2 half-lives of the drug have elapsed), only serious adverse events (SAEs) related to emapalumab will be collected In case of pregnancy, study treatment must be discontinued permanently
Efficacy Endpoints:	Primary efficacy endpoint: • Overall Response, i.e. achievement of either a Complete or Partial Response, at Week 4 (or EoT if earlier) Secondary efficacy endpoints: • Best response on treatment • Overall Response at EoT • Overall survival • Time to Complete or Partial Response • Duration of response • HLH Relapse
Safety Endpoints:	• Incidence, severity, causality and outcomes of AEs (serious and non-serious) • Clinically significant changes in blood tests, physical examinations, vital signs, ECGs
PK/PD Endpoints:	• Serum concentrations of emapalumab at specified time points • Serum concentrations of total IFNγ and CXCL9, at specified time points • Serum concentrations of other relevant markers, including but not limited to sCD25 and IL-6, at specified time points • Incidence of anti-drug antibodies (ADAs) against emapalumab
Statistical Analysis:	The primary analysis for each etiology (i.e. M-HLH and non-malignancy-associated HLH) will evaluate the Overall Response (OR) rate at 4 weeks and use a binomial test with a one-sided significance level of 5% to calculate the p-value. The null hypothesis is that the OR rate is at most 40%, which is the assumed value historically. An improvement in the OR rate up to 60% is being targeted In this adaptive design, it is proposed to review the data periodically in order to assess each of the 2 etiologies (i.e. M-HLH and non-malignancy-associated HLH) for futility and efficacy. The first analyses for each etiology would be after 10 patients recruited with that etiology, and further analyses for each etiology would take place after

	every subsequent 5 patients. The decision rule for stopping for futility shall be based on a one-sided p-value looking to see whether the OR rate was significantly below 60%, while the decision rule for consideration for efficacy shall be based on a one-sided p-value looking to see whether the OR rate was significantly above 40% Descriptive statistics and graphical methods will be used for the evaluation of the secondary efficacy endpoints Safety data will be listed and summarized using descriptive statistics To support regulatory interactions on the confirmatory strategy, a descriptive evaluation of the efficacy and safety results will be made after a small number of patients, i.e. no more than 10 patients overall (irrespectively of etiology), have completed 4 weeks of treatment

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
AUC	Area Under the Curve
BAL	Bronchoalveolar lavage
BCG	Bacillus Calmette-Guérin
CBC	Complete blood cell count
CFR	Code of Federal Regulation
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CRA	Clinical research associate
CRF	Case report form
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CU	Compassionate Use
eCRF	Electronic case report form
DMC	Data Monitoring Committee
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EOT	End of treatment
FDA	Food and Drug Administration

FHL	Familial hemophagocytic lymphohistiocytosis
G-CSF	Granulocyte-colony-stimulating factor
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
HSCT	Hematopoietic stem cell transplantation
HV	Healthy volunteer
HZ	Herpes Zoster
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IFNγ	Interferon gamma
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IgG1	Immunoglobulin G1
IMP	Investigational medicinal product
IRR	Infusion-related reaction
IT	Intrathecal
IVIG	Intravenous immunoglobulin
LCMV	Lymphocytic choriomeningitis virus
LDH	Lactate dehydrogenase
LPLV	Last patient last visit
mAb	Monoclonal antibody
MAS	Macrophage Activation Syndrome
M-HLH	Malignancy associated HLH
MRI	Magnetic resonance imaging
NK	Natural killer
NaCl	Sodium Chloride
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level

ORR	Overall response rate
OS	Overall Survival
PCR	Polymerase chain reaction
PD	Pharmacodynamic
pHLH	Primary hemophagocytic lymphohistiocytosis
PPD	Purified protein derivative
PK	Pharmacokinetic
PR	Partial response
PT	Prothrombin Time
ROC	Receiver Operating Characteristic
SAE	Serious adverse event
SAP	Statistical analysis plan
sCD25	soluble CD25 (i.e., soluble IL-2 receptor)
SD(n)	Study Day number (e.g., Study day 1 = SD1)
sHLH	Secondary hemophagocytic lymphohistiocytosis
sJIA	systemic Juvenile Idiopathic Arthritis
SUSARs	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event
TB	Tuberculosis
TMF	Trial Master File

Table 1: Schedule of Assessments – Screening and Treatment Period

Assessment		Screening Visit (up to 2 Weeks prior to Visit 1)	Week 1			Week x →	Week 4 Assessment Visit [b] (3 ± 1 day)	EoT (3±1 day after last infusion)
			Visit 1 / SD0	Visit 2 / SD3	Visit 3 / SD6	Visit 4 onwards [a]	Visit `Wk4 Assessment`	Visit `EoT`
Informed Consent		X						
Review of Inclusion/Exclusion Criteria		X	X (pre-infusion)					
Patient Information [c]		X						
Background Dexamethasone/Glucocorticoids [d]		X	X	X	X	X	X	X
Anti-viral Prophylaxis [e]		X	X	X	X	X	X	X
Emapalumab infusion [f]			X	X	X	X	X (if applicable)	
Clinical Assessment	Vital Signs [g]	X	X (Pre/post-inf.)	X (Pre/post-inf.)	X (Pre/post-inf.)	X (Pre/post-inf.)	X (Pre/post-inf., if applicable)	X
	Body weight	X	X (pre-inf)	X (pre-inf)	X (pre-inf)	X (pre-inf)	X (pre-inf, if applicable)	X
	Height	X						
	ECOG Performance Status	X	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (pre-inf, if applicable)	X
	Physical Examination	X	X (Pre-inf.) [p]	X (Pre-inf.) [p]	X (Pre-inf.) [p]	X (Pre-inf.) [p]	X (pre-inf, if applicable) [p]	X [p]
Procedure	ECG	X						X
Evaluation for Infection [q]	TB [h]	X	Every 4 weeks					
	Adenovirus, EBV, CMV (viral load)	X	If infection suspected					
	HIV, Hep B, Hep C	X						
	Atypical mycobacteria, *Histoplasma capsulatum*, *Leishmania*	X	If infection suspected					

Assessment		Screening Visit (up to 2 Weeks prior to Visit 1)	Week 1			Week x →	Week 4 Assessment Visit [b] (3 ± 1 day)	EoT (3±1 day after last infusion)
			Visit 1 / SD0	Visit 2 / SD3	Visit 3 / SD6	Visit 4 onwards [a]	Visit `Wk4 Assessment`	Visit `EoT`
Laboratory	CBC	X	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (pre-inf, if applicable)	X
	Biochemistry	X	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (pre-inf, if applicable)	X
	Coagulation	X	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (Pre-inf.)	X (pre-inf, if applicable)	X
	Pregnancy test (if applicable)	X	Every 4 weeks					X
	Urinalysis [i]		X					X
Imaging	Abdominal Ultrasound [j]	X	X [o]	Every 2 weeks			X	X
	Chest X-ray	X	If clinically indicated					X
	Brain MRI	X [k]	If clinically indicated					
Histopathology	CSF Analysis (only if CNS disease and if coagulation allows) [l]	X [l]	If clinically indicated [l]					
Investigator assessment of clinical response			X	X	X	X	X	X
AE recording		X	X	X	X	X	X	X
Concomitant medications recording		X	X	X	X	X	X	X
PK [m]			X (Pre - post inf.)	X (Pre - post inf.)	X (Pre - post inf.)	X (Pre - post inf.)	X (Pre - post inf., if applicable)	X
PD [n]			X (Pre inf.)	X (Pre inf.)	X (Pre inf.)	X (Pre inf.)	X (pre-inf, if applicable)	X
Immunogenicity (ADA)			X (Pre inf.)				X [s] (pre-inf, if applicable)	X [r]

Abbreviations: ADA, anti-drug antibodies; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine transaminase, aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CBC, complete blood count; CMV, cytomegalovirus; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; ECG, electrocardiogram; EOT, end of treatment; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; IGRA, interferon-gamma release assays; SD, study day; IFNγ, interferon gamma; inf, infusion; IMP, investigational medicinal product; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PD, pharmacodynamic; PK, pharmacokinetic; PPD, purified protein derivative; PT, prothrombin time; TB, tuberculosis; US, ultrasound

CBC: complete blood count (white blood cells and subsets, red blood cells including hemoglobin, hematocrit, platelets). **Coagulation:** aPTT and/or aPTT ratio; PT and/or PT/INR, D-dimer, fibrinogen. **Biochemistry:** glucose, CRP, ferritin, triglyceride (fasting whenever possible), liver (AST, ALT, LDH, ALP, total bilirubin) and renal function (albumin, creatinine and urea)

From SD0 on, clinical assessments and procedures, evaluation for infections, laboratory and imaging assessments, Investigator assessment of clinical response shall be performed pre-infusion, ideally on the day of the infusion, and in any case no more than 1 day prior to the infusion

[a] **Visit X:** Sequential visit numbers will be used. Visit X lists all assessments required at any infusion visit, occurring either before or after the Week 4 Assessment Visit

[b] **Week 4 Assessment Visit:** The primary endpoint will be evaluated 3 days after the last emapalumab infusion administered in Week 4 (or at the EoT visit, for patients who discontinued treatment earlier)

[c] **Patient Information:** includes demographics (including race and ethnicity where allowed), medical history, medications at Screening, prior HLH therapy received (when applicable), date of HLH diagnosis, molecular diagnosis and relevant functional tests performed for the diagnosis of HLH (if available); for treatment experienced patients with non M-HLH, recording of reasons to determine failure of conventional therapy, as per Investigator`s assessment; for patients diagnosed with idiopathic HLH, recording of outcome of investigations performed to exclude an underlying malignancy

[d] **Background Dexamethasone/Glucocorticoids:** starting from SD minus1 (at latest). For details, see Section 6.1.2

[e] **Anti-viral prophylaxis:** for patients not vaccinated against Herpes Zoster, starting from SD minus 1 (or, at the latest, before the first emapalumab infusion) and until 2 half-lives after the last administration of emapalumab. Patients will receive any additional prophylactic antimicrobial treatment according to local guidelines for HLH.

[f] **Infusion:** to be performed over 1-2 hours, every 3 days until SD15, and then twice-a-week, not more than 4 days apart; the second infusion must be administered on SD3

[g] **Vital Signs:** includes body temperature, blood pressure, heart rate, respiratory rate. To be measured pre-infusion, at the end of the infusion, and 1 and 2 hours after the end of the infusion, except for body temperature, to be taken only pre-infusion

[h] **TB:** search for tuberculosis mycobacteria: at Screening: IGRA/PPD and PCR; after Screening by PCR if infection is suspected

[i] **Urinalysis:** glucose, blood, protein, leukocytes, ketones

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

[k] **Brain MRI:** only in cases of CNS disease and/or as clinically indicated

[l] **CSF analysis:** if lumbar puncture is performed for monitoring/therapy of CNS disease, spared sample (if any) may be analyzed for PK and PD parameters, if clinically indicated

[m] **PK:** emapalumab concentration

[n] **PD:** CXCL9, sCD25, total IFNγ, and other exploratory biomarkers

[o] **Abdominal ultrasound**: required at SD0 only if 2 weeks or longer elapsed between the Screening visit and SD0

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

[q] **Evaluation for infection**: if a patient's medical condition warrants rapid treatment initiation, availability of the results for infection screening is not required prior to initiation of emapalumab, provided that there are no clinical findings suggestive of any of the infections which represent exclusion criteria. However, samples for infection screening need to be collected for analysis prior to first administration of emapalumab according to the protocol requirements. As *Leishmania* is not endemic in North America, only patients who have been in endemic regions (e.g., South America) during the 6 months prior to screening, are required to be actively screened for *Leishmania*

[r] **ADA:** for patients who received the last emapalumab dose at Week 4, no ADA sampling is required at EoT

[s] **ADA:** for patients who remain on study drug beyond the Week 4 Assessment Visit, ADA sampling is required every 3 months after the Week 4 Assessment Visit.

Table 2: Schedule of Assessments - Follow-up Period

Assessments		Follow-up pre-HSCT [a]		Follow-up after last emapalumab infusion or after HSCT							UV [f]
		EOT [b]	Pre Conditioning visit [c]	Weekly visits wk 1 – 2 – 3 [d] (± 2 days)	D+30 visit [d] (± 2 days)	D+60 visit [d] (± 2 weeks)	D+100 visit [d] (± 2 weeks)	6 month visit [d] (± 4 weeks)	1 year visit [d]/ WD [e] (± 4 weeks)		
Clinical Assessments	Vital signs	As indicated in Table 1	X	X	X	X	X	X	X		
	Physical Examination [g]		X	X	X	X	X	X	X		
	ECOG Performance Status		X		X	X	X	X	X		
	Post-HSCT outcome [h]			X	X	X	X	X	X		
	Survival		X	X	X	X	X	X	X		
Laboratory	CBC		X	X	X	X	X	X	X		
	Biochemistry		X	X	X	X	X	X	X		
	Coagulation		X	X	X	X	X	X	X		
	Pregnancy test (if applicable)		X		X	X	X	X	X		
	Urinalysis								X		
Search for infection	TB [i]		Every 4 weeks until D+60; then at D+100, 6 month and 1 year visits								
	Adenovirus, EBV, CMV		If infection suspected								
Imaging	Chest X-ray [i]		If infection suspected						X		
	Abdominal US [j]		X				X		X		
Investigator assessment of clinical response			X	X	X	X	X	X	X		
AE recording			X	X	X	X	Only SAEs related to IMP				X
Concomitant medications			X	X	X	X	X	X	X		
PK/PD [k]			X	X	X	X	X	X	X		
Immunogenicity (ADA)					X		X		X		

Abbreviations: ADA, anti-drug antibodies; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine transaminase, AST, aspartate transaminase; CBC, complete blood count; CMV, cytomegalovirus; CRP, C-reactive protein; D, day; EOT, end of treatment; EBV, Epstein-Barr virus; HSCT, hematopoietic stem cell transplantation; IFNγ, interferon gamma; mo, month; PD, pharmacodynamic; PK, pharmacokinetic; TB, tuberculosis; US, ultrasound; UV, unscheduled visit; WD, withdrawal visit; wk, week; yr, year

CBC: white blood cells and subsets, red blood cells including hemoglobin, hematocrit, platelets. **Coagulation:** aPTT and/or aPTT ratio; PT and/or PT/INR, D-dimer, fibrinogen. **Biochemistry:** glucose, CRP, ferritin, triglycerides (fasting whenever possible), liver (AST, ALT, LDH, ALP, total bilirubin) and renal function (albumin, creatinine and urea)

During the follow-up after last emapalumab infusion or after HSCT, all assessments shall be performed ideally on the day of the visit, and in any case no more than 1 day prior to the visit

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

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

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

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

[e] **WD (Withdrawal Visit):** assessments as indicated for the 1-year visit are to be performed in case of premature study discontinuation

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

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

[h] **Post-HSCT outcome:** applies to patients who undergo HSCT. Includes engraftment rate, donor chimerism (as available), acute and chronic GvHD

[i] **TB search and chest X-ray**: to be performed as long as emapalumab serum concentrations are detectable, thereafter only if clinically indicated (except for one chest X-ray required at 1 year visit)

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

[k] **PK/PD: to be collected** if serum levels of emapalumab were still measurable at the previous visit; if serum levels of emapalumab were not measurable at the previous visit, PD can be collected if clinically indicated.

1 BACKGROUND INFORMATION

1.1 ADULT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Adult-onset hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening syndrome that has historically been diagnosed using criteria extrapolated from pediatric-onset HLH. These criteria include fever, splenomegaly, peripheral blood cytopenias (at least two lineages), hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in the bone marrow, spleen, or lymph nodes, hyperferritinemia, high levels of soluble IL2 receptor (i.e. sCD25), and low or absent NK-cell activity. The diagnosis relies on fulfilling 5 of the 8 criteria (Henter JI(c) 2007). Importantly, although the original criteria posit the absence of malignancy in pediatric HLH (Henter JI(b) 2002), a similar syndrome occurs in adults with specific types of cancer, especially NK/T-cell lymphomas and leukemia. In addition, HLH can complicate certain types of infection and specific rheumatologic diseases or be idiopathic. Therefore, while pediatric HLH is largely genetically defined by mutations affecting cytotoxic lymphocyte function, adult HLH is more heterogeneous in its etiology.

Despite the multiple triggers for adult-onset HLH and its less clearly defined genetic basis compared to pediatric HLH, the underlying pathophysiology is conserved: HLH is a syndrome characterized by a severe impairment or absence of cytotoxic function by natural killer (NK) and CD8+ T cells leading to striking activation of the immune system, manifested by hypercytokinemia and hemophagocytosis. These, in turn, cause all of the typical signs and symptoms of HLH (Dhote R 2003, Risdall RJ(b) 1984), leading to organ failure, and often to death.

The incidence of adult-onset HLH is unclear but is probably higher than generally realized. At the Mayo Clinic, the incidence has been estimated at 1 in every 2000 inpatient admissions (Parikh SA 2014) . For comparison, the incidence in the pediatric population has been estimated at 1 in every 3000 inpatient admissions (Jordan MB 2011) . The incidence of malignancy-associated HLH in adults has been reported as 0.36/100,000 individuals/year (Machaczka M 2011). Adult patients who respond to therapy can relapse, but the incidence of relapse has not been documented. Many patients do not have the opportunity to relapse because of initial difficulty in achieving disease control.

Clinically, adult patients with HLH do notoriously poorly. In one of the largest case series reported to date, 67 adult patients meeting strict criteria for HLH were found to have a median overall survival of only 4 months. Patients with malignancy-associated HLH had the worst prognosis, with a median overall survival of 2.8 months and only 0.9 months in the setting of myeloid malignancies. Patients with HLH but without malignancy had a median overall survival of 10.7 months (Schram AM 2016). Other studies have reported similarly dismal outcomes, especially in patients with concomitant hematologic malignancies (Li J 2014, Parikh SA 2014, Rivière S 2014, Takahashi N 2001). In all causes of HLH in adults, the overall mortality is significant at 41%, ranging from 5 to 39% in autoimmune disease-associated HLH, and between 42% and 88% in malignancy-associated HLH (Carter SJ 2019).

The scientific literature suggests a correlation between clinical response and probability of survival. However, there are no standardized criteria or time points to define clinical response in the few published studies. Published overall response rates range from 32% (Assi R 2018) to 76% (Wang Y 2015, Shin HJ 2008), where the latter study uses a definition of partial response of at least a 25% improvement in 2 or more quantifiable symptoms and laboratory markers.

There are no validated treatment protocols for HLH in adults. Treatment regimens have been informed by experience in pediatric HLH and by retrospective case series and case reports. One single prospective

study has been conducted in adults, investigating the efficacy of DEP regimen in patients with refractory HLH (Wang Y 2015).

In general, adult patients with HLH receive therapy directed at the underlying etiology such as infection or malignancy (Rivière S 2014, Schram AM 2016). Many also receive therapy more specifically directed at HLH, for instance glucocorticoids and/or etoposide with or without cyclosporine (La Rosée P 2015, Rivière S 2014, Schram AM 2016). These treatments are extrapolated from experience in pediatric HLH (Henter JI(b) 2002). In certain cases, intravenous immunoglobulin (IVIG) and other therapies have been used (Larroche C 2000, Li J 2014, Parikh SA 2014, Rivière S 2014, Schram AM 2016, Takahashi N 2001). Although the inclusion of etoposide in the treatment of adult-onset HLH has not been shown to confer a statistically significant survival benefit, there is a trend toward improved survival (Arca M 2015, Schram AM 2016). Many physicians treating adults with HLH are hesitant to use etoposide, a chemotherapeutic agent, unless the HLH is related to malignancy. This is due primarily to concerns regarding toxicity in very sick patients, often with multi-system organ failure (elevated creatinine and bilirubin), as well as to more long-term risks, such as secondary leukemia. The relative benefits of the other therapies in the adult population have not been conclusively demonstrated. Because of the high mortality rates associated with adult-onset HLH, stem cell transplantation is often considered. This can be curative but carries its own unique set of risks and cannot be contemplated unless the HLH is controlled. The overall median survival for patients who undergo stem cell transplantation has been reported as 21.5 months (Schram AM 2016) and may be better than this (Nikiforow S 2015).

Emapalumab (previously referred to as NI-0501, trade name Gamifant®) is an anti-interferon gamma (IFNγ) monoclonal antibody that binds to and neutralizes IFNγ. It is approved by FDA for the treatment of patients with primary HLH who have refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.

The central role of IFNγ in the pathogenesis of secondary HLH (sHLH) is supported by pre-clinical data: two animal models of sHLH have been investigated to elucidate the pathogenetic role of IFNγ, a murine model that mimics an infection-driven HLH through repeated administrations of CpG and activation of TLR9 (Strippoli R 2012), and a model of IL-6 transgenic mice expressing high levels of IL-6 that mimics the condition of patients with sJIA, the rheumatic disease most frequently associated with secondary forms of HLH (Prencipe G 2018). In both models, when IFNγ was neutralized by the administration of an anti-IFNγ antibody, clinical and laboratory features of the disease were reverted (Strippoli R 2012), and survival markedly improved (Prencipe G 2018).

Consistent with a central role for IFNγ in human HLH, elevated levels of this cytokine are found in paediatric as well as adult patients with HLH (Akashi K 1994, Ohga S 1993, Maruoka H 2014, Henter JI(a) 1991).

Further evidence has been gathered in an observational study conducted in patients with secondary forms of HLH, either consequent to infections, or of unknown origin or with MAS occurring in the context of sJIA. In 14 patients with secondary HLH (in 7 of whom an underlying infection was identifiable), serum samples were analyzed during active full-blown disease and during disease remission. Levels of IFNγ and CXCL9 and CXCL10 (two IFNγ-induced chemokines) were markedly higher in the active phase compared to disease remission. The levels of IFNγ and chemokines (in particular CXCL9) correlated significantly with parameters of disease severity, such as neutrophil and platelet counts, ferritin and ALT, further supporting the pathogenic role of IFNγ in sHLH (Buatois V 2017).

Similar findings have been shown in patients with MAS occurring in patients with sJIA. Serum concentrations of IFNγ, IFNγ-inducible chemokines (CXCL9, CXCL10, CXCL11) and IL-6 were measured in 54 patients with sJIA, of whom 20 had MAS. The levels of IL-6 were comparable in patients with full-blown

MAS and those with active sJIA but without MAS at the time of sampling. On the contrary, circulating IFNγ and chemokine levels were significantly higher in MAS, particularly for CXCL9. Levels of IFNγ also correlated with laboratory parameters of disease severity, with the exception of LDH for which statistical significance was not achieved (Bracaglia C 2017).

Observational studies have been initiated by the Sponsor (in malignancy-associated HLH in study NI-0501-07, in adult HLH in study NI-0501-08; data on file) to characterize the levels of IFNγ and the IFNγ-inducible chemokines CXCL9 and CXCL10 in adult HLH, using in-house validated assays. The majority of the patients had elevated levels of IFNγ, CXCL9 and CXCL10, confirming the presence of an IFNγ-signature in adult HLH. The range of IFNγ, CXCL9 and CXCL10 levels at disease onset in the adult HLH patient sera was similar to the range observed in the paediatric HLH population (NI-0501-04 study and CU patients).

Given the central role of IFNγ in mediating the immune dysregulation and severe inflammation in all forms of HLH, it is hypothesized that neutralization of IFNγ will improve outcomes in patients with adult-onset HLH. The anti-IFNγ antibody emapalumab has been developed for this purpose, and has demonstrated efficacy in primary HLH.

The need for such a therapy in adult-onset HLH is clear based on the poor early outcomes obtained with existing treatment options and the fact that these must often be dose-reduced or withheld due to kidney and/or liver impairment.

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-interferon gamma (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 from 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 emapalumab program.

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 pharmacologic 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 IFNy 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 in these studies was therefore determined to be the highest dose-level tested of 150 mg/kg.

More details are available in the Investigator`s Brochure. Please refer to the most recent version of the Investigator`s Brochure.

1.2.3 Clinical Data

1.2.3.1 Phase 1 experience

A randomized, double-blinded, placebo-controlled, single ascending dose Phase 1 study (protocol NI-0501-03) has been performed in 20 healthy adult subjects, of which 14 received emapalumab IV at doses up to 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 infusion of emapalumab was well tolerated and the 8-week monitoring after drug infusion, then extended up to week 44, did not reveal any serious or unexpected off–target safety or immunogenicity concerns. A *Herpes Zoster* infection was reported as a serious adverse reaction in the highest dose group (3 mg/kg), and resolved.

More details are available in the Investigator`s Brochure. Please refer to the most recent version of the Investigator`s Brochure.

1.2.3.2 Phase 2/3 experience

An open-label, single arm, international, multicenter Phase 2/3 study is ongoing to evaluate the efficacy and safety of emapalumab in pediatric patients with primary HLH (pHLH) (protocol NI-0501-04). The protocol enrols both treatment-naïve and second-line patients.

At the BLA/MAA cut-off date of 20 July 2017, 34 patients (16 M, 18 F) have been treated, of whom 7 patients have received emapalumab as front-line therapy.

The patients' median age was 12 months (range: 1 month-13 years), and 27 patients (79%) had a documented mutation in known HLH causative genes.

The primary efficacy endpoint of the study was met. Overall Response Rate (ORR) 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).

Response occurred early during treatment and was generally sustained.

The majority of patients proceeded to HSCT (65% of all treated patients and 70% of second-line patients), with a survival benefit that persisted after HSCT. Three patients completed emapalumab treatment achieving and maintaining control of HLH disease, without proceeding to HSCT upon decision of the treating physician in the patient's best interest.

Overall, 70.6% of all treated patients and 74.1% of second-line 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 and 89.5% of second-line 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 have been well tolerated.

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

At the BLA/MAA cut-off date, ten patients had died; none of the deaths was assessed to be related to emapalumab by Investigator, Sponsor and iDMC.

Study NI-0501-04 completed enrolment on the 25th Jan 2019: a total of 45 patients have been recruited.

In addition to the patients enrolled in the NI-0501-04 study, 26 patients with HLH have received emapalumab treatment in compassionate use (CU). Approximately 450 infusions up to 10 mg/kg have been administered and were well tolerated. No SAEs related to emapalumab administration have been reported.

An open-label, single arm, multicenter Phase 2 study is ongoing to evaluate the efficacy and safety of emapalumab in sJIA patients developing active MAS/sHLH. The dosing regimen foresees emapalumab administration at the initial dose of 6 mg/kg and continuation at the dose of 3 mg/kg every 3 days (until SD15) and twice-a-week afterwards.

As of 14 November 2018, 6 patients with MAS have been enrolled and treated: in all of them, a complete response (as per protocol defined criteria) has been achieved, and all patients are continuing in study NI-0501-05 for long-term follow-up. The tolerability and safety profile of emapalumab appears to be favorable, with all infusions completed. Three SAEs have been reported in two patients, of which one (CMV reactivation, of moderate intensity) was assessed to be related to emapalumab by the Investigator.

A safety long-term follow-up study is ongoing (protocol NI-0501-05) to enable the long-term surveillance of patients who have received at least one infusion of emapalumab. The protocol includes a follow-up period of one year after HSCT or after last emapalumab infusion, if no HSCT is performed.

No safety concern has emerged from the long-term safety surveillance.

For more details on the clinical experience, please refer to the most recent version of the Investigator`s Brochure.

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 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 significant drug-drug interactions has been reported to date.

For more details, please refer to the most recent version of the Investigator`s Brochure.

2 OBJECTIVES

- Primary efficacy objective: to assess the efficacy of emapalumab in adult patients with HLH, as measured by Overall Response Rate.
- Secondary efficacy objectives:
  - to assess the efficacy of emapalumab as measured by overall survival, time to response, best response on treatment, duration of response, and other efficacy parameters.
  - To evaluate the safety and tolerability of emapalumab.
  - To determine the pharmacokinetic (PK) profile of emapalumab.
  - To determine the pharmacodynamic (PD) profile of emapalumab.

3 STUDY DESIGN

3.1 OVERALL DESIGN

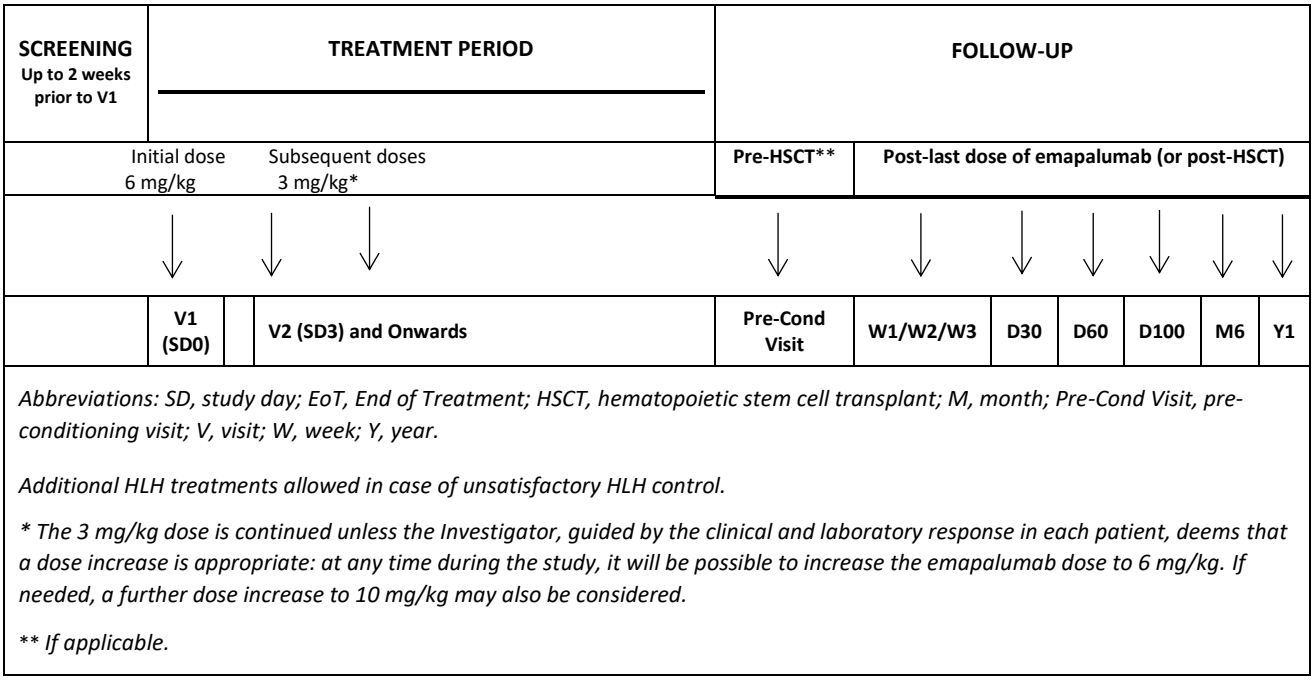
Study NI-0501-10 is an open-label, single arm, multicenter, Phase 2/3 interventional study.

The study enrols adult patients with hemophagocytic lymphohistiocytosis (HLH), specifically newly diagnosed patients with malignancy-associated HLH (M-HLH), and newly diagnosed or previously treated patients with non-malignancy-associated HLH.

The study includes an initial phase enrolling 10 patients. If no untoward significant safety signal attributable to emapalumab treatment (as judged by an iDMC) is identified, enrolment will be broadened; subsequently, the iDMC will meet (at a minimum) every time data for an additional 10 patients in total are available, to confirm that the safety profile of emapalumab remains favorable and the benefit/risk of treating remains positive. The details of the iDMC are provided in the iDMC Charter.

The patient's participation in the study comprises three parts: screening, treatment period, and follow-up, as shown in Figure 1.

Figure 1: NI-0501-10 Study Design



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

Additional HLH treatments allowed in case of unsatisfactory HLH control.

** The 3 mg/kg dose is continued unless the Investigator, guided by the clinical and laboratory response in each patient, deems that a dose increase is appropriate: at any time during the study, it will be possible to increase the emapalumab dose to 6 mg/kg. If needed, a further dose increase to 10 mg/kg may also be considered.*

*** If applicable.*

3.2 SCREENING PERIOD

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

After giving written informed consent, patients who are willing to participate in the study will undergo screening assessments within 2 weeks prior to the baseline visit (SD0), as detailed in the Schedule of Assessments (Table 1).

Patients must fulfill all the entry criteria for participation in the study and the results must be available prior to the baseline visit. However, if a patient's medical condition warrants rapid treatment initiation, availability of the results for infection screening is not required prior to initiation of emapalumab, provided that there are no clinical findings suggestive of any of the infections which represent exclusion criteria. However, samples for infection screening need to be collected for analysis prior to first administration of emapalumab according to the protocol requirements.

In rare cases of unexpected delay due to logistical or technical reasons, it may be necessary to extend the screening period by a few days. Extending the screening period beyond 2 weeks must be prospectively approved by the Sponsor and should be in exceptional circumstances only; careful scheduling should remain a priority.

Patients may be rescreened if there is a substantial change in the patient's condition (e.g., a prohibited medication was stopped) and if recruitment for the study is still ongoing; all inclusion criteria and none of the exclusion criteria have to be met at the re-screening.

Patients may be rescreened if the protocol is amended and, as a result of this, the patients satisfy the amended criteria, and if recruitment for the study is still ongoing.

A patient eligibility checklist that documents the investigator's assessment of each screened patient with regard to the study's inclusion and exclusion criteria is to be completed by the Investigator. A screening

log must be maintained by the Investigator. In addition, an Eligibility Review Form (please see Appendix 1) must be completed and shared with the Sponsor upon identification and consent of any potentially eligible patient. The Sponsor will review the form and be available to answer any potential questions.

3.3 TREATMENT PERIOD

It is not expected that treatment duration will be the same across the study population.

Treatment shall continue until a clinically satisfactory response is achieved. Shall the duration of treatment exceed 12 weeks, an assessment of a favorable benefit/risk profile must be provided and confirmed by the iDMC.

If HSCT is planned, treatment can be administered until HSCT.

In all cases, treatment can be discontinued upon achievement of complete clinical response, if at least two infusions of emapalumab at the dose of 3 mg/kg have been administered.

Patients will undergo a Week 4 Assessment Visit 3 days after the last emapalumab infusion administered in Week 4.

Treatment may be shorter, and in such instance an End of Treatment (EoT) visit shall be performed 3 days after the last administration of emapalumab.

Whenever a patient receives treatment beyond Week 4, both a Week 4 Assessment Visit and an End of Treatment (EoT) visit shall be performed.

If HLH recurs or reactivates during the off-drug follow-up period, treatment with emapalumab can be reinstated, upon discussion with the Sponsor. While receiving emapalumab, patients will undergo the same assessments planned during the initial treatment phase, as described in the Schedule of Assessments – Screening and Treatment Period (Table 1) for the "Week x" visits. They will enter the follow-up period after completion of the re-treatment.

3.4 FOLLOW-UP PERIOD

After treatment discontinuation (for any reason), patients will continue in the study for long-term follow-up until 1 year after last emapalumab administration (or after HSCT, if performed).

3.5 STUDY END

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

4 TARGET POPULATION

Male and female patients aged 18 and older at the time of diagnosis, who meet HLH-2004 clinical criteria for the diagnosis of HLH (with or without malignancy) and who have no primary HLH are eligible. Patients with M-HLH must be newly diagnosed (i.e. must have received no previous HLH treatments, with the exception of initial glucocorticoids), while patients with non-malignancy-associated or idiopathic HLH may have previously received HLH therapies (therefore they can be either treatment naïve or treatment experienced).

4.1 ELIGIBILITY CRITERIA

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

4.1.1 Inclusion Criteria

1. Male and female patients of age 18 and older at the time of HLH diagnosis
2. Fulfilment of HLH-2004 clinical criteria, i.e., five of the eight criteria below:
    a. Fever
    b. Splenomegaly
    c. Cytopenias affecting 2 of 3 lineages in the peripheral blood (hemoglobin <90 g/L; platelets <100 x 10^9/L; neutrophils <1 x 10^9/L)
    d. Hypertriglyceridemia (fasting triglycerides ≥3 mmol/L or ≥265 mg/dL) and/or hypofibrinogenemia (fibrinogen ≤1.5 g/L)
    e. Hemophagocytosis in bone marrow, spleen or lymph nodes
    f. Low or absent natural killer (NK)-cell activity
    g. Ferritin ≥500 µg/L
    h. Soluble CD25 (sCD25, i.e., soluble IL-2 receptor) ≥2400 U/mL *(or equivalent, in case the local lab uses different units)*
3. Patients diagnosed with M-HLH must be treatment naïve; patients diagnosed with HLH driven by any other etiology or idiopathic can be either treatment naïve or treatment experienced
4. Patients with non-malignancy-associated or idiopathic HLH who have already received conventional therapy for HLH must have failed prior treatment as per the treating physician`s judgement. At the time of enrolment, eligible treatment experienced patients may or may not be receiving conventional therapy
5. JAK inhibitors, if administered, must be discontinued before emapalumab initiation
6. Informed consent signed by the patient or by the patient's legally authorized representative(s) (as required by local law)
7. Willing to use highly effective methods of contraception from study drug initiation to 6 months after the last dose of study drug, if female and of childbearing potential.

4.1.2 Exclusion Criteria

1. Primary HLH (documented by the presence of known causative genetic mutations or by the presence of family history)
2. Current (within 60 days from SD0) or scheduled administration of therapies known to trigger the cytokine release syndrome (e.g. chimeric antigen receptor (CAR)-modified T cells, bispecific T cell-engaging antibodies)
3. Current (within 60 days from SD0) or scheduled administration of PD-1/PD-L1/ CTLA-4 inhibitors
4. Life-expectancy associated with the underlying disease (triggering HLH) < 3 months
5. Ongoing participation in an investigational trial, or administration of any investigational treatment within 30 days
6. History of hypersensitivity or allergy to any components of emapalumab
7. Active mycobacteria*, Histoplasma capsulatum*, or *Leishmania* infections

8. Evidence of latent tuberculosis
9. Infection with HIV (HIV ELISA or PCR positive), hepatitis B (HBsAg positive), Hepatitis C (anti-HCV positive) unless the viral load is negative
10. Concomitant diseases that in the opinion of the Investigator may significantly affect the likelihood of a response to treatment and/or the assessment of emapalumab safety and/or efficacy
11. Receipt of a bacille Calmette-Guerin (BCG) vaccine within 12 weeks prior to Screening
12. Receipt of a live or attenuated live (other than BCG) vaccine within 6 weeks prior to Screening
13. Pregnancy or lactation (female patients).

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. Concentrated product is filled in single-use glass vials. A dilution is required 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.

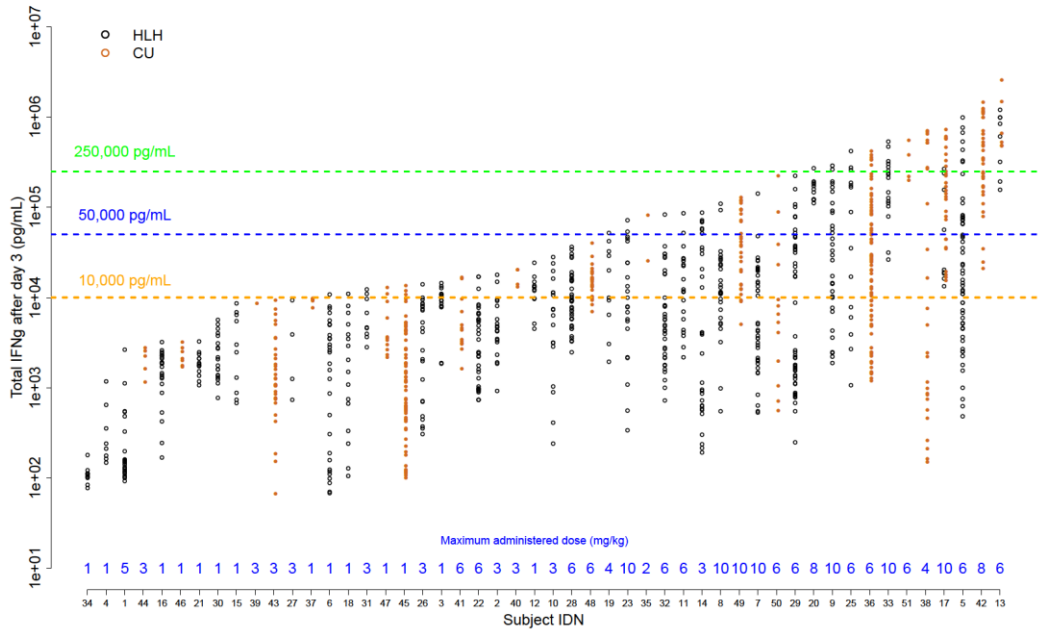
5.2 RATIONALE FOR DOSING SCHEMA

PK-PD-efficacy data from studies NI-0501-04 and NI-0501-05 in primary HLH patients and from the CU experience in both primary and secondary HLH patients receiving emapalumab have previously been analyzed in order to explore the structural and quantitative relationships between emapalumab, total IFNγ (free + complex with emapalumab), and CXCL9, a chemokine specifically induced by IFNγ. The results revealed that:

- the PK and PD of emapalumab were significantly influenced by the level of IFNγ, which varied significantly between patients and within patients as a function of time, as shown in Figure 2.

- CXCL9 appeared to be the biomarker of choice of the biological and pharmacological effects of IFNγ (key player in the disease) and emapalumab, and was an indicator of the probability of overall clinical response in HLH patients treated with emapalumab.
-

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



Primary HLH and adult-onset HLH share numerous clinical and pathophysiological features, including the presence of elevated serum levels of IFNγ and IFNγ-inducible chemokines (Marukoa et al., 2013; data on file).

Secondary forms of HLH in adults are associated with significant mortality rates and, particularly in the setting of M-HLH, overall survivals that dismal.

To achieve rapid IFNγ neutralization, an initial dose of 6 mg/kg emapalumab will be administered. To maintain further IFNγ neutralization, emapalumab treatment will be continued at the dose of 3 mg/kg, every 3 days until SD15, and then twice-a-week until a clinically satisfactory response is achieved. A similar dosing regimen is currently under investigation in the NI-0501-06 study (i.e. emapalumab in sJIA patients developing MAS).

Simulations using the most current emapalumab model for this dosing scheme are shown in Figure 3. Simulations representing a dose increase to 6 mg/kg from SD6 onwards and a dose increase to 10 mg/kg from SD9 onwards (i.e. worst-case scenario) are shown in Figures 4 and 5 respectively.

In these Figures, the concentration of emapalumab (graphs on the left) and CXCL9 (graphs on the right) are represented at three different production rates of IFNγ (represented by total IFNγ levels), namely a "relatively low" production of 10,000 pg/mL (orange line), a "medium" production of 50,000 pg/mL (blue line), and a "high" production of 250,000 pg/mL (green line). As reference on these graphs: the grey area on the left graph indicates the mean of the individual three highest peak and trough concentrations observed in Studies NI-0501-04 and NI-0501-05 and in CU patients (cut-off date 20 July 2017). The black line (mean) and grey shadowed area (90% CI) on the right graph indicate CXCL9 levels at week 2 and end of treatment that appear to be associated with the probability of clinical response at end of treatment in

the HLH paediatric population as indicated by exploratory Receiver Operating Characteristic (ROC) analyses.

Figure 3: Emapalumab and CXCL9 Concentrations at the Initial Dose of 6 mg/kg Followed by 3 mg/kg/3d and then 3 mg/kg Maintained Twice a Week During the Treatment Course

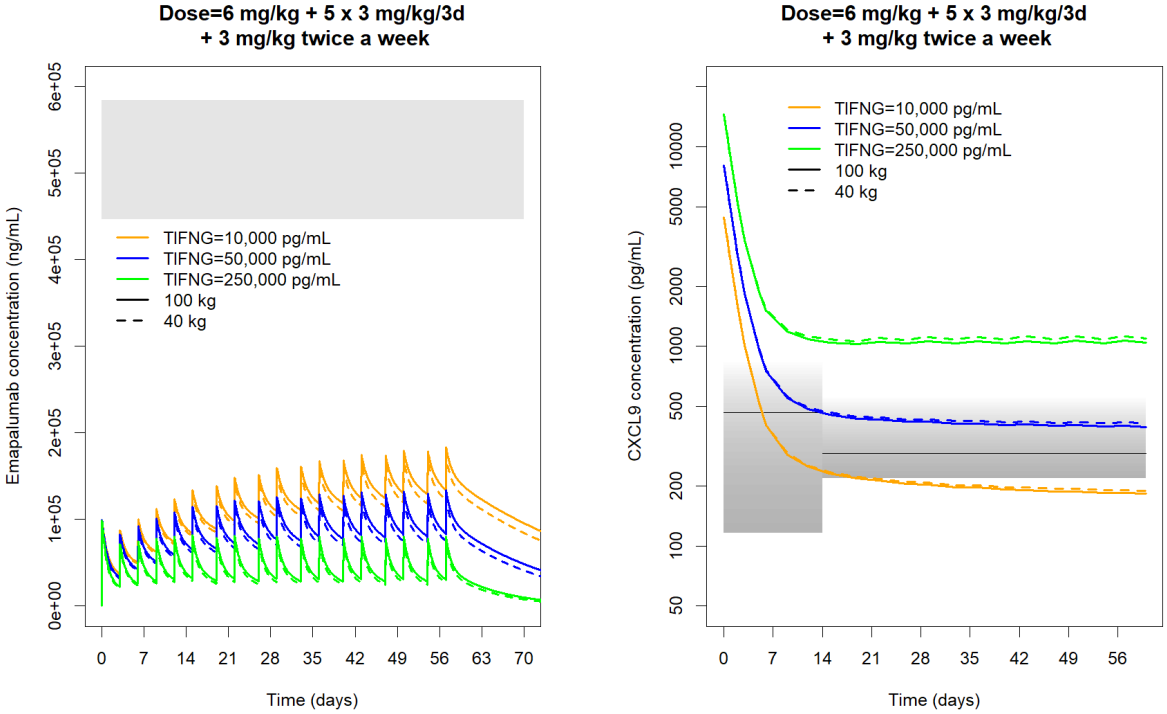


Figure 4: Emapalumab and CXCL9 Concentrations at the Initial Dose of 6 mg/kg Reduced to 3 mg/kg on Day 3 Followed by 6 mg/kg/3d and then 6 mg/kg Maintained Twice a Week During the Treatment Course

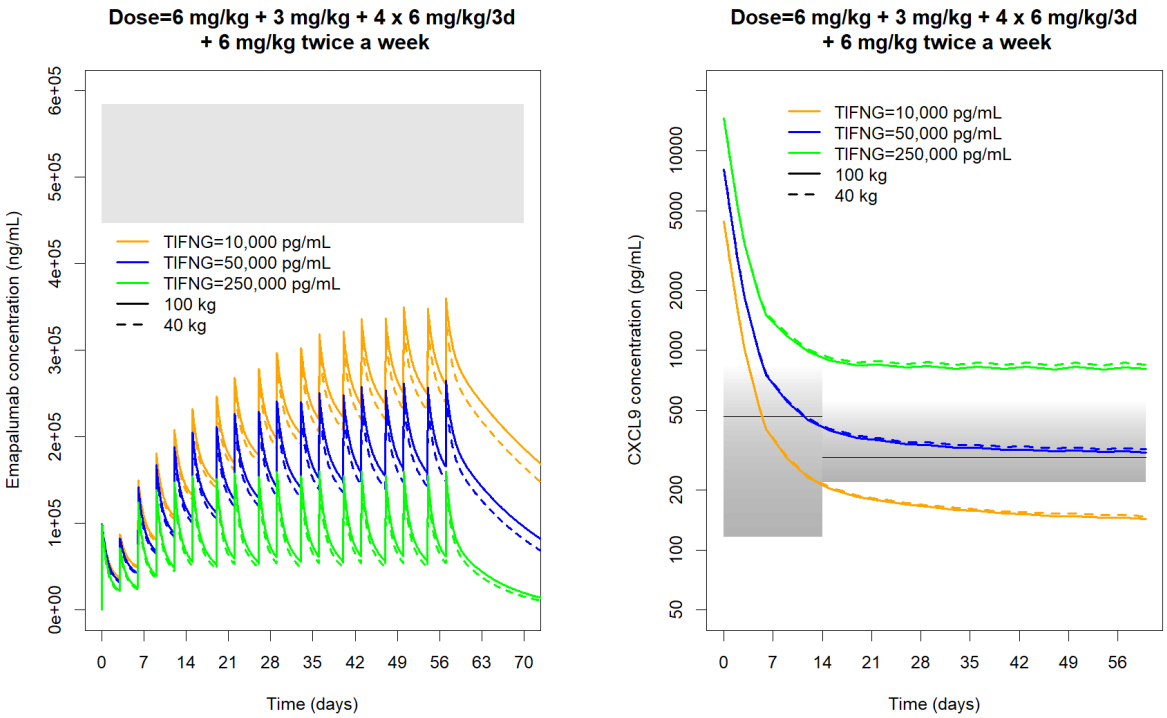
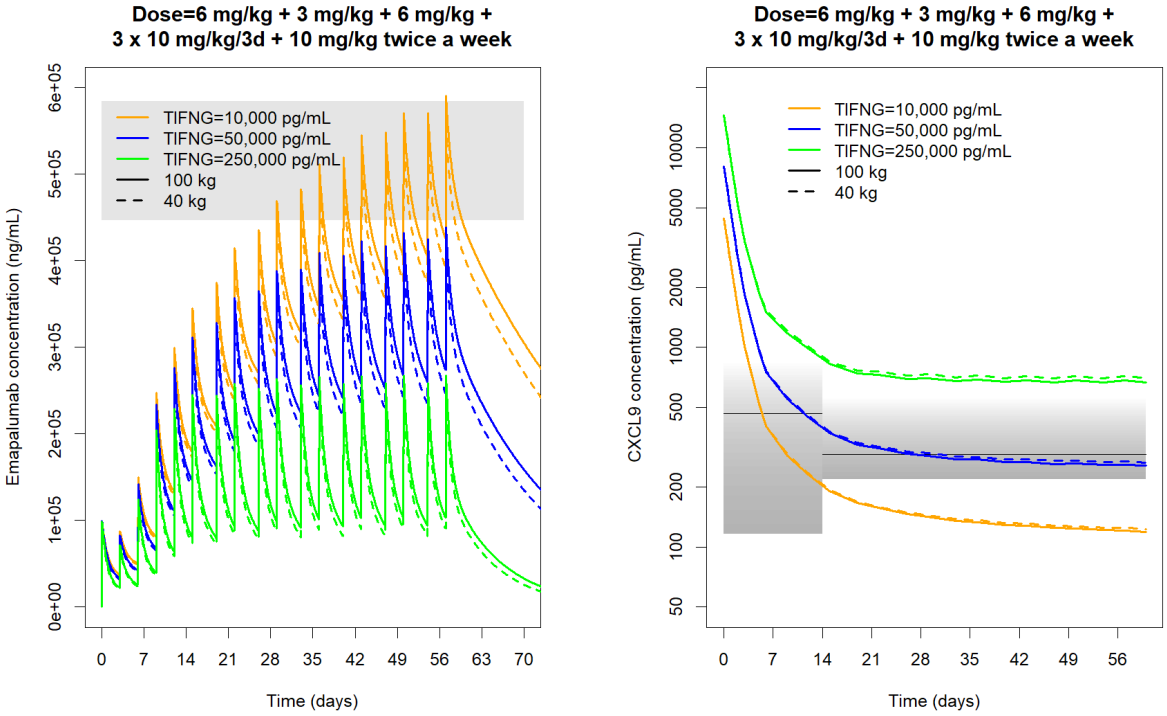


Figure 5: Emapalumab and CXCL9 Concentrations at the Initial Dose of 6 mg/kg Followed by 3 mg/kg on Day 3, 6 mg/kg on Day 6, 10 mg/kg/3d and then 10 mg/kg Maintained Twice a Week During the Treatment Course



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

5.3 DOSING SCHEMA

If not already hospitalized, patients will be in the treating unit from the day before the first administration of emapalumab.

Emapalumab will be administered by intravenous (IV) infusion over a period of 1 to 2 hours depending on the volume to be infused, at an initial dose of 6 mg/kg.

Emapalumab treatment will be continued at the dose of 3 mg/kg, every 3 days until SD15, and then twice-a-week.

If the treating physician deems appropriate, the dose of emapalumab may be increased (back to 6 mg/kg, and up to 10 mg/kg), guided by clinical and laboratory response. During the initial phase of the study, PK/PD data may also be considered.

Treatment can be discontinued upon achievement of complete clinical response; however, at least two infusions of emapalumab at the dose of 3 mg/kg have to be administered.

Patients will be discharged whenever deemed clinically appropriate by the Investigator.

Table 3: Clinical and Laboratory Criteria to Guide Dose Increases

On Visit / Study Day (SD)	Emapalumab Dose	
On Visit 1/SD0	6 mg/kg	
On Visit 2/SD3	3 mg/kg	
On Any Visit, from Visit 3/SD6 onwards	Increase to 6 mg/kg	Upon an overall assessment by the Investigator that improvement in clinical conditions is unsatisfactory and presence of at least 1 of the following: *Fever* → persistence or reoccurrence *Platelet counts** → lack of normalization[1] or Worsening *ANC** → lack of normalization[2] or Worsening *Ferritin* → less than 30% decrease or Worsening *Splenomegaly* → worsening (at clinical exam or US examination) *Coagulopathy* (either D-dimer or fibrinogen) → lack of normalization[3] or Worsening
On Any Visit, from Visit 4 onwards	Increase up to 10 mg/kg	Upon assessment by the Investigator that a further increase of emapalumab dose may provide additional benefit and presence of 1 of the criteria listed above

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

*To be considered carefully if not HLH-related, e.g. in patients receiving chemotherapy to treat the underlying disease

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

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

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

5.4 INVESTIGATIONAL MEDICINAL PRODUCT HANDLING

5.4.1 Packaging and Labelling

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 25mg/ml. Labelling and packaging will be prepared to meet local regulatory requirements. The Investigational Medicinal Product (IMP) Manual provides further details.

5.4.2 Investigational Medicinal Product Supply

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

5.4.3 Investigational Medicinal Product Receipt and Storage

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

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

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

Emapalumab vials must be visually inspected before preparing the infusion, as described in the IMP Manual.

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

5.4.4.1 Preparation

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

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

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

5.4.4.2 Administration

The patient should receive the designated volume of the infusion material through an infusion pump over 1 to 2 hours depending on the volume to infuse. A 0.2 µm filter must be 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 electronic Case Report Form (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.

5.4.4.3 Accountability

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

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

Drug accountability records shall include:

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

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

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

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

5.4.4.4 Destruction, Return, and Disposal

Periodically during the study and at the conclusion of participation of the study by the site, the clinical research associate (CRA) will monitor and collect the Drug Accountability Forms, before making arrangements for study drug return or authorizing certified destruction by the study site.

6 PROTOCOL TREATMENT PLAN

Patients will receive emapalumab as outlined in section 5. Patients are permitted to have a treatment delayed for up to 1 day for a major life event or weather-related issues (e.g., serious illness in a family member, infusion center closed due to snow) without this being considered a protocol violation. Justification for the delay should be provided to the Sponsor.

6.1 CONCOMITANT THERAPY

6.1.1 Malignancy-related treatments

Patients with malignancy-associated HLH will undergo concomitant treatment directed at the underlying malignancy. In general, the malignancies are expected to be hematologic malignancies such as lymphomas and leukemias. Any standard chemotherapy-based therapy, such as CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone), will be permitted, except for the treatments listed as exclusion criteria.

6.1.2 Dexamethasone

All patients are required to receive glucocorticoids starting no later than SD-1:

- Therapy with dexamethasone at a dose of 10 mg/m^2 daily will be initiated in any patient not receiving glucocorticoids at the time of emapalumab start.
- If a patient is already receiving glucocorticoids, he/she will continue at their current dose, as long as it corresponds to at least 5 mg/m^2 daily dexamethasone.
- Lower doses at study entry are allowed in the case of documented intolerance to glucocorticoids (e.g., psychosis).
- Glucocorticoids tapering may be initiated as soon as the patient's conditions allow, according to the Investigator's assessment. The tapering scheme can be selected by the Investigator.
- In the event of disease worsening after glucocorticoids tapering, a higher dose can be re-introduced and maintained until a satisfactory response is achieved according to the Investigator.

For patients with M-HLH, glucocorticoids are often administered with malignancy-directed therapy; dexamethasone can be used at the discretion of the Investigator.

6.1.3 Infection prophylaxis

Unless a patient has been previously vaccinated, prophylaxis against *Herpes Zoster* virus infection must be in place on study day minus 1 (or, at the latest, before initiation of emapalumab treatment) and must be maintained for 2 half-lives (approximately 44 days) after the last administration of emapalumab.

Patients will receive any additional required prophylactic antimicrobial treatment according to local practice.

6.1.4 Calcineurin inhibitors

Calcineurin inhibitors can be continued, if administered at screening. Calcineurin inhibitors can be withdrawn at any time, upon the judgment of the Investigator.

6.1.5 Intrathecal Therapy

For patients receiving intrathecal (IT) therapy (e.g., methotrexate and glucocorticoids) at the time of emapalumab treatment initiation, this therapy will be continued until clinically indicated.

The introduction of IT therapy is allowed should CNS signs and symptoms occur during the study, as clinically indicated.

6.1.6 Other Concomitant Therapies

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

Granulocyte-colony-stimulating factor (G-CSF) is permitted in case of prolonged neutropenia or if required for treatment of malignancy-associated HLH as part of a standard protocol.

As long as emapalumab is being administered, concomitant use of other biologic drugs shall not occur, except for rituximab in the setting of documented EBV infection. The use of any biologic drugs other than rituximab shall be prospectively discussed with the Sponsor.

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

Guidance on concomitant medications recording will be provided in a separate document.

6.1.7 Contraception guidance

Females of childbearing potential require the use of highly effective contraceptive measures (failure rate of less than 1% per year) from study drug initiation to 6 months after last dose of emapalumab.

Highly effective contraceptive measures include:

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

6.2 PROHIBITED THERAPIES

6.2.1 Advanced therapies and JAK inhibitors

Administration of advanced therapies known to trigger the cytokine release syndrome (e.g., chimeric antigen receptor (CAR)-modified T cells, bispecific T cell-engaging antibodies, PD-1 inhibitors) and the administration of JAK inhibitors are prohibited.

6.2.2 Vaccines

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

6.3 ADDITIONAL HLH TREATMENTS

The administration of additional HLH treatments (e.g., etoposide, T-cell depleting agents) will be allowed in case of documented unsatisfactory HLH control, provided that at least 3 doses of emapalumab have been administered.

Unsatisfactory HLH control is defined as follows:

- patients who present a clinically relevant worsening
- patients who have not achieved or maintained a disease control and general conditions that would allow to proceed to transplant (if applicable) and/or to receive required concomitant treatments for the underlying disease.

If an additional HLH treatment is needed, etoposide is the drug of choice, unless there is evidence indicating that an alternative agent should be selected. In this circumstance, the Investigator has to fully document the rationale for an alternative choice in the patient's medical file and in the eCRF.

6.4 EMERGENCY TREATMENT

Emapalumab will be administered to patients under close medical supervision in a setting with access to emergency equipment and staff who are trained to monitor and respond to medical emergencies.

7 ENDPOINTS

7.1 EFFICACY ENDPOINTS

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

Given the absence of validated endpoints, the experience gathered in the registrational trial of emapalumab in pHLH, input from recognized experts in the field of adult HLH and data in the scientific literature have been used to compile the response criteria.

Week 4 has been chosen as the time point to evaluate the primary endpoint taking into consideration the heterogeneity of the enrolled population and the clinical course of the different medical conditions triggering HLH, and acknowledging the absence of experience with emapalumab in these diseases: while an initial response to emapalumab is expected early during treatment, based on the mechanism of action of the molecule and the experience accumulated to date in pHLH and MAS in sJIA, the data collected in the initial phase of this study will provide support to the hypothesis. The secondary endpoints (i.e. best response on treatment, time to response) will aid in the overall interpretation of the potential efficacy of emapalumab in this study.

Primary efficacy endpoint

- Overall Response, i.e. achievement of either a Complete or Partial Response at Week 4 (or EoT if earlier)

Secondary efficacy endpoints:

- Best response on treatment
- Overall Response at EoT
- Overall survival
- Time to complete or partial response
- Duration of response
- HLH Relapse.

Treatment response may be analysed using other sets of clinical criteria (to be described in the Statistical Analysis Plan), if supported by evolving medical knowledge and/or scientific literature.

Table 4: Definition of Response

Overall Response	
Complete Response	Complete Response is adjudicated if: - No fever = body temperature <37.5°C - Normal spleen size - No cytopenia* = Absolute Neutrophil Counts $\geq 1.0 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L [absence of G-CSF and transfusion support must be documented for at least 4 days to report no cytopenia] - No hyperferritinemia = serum level is <2000 μg/L - No evidence of coagulopathy, i.e., normal D-Dimer and/or normal (>150 mg/dL) fibrinogen levels - No neurological and CSF abnormalities attributed to HLH - No sustained worsening of sCD25 (as indicated by at least two consecutive measurements that are > 2-fold higher than baseline)
Partial Response	Partial Response is adjudicated if: - Improvement (>50% change from baseline or normalization) of at least 3 HLH clinical and laboratory abnormalities (including CNS abnormalities)

*Not to be assessed if not HLH-related, such as cytopenia induced by drugs administered to treat the underlying disease (e.g. chemotherapy)

7.2 SAFETY ENDPOINTS

Safety and tolerability of emapalumab will be assessed as follows:

- Incidence, severity, causality and outcomes of AEs (serious and non-serious)
- Clinically significant changes in blood tests, physical examinations, vital signs, ECGs.

7.3 PHARMACOKINETIC ENDPOINTS

The serum concentration of emapalumab will be measured as a function of time to determine the emapalumab PK profile in this patient population and to confirm adequacy of the proposed dosing regimen.

All PK data will be summarised using appropriate graphical and tabular presentations and the following PK parameters will be reported: C_{max} (peak serum concentration), C_{trough} (concentration just before administration), $C_{meantau}$ (mean concentration over a dosing interval) and AUC_{tau} (area under curve of a dosing interval).

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

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

7.4 PHARMACODYNAMIC ENDPOINTS

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

- Levels of circulating total IFNγ (free + bound)

- Markers of IFNγ neutralization, i.e. CXCL9
- Other relevant markers, including but not limited to sCD25 and IL-6
- Incidence of anti-drug antibodies (ADAs) against emapalumab.

Population PK/PD analysis using non-linear mixed effects modelling will be undertaken.

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

Individual and mean PD parameters will be tabulated.

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

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

8 OUTLINE OF STUDY PROCEDURES

If not already hospitalized, the patient will be in the treating unit from the day before the first administration of emapalumab (SD-1).

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

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

The Informed Consent Form must be signed by the patient or his/her legally authorized representative prior to any study-related procedures.

During treatment with emapalumab, visits for infusion will occur on SD0 (i.e. enrolment time point), SD3, every 3 days until SD15, and twice-a-week thereafter (not more than 4 days apart). A Week 4 Assessment Visit shall be performed 3±1 days after the last emapalumab infusion administered in Week 4. If emapalumab treatment is shortened, an EoT Visit has to be performed 3±1 days after the last emapalumab infusion. If emapalumab treatment continues beyond the Week 4 Assessment Visit, an additional EoT Visit has to be performed 3±1 days after the last emapalumab infusion.

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

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

If HSCT is not performed, the above schedule describes the time points after the last emapalumab infusion, rather than after HSCT.

During treatment, emapalumab and biomarker concentrations may be measured in matrices other than blood, such as CSF or BAL, if samples obtained in procedures which are performed for

diagnostic/therapeutic purposes can also be available for these exploratory investigations, and if clinically indicated.

8.1 SCREENING

Patients will be screened for eligibility prior to enrollment into the study. A screening log will be maintained by the Investigator with specification of reasons for non-eligibility.

Screening evaluations should be completed within 2 weeks prior to the first administration of study drug (Visit 1/SD0).

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

Patient information:	▪ Informed consent ▪ Demographics (including race and ethnicity where allowed) ▪ Medical history ▪ Medications at Screening ▪ Any HLH therapy previously received ▪ Date of HLH diagnosis and HLH history ▪ Molecular diagnosis of HLH, if available ▪ Perforin expression and other functional tests performed for the diagnosis of HLH, if available ▪ Review of Inclusion/Exclusion Criteria ▪ For treatment experienced patients with non M-HLH, recording of reasons to determine failure of conventional therapy, as per Investigator`s assessment ▪ For patients diagnosed with idiopathic HLH, recording of outcome of investigations performed to exclude an underlying malignancy
Clinical Assessment:	▪ Vital signs including body temperature, blood pressure, heart rate, respiratory rate ▪ Height and body weight ▪ Eastern Cooperative Oncology Group (ECOG) performance status ▪ Complete physical examination
Procedure:	▪ Single, standard 12-lead ECG
Search for infections[i]*:*	▪ HIV, hepatitis B (including surface antigen), and hepatitis C testing (the latter with reflex to PCR if serologies are positive) ▪ *Tuberculosis mycobacteria* via IGRA/PPD test and polymerase chain reaction (PCR). In a patient having received BCG vaccination, a PPD test must be performed and combined with IFNγ-release assay if the PPD result is ≥5 mm. In addition, search for Tuberculosis via PCR in any relevant specimen should be performed to have a baseline, as

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

this test will be used during the course of the study to perform regular TB monitoring.

- Adenovirus, EBV, CMV (viral load)
- Atypical mycobacteria, *Histoplasma Capsulatum* and *Leishmania*[ii], as appropriate. The presence of *Leishmania* can also be ascertained by direct bone marrow observation. A first screening for Histoplasma Capsulatum may be performed using galactomannan assay; however, if the test is positive, confirmation should be obtained by using a Histoplasma Capsulatum specific test.

Laboratory:

- CBC with differential count
- Coagulation tests: activated partial thromboplastin time and/or aPTT ratio (if both available, both to be recorded), prothrombin time and/or PT INR (if both available, both to be recorded), D-dimer and fibrinogen
- Biochemistry: ferritin, C-reactive protein (CRP), glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, albumin, creatinine, urea, triglycerides (fasting whenever possible)
- Pregnancy test, if applicable

Imaging:

- Abdominal ultrasound (spleen longitudinal measure)
- Chest X-ray
- Brain MRI (only in cases of CNS disease and/or as clinically indicated)

Histopathology:

- CSF Analysis (only in cases of CNS disease and only if coagulation parameters allow)

Safety:

- Recording of any AEs that have occurred since signature of the ICF

8.2 VISIT 1 AND ONWARDS (Infusion 1 of Emapalumab, SD0 and onwards)

The following assessments are to be performed **pre-infusion** (i.e. ideally on the day of the infusion, and in any case no more than 1 day prior to the infusion) at all visits from Visit 1 (SD0, enrolment time point) onwards, unless specified differently:

Patient information:

- Review of Inclusion/Exclusion Criteria (only at SD0)

Clinical Assessment:

- Vital signs including body temperature, blood pressure, heart rate, respiratory rate
- Body weight

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

	▪ Eastern Cooperative Oncology Group (ECOG) performance status ▪ Physical examination, including liver and spleen size (by palpation), and neurological examination ▪ Investigator assessment of clinical response
Search for infections:	▪ TB by PCR (every 4 weeks) ▪ Adenovirus, EBV, CMV (viral load) - in case of suspicion of infection ▪ Atypical mycobacteria, *Histoplasma* Capsulatum, *Leishmania* - if an infection is suspected
Laboratory:	▪ CBC with differential count ▪ Coagulation tests: activated partial thromboplastin time and/or aPTT ratio (if both available, both to be recorded), prothrombin time and/or PT INR (if both available, both to be recorded), D-dimer, and fibrinogen ▪ Biochemistry: ferritin, C-reactive protein (CRP), glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, albumin, creatinine, urea, triglycerides (fasting) ▪ Pregnancy test, if applicable ▪ Urinalysis: glucose, blood, protein, leukocytes, ketones (only at SD0)
Imaging:	▪ Abdominal ultrasound (spleen longitudinal measure), at SD0 if 2 weeks or more elapsed between the screening visit and SD0, then every 2 weeks during emapalumab treatment ▪ Chest X-ray - in case of clinical suspicion of pulmonary infection
Safety:	▪ Recording of any AEs that have occurred since the last visit
PK:	▪ Emapalumab serum concentrations
PD:	▪ CXCL9, sCD25, total IFNγ
Immunogenicity:	▪ ADAs (at SD0)
IMP Handling:	▪ Preparation, dispensing, and accountability
Medications:	▪ Concomitant medications recording.

The following assessments are to be performed **post-infusion**:

Clinical assessment:	▪ Vital signs including blood pressure, heart rate and respiratory rate, at the end of the infusion and at 1 and 2 hours after the end of the infusion
PK:	▪ Emapalumab serum concentration.

8.3 WEEK 4 ASSESSMENT (3 ±1 Days After last Week 4 Infusion) AND END OF TREATMENT VISIT (3 ±1 Days After Last Infusion)

These visits will include a full patient's assessment.

The Week 4 Assessment Visit will be performed 3 (±1) days after the last emapalumab infusion administered in Week 4. If treatment with emapalumab is completed before Week 4, only an EoT visit will be performed 3 (±1) days after the last infusion.

For patients continuing treatment beyond Week 4, an EoT visit will be conducted 3 (±1) days after the last emapalumab infusion.

The following assessments are to be performed (i.e. ideally on the day of the visit, and in any case no more than 1 day prior to the visit), pre-infusion in case emapalumab treatment continues beyond Week 4:

Clinical Assessment:	▪ Vital signs, including body temperature, heart rate, blood pressure, and respiratory rate ▪ Weight ▪ Eastern Cooperative Oncology Group (ECOG) performance status ▪ Physical examination, including as a minimum spleen and liver size (by abdominal palpation), and neurological examination ▪ Investigator assessment of clinical response
Procedure:	▪ ECG (only at EOT)
Search for infections:	▪ TB by PCR (if not performed within the last 4 weeks) ▪ Adenovirus, EBV, CMV (viral load) – only in case of suspicion of infection ▪ Atypical mycobacteria*, Histoplasma Capsulatum, Leishmania* – only if an infection is suspected
Laboratory:	▪ CBC with differential count ▪ Coagulation tests: activated partial thromboplastin time and/or aPTT ratio (if both available, both to be recorded), prothrombin time and/or PT/INR (if both available, both to be recorded), D-dimers, and fibrinogen ▪ Biochemistry: ferritin, C-reactive protein (CRP), glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, albumin, creatinine, urea, triglycerides (fasting) ▪ Pregnancy test, if applicable ▪ Urinalysis: glucose, blood, protein, leukocytes, ketones (only EOT)
Imaging:	▪ Abdominal ultrasound with spleen longitudinal measure
Safety:	▪ Recording of any AEs that have occurred since the last visit
Medications:	▪ Concomitant medications recording
PK:	▪ Emapalumab serum concentration
PD:	▪ CXCL9, sCD25, total IFNγ
Immunogenicity:	▪ ADAs.

If emapalumab treatment is continued, and Week 4 Assessment Visit is performed on the same day of the subsequent infusion, the infusion will be administered, and the following assessments will be performed **post-infusion**:

Vital sign assessment:	▪ Vital signs including blood pressure, heart rate and respiratory rate, at the end of the infusion and at 1 and 2 hours after the end of the infusion
PK:	▪ Emapalumab serum concentration

For patients who remain on study drug beyond the Week 4 Assessment Visit, ADA sampling is required every 3 months after the Week 4 Assessment Visit.

8.4 FOLLOW-UP PERIOD

Long-term follow up will be conducted after the discontinuation of emapalumab treatment, until 1 year after last administration of emapalumab or HSCT.

If HLH recurs or reactivates during the off-drug follow-up period, treatment with emapalumab can be reinstated, upon discussion with the Sponsor While receiving emapalumab, patients will undergo the same assessments planned during the initial treatment phase, as described in the Schedule of Assessments (Table 1), for the "Week x" visits. They will enter the follow-up period after completion of the re-treatment.

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

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

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

Clinical Assessment:	▪ Vital signs, including body temperature, heart rate, blood pressure, and respiratory rate ▪ Eastern Cooperative Oncology Group (ECOG) performance status ▪ Physical examination, including as a minimum spleen and liver size (by abdominal palpation), and neurological examination ▪ Survival ▪ Investigator assessment of clinical response
Laboratory:	▪ CBC with differential count ▪ Coagulation tests: activated partial thromboplastin time and/or aPTT ratio (if both available, both to be recorded), prothrombin time and/or PT/INR (if both available, both to be recorded), D-dimers, and fibrinogen ▪ Biochemistry: ferritin, C-reactive protein (CRP), glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, albumin, creatinine, urea, triglycerides (fasting) ▪ Pregnancy test, if applicable
Imaging:	▪ Abdominal ultrasound with spleen longitudinal measure
Safety:	▪ Recording of any AEs occurred since last visit
Medications:	▪ Concomitant medications recording

PK:
- Emapalumab serum concentration

PD:
- CXCL9, sCD25, total IFNγ.

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

The following assessments will be performed at the time points specified in the Schedule of Assessments - Follow-up Period (Table 2). Ideally all assessments shall be performed on the day of the visit, and in any case no more than 1 day prior to the visit.

Clinical Assessment:
- Vital signs, including body temperature, heart rate, blood pressure, and respiratory rate
- Physical examination, including as a minimum spleen and liver size (by abdominal palpation), and neurological examination
- Eastern Cooperative Oncology Group (ECOG) performance status (only at D+30, D+60, D+100, 6 month visits)
- Post HSCT outcome, if applicable and as per available information
- Survival
- Investigator assessment of clinical response

Laboratory:
- CBC with differential count
- Coagulation tests: activated partial thromboplastin time and/or aPTT ratio (if both available, both to be recorded), prothrombin time and/or PT/INR (if both available, both to be recorded), D-dimers, and fibrinogen
- Biochemistry: ferritin, C-reactive protein (CRP), glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, albumin, creatinine, urea, triglycerides (fasting)
- Pregnancy test, if applicable

Search for infections:
- TB by PCR in any relevant specimen, every 4 weeks until D+60; then at D+100, 6 month and 1 year visits as long as serum levels of emapalumab are detectable
- Adenovirus, EBV, CMV – in case of suspicion of infection

Imaging:
- Chest X-ray – in case of suspicion of infection
- Abdominal ultrasound with spleen longitudinal measure (at Day 100 visit only)

Safety:
- Recording of any AEs occurred since last visit until D+60. Afterwards, recording of SAEs related to study drug

Medications:
- Concomitant medications recording

PK:
- Emapalumab concentrations (if serum levels of emapalumab were still measurable at the previous visit)

PD:
- CXCL9, sCD25, total IFNγ (if serum levels of emapalumab were still measurable at the previous visit; then only if clinically indicated)

Immunogenicity:
- Assessment for ADAs (at Day +30 and Day +100 visits only).

8.4.3 1-Year Visit After Last Emapalumab Infusion or After HSCT/ Withdrawal Visit

The 1-Year visit represents the last visit of the study. The assessments indicated for the 1-year visit are to be performed also in case of premature withdrawal/discontinuation from the study, i.e. at the end of the study.

The following assessments will be performed for the 1-Year visit:

Clinical Assessment:	▪ Vital signs, including body temperature, heart rate, blood pressure, and respiratory rate ▪ Eastern Cooperative Oncology Group (ECOG) performance status ▪ Physical examination, including as a minimum spleen and liver size (by abdominal palpation), and neurological examination ▪ Post HSCT outcome, if applicable and as per available information ▪ Survival ▪ Investigator assessment of clinical response
Laboratory:	▪ CBC with differential ▪ Coagulation tests: activated partial thromboplastin time and/or aPTT ratio (if both available, both to be recorded), prothrombin time and/or PT/INR (if both available, both to be recorded), D-dimers, and fibrinogen ▪ Biochemistry: ferritin, C-reactive protein (CRP), glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, albumin, creatinine, urea, triglycerides (fasting) ▪ Pregnancy test, if applicable ▪ Urinalysis: glucose, blood, protein, leukocytes, ketones
Search for infections:	▪ TB by PCR in any relevant specimen (if serum levels of emapalumab were still measurable at the previous visit) ▪ Adenovirus, EBV, CMV – in case of suspicion of infection
Imaging:	▪ Chest X-ray ▪ Abdominal ultrasound with spleen longitudinal measure
Safety:	▪ Recording of SAEs related to study drug occurred since last visit
Medications:	▪ Concomitant medications recording
PK:	▪ Emapalumab concentrations (if serum levels of emapalumab were still measurable at the previous visit)
PD:	▪ CXCL9, sCD25, total IFNγ (if serum levels of emapalumab were still measurable at the previous visit, or if clinically indicated)
Immunogenicity:	▪ Assessment for ADAs.

8.5 UNPLANNED/UNSCHEDULED VISITS

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

8.6 UNPLANNED ASSESSMENTS

Additional PK/PD samples may be required to better characterize the PK/PD profile and/or for safety reasons. The number of additional samples taken will depend on the weight and health status of the patient.

9 SAFETY MONITORING

9.1 STUDY SCIENTIFIC OVERSIGHT

A review of the data at regular intervals will be conducted by the iDMC, to ensure that the safety profile of emapalumab remains favorable and the benefit/risk of treating remains positive: initially, data will be reviewed after the first 10 patients are enrolled, subsequently (and at a minimum) every time data for an additional 10 patients in total are available. In addition, the iDMC will monitor the efficacy results, as described in Section 11.3.2.

The details of the iDMC are provided in the iDMC Charter.

9.2 DESCRIPTION AND DEFINITIONS OF SAFETY PARAMETERS

Safety assessments will consist of monitoring and recording adverse events, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 9.3.2.

9.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

• Any unfavorable and unintended sign or symptom temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

• Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).

9.2.2 Serious Adverse Events

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death);
- 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 in a neonate/infant born to a mother exposed to study drug;
- is a significant medical event in the Investigator’s judgment (e.g. may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e. no more than 24 hours after learning of the event; see Section 9.3.2 for reporting instructions).

For the purposes of this study, the following will not be considered as SAEs:

- elective hospitalizations for surgical procedures that are a result of a patient's pre-existing condition(s) which have not worsened since receiving IMP;
- hospitalization requested for emapalumab infusion and study visits (including a possible hospital stay overnight, if due to logistic convenience).

9.3 RECORDING AND REPORTING SAFETY PARAMETERS

9.3.1 Adverse Events

All AEs reported spontaneously by the patients or observed by study personnel will be recorded in the patient's medical record and on the Adverse Event eCRF.

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

Any AE that occurs after the start of first IMP administration will be considered as a Treatment Emergent Adverse Event (TEAE).

After initiation of study drug, all adverse events (serious and not serious) will be reported until the Day+60 Visit (i.e. once at least 2 half-lives of the drug have elapsed). After this period, the Investigator should report serious adverse events deemed as related to emapalumab (see Section 9.2.2).

For each AE, the Investigator will make an assessment of seriousness (see Section 9.3.2), severity, and causality.

Severity of AEs will be graded on a three-points scale (mild, moderate, severe), using the following definitions:

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

Regardless of the severity, some events may also meet seriousness criteria. Refer to the definition of serious adverse event in Section 9.2.2.

The relationship of AEs to the IMP will be assessed by the Investigator using a "Yes/No" classification. In this study, emapalumab is the only IMP.

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.

Specific situations:

- HLH signs and symptoms are not to be reported as AEs
- If changes in HLH signs and symptoms indicate HLH worsening or reactivation, HLH worsening or reactivation shall be reported as an AE
- Infections characterized by clinically significant manifestations and identification of their etiology will be monitored by means of collection of viral load positivity over time.

9.3.2 Serious Adverse Events

The Investigator must report SAEs to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event.

For the purposes of this study, the following will not be considered as SAEs:

- elective hospitalizations for surgical procedures that are a result of a patient's pre-existing condition(s) which have not worsened since receiving IMP;
- hospitalization requested for emapalumab infusion and study visits (including a possible hospital stay overnight, if due to logistic convenience).

For the initial SAE report, the Investigator should report all available details, using the Sobi AG SAE reporting form.

Sobi AG contact information for SAE reporting:

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

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

• New signs or symptoms or a change in the diagnosis

• Significant new diagnostic test results

• Change in causality based on new information

• Change in the event's outcome, including recovery

• Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

All SAEs will also be recorded on the appropriate page of the eCRF.

9.4 PROCEDURES FOR RECORDING ADVERSE EVENTS

9.4.1 Diagnosis versus Signs and Symptoms

For any adverse event, a diagnosis should be recorded on the Adverse Event eCRF rather than individual signs and symptoms. However, if a constellation of signs and/or symptoms cannot be characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

9.4.2 Persistent and recurrent adverse events

A persistent adverse event is one that extends without resolution between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

9.4.3 Managing Abnormal Laboratory Test Values

All laboratory tests performed locally will be captured in the database and should not be reported as AEs even if qualified as 'clinically significant' at site, unless requiring a specific intervention for correction, or leading to a modification of the dose/regimen of study drug. If a laboratory abnormality leads to a new clinical diagnosis (e.g., high white cell count is found to be due to incidental leukemia), the new clinical diagnosis should be reported as an AE rather than the laboratory abnormality. If reported as AEs, abnormal laboratory values will follow the AE/ SAE reporting process described in this section.

Laboratory abnormalities which are common HLH signs and symptoms will not be reported as AEs. If laboratory abnormalities are indicative of an HLH reactivation or worsening, the reactivation or worsening of HLH will be reported as the AE, and not the laboratory abnormalities themselves

9.4.4 Deaths

Death should be considered an outcome and not an adverse event term. The event or condition that caused or contributed to the fatal outcome should be recorded as Adverse Event. Generally, only one such event should be reported.

9.4.5 Worsening of preexisting medical conditions

A preexisting medical condition is one that is present at the screening visit for this study.

Such conditions should be recorded on the Medical History eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study.

9.4.6 Pregnancy

In the event that a pregnancy occurs during the study, it must be reported to Sobi AG within 24 hours of awareness. This includes pregnancies occurring in partners of male patients. All information pertaining to pregnancy should be reported using the Sobi AG Pregnancy form. Pregnancy is not to be reported as an AE.

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

Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

9.5 FOLLOW-UP OF SAFETY PARAMETERS

9.5.1 Investigator Follow-up of Adverse Events

The Investigator should follow each adverse event until the event has resolved (returned to baseline grade or better), the event is assessed as stable by the Investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious AEs considered related to study drug or trial-related procedures until a final outcome can be reported.

All pregnancies reported during the study should be followed until pregnancy outcome.

9.5.2 Sponsor Follow-up

For serious adverse events and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

9.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the Investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period, if the event is believed to be related to prior study drug.

The Investigator should report these events directly to the Sponsor, by scanning and emailing the Serious Adverse Event Form using the email address provided to Investigators.

9.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events against cumulative experience with study drug to identify and expeditiously communicate possible new safety findings to Investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the emapalumab Investigator’s Brochure.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

9.8 BENEFIT/RISK MANAGEMENT

9.8.1 Safety Surveillance Management

The safety of patients who participate in this trial will be ensured through the use of stringent inclusion and exclusion criteria, and close monitoring of patients. Investigators will assess the occurrence of adverse events and serious adverse events at all patient evaluation timepoints during the study. All adverse events and serious adverse events, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be recorded in the patient's medical record and on the appropriate adverse event eCRF. Patients will be carefully followed for adverse events during the study, including a long-term follow-up period off study drug.

An iDMC will review safety and efficacy data at regular intervals.

The iDMC can recommend treatment discontinuation for individual patients as well as to halt the entire study temporarily or permanently.

9.8.2 General Benefit/Risk Considerations

9.8.2.1 Potential benefits

Therapies specifically directed at HLH in adult patients are extrapolated from experience in pediatric HLH. These treatments are either with high toxicity (i.e. etoposide) or without conclusively demonstrated benefit to the condition.

Given the central role of IFNγ in mediating the immune dysregulation and severe inflammation in all forms of HLH, it is hypothesized that neutralization of IFNγ will improve outcomes in patients with adult-onset HLH.

The expected benefit of a partial or complete resolution of clinical and laboratory signs of HLH activity in pHLH patients receiving treatment with emapalumab has been demonstrated in the NI-0501-04 and NI-0501-05 studies, with the majority of patients being able to receive HSCT and experiencing a survival benefit which persisted after HSCT. The results of the study have confirmed that emapalumab, as a targeted treatment, could control HLH activity while being safe and well tolerated in a very fragile pediatric population. Furthermore, emapalumab treatment could be continued safely and effectively beyond 8 weeks in patients for whom the search for a donor was longer than expected. Since non-active or minimally active disease at the time of HSCT has been reported to correlate with overall survival in HLH, this has represented a major benefit for pHLH patients.

On the basis of the data available so far, the FDA has approved emapalumab as the first specific treatment for pHLH patients who have refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.

Based on these considerations, adult onset HLH patients are expected to benefit from a targeted therapy with emapalumab.

For more details, refer to the latest Investigator's Brochure.

9.8.2.2 Risks analysis

Based on the available pre-clinical and clinical data, the nature and mechanism of action of emapalumab, the acquired experience from fontolizumab (a humanized anti-IFNγ monoclonal antibody) and other immunomodulatory antibodies, attention should be paid to:

- Risks related to the neutralization of the target (IFNγ):

  As to the development of infections caused by pathogens reported to be potentially favored by the absence of IFNγ biological activity, among the 73 patients treated with emapalumab at the cut-off date of 14 November 2018, 1 patient developed disseminated histoplasmosis which resulted in treatment discontinuation. The infection resolved with adequate antifungal therapy while emapalumab was still at measurable concentrations in blood. One case of Herpes Zoster infection was reported in the Phase 1 study in healthy volunteers, and recovered.

As to the development of other infections (bacterial, viral, fungal), which are expected and commonly reported in immunocompromised patients, based on the experience gained so far, the following considerations can be made:

- the presence of an active infection (not being an exclusion criteria of the pHLH protocols) did not prevent initiation of emapalumab treatment
- infections occurring during emapalumab treatment, when in the presence of satisfactory HLH control and with appropriate anti-microbial treatment, generally resolved
- the severity and duration of neutropenia, a hallmark of HLH, as well as a potential consequence of previous HLH treatments or HSCT conditioning, seemed to significantly contribute to the development of infections.

- Hypersensitivity and infusion related reactions:

  Infusion related reactions (IRRs) are reported with monoclonal antibodies (mAbs) and have been reported as anaphylaxis, anaphylactoid reactions and cytokine release syndrome, among other terms used. They are defined as signs or symptoms timely related to the administration of an infusion, occurring typically between 30 minutes to 2 hours following the start, although symptoms may be delayed for up to 24 hours. Anaphylactic and anaphylactoid reactions are the most severe forms of acute allergic reactions.

  With regard to emapalumab, no signal has been identified in the pre-clinical studies and in the Phase 1 study in HV.

  During emapalumab treatment in the NI-0501-04 and -05 studies, 11 of 45 (24%) treated patients experienced at least 1 IRR. The most frequently reported IRRs were hyperhidrosis (4 patients), cutaneous reactions coded drug eruption, rash or erythema or erythematous rash (7 patients) or pyrexia (3 patients).

  All IRRs were of mild intensity, except for 1 event of moderate pyrexia. No IRR was reported as a serious adverse event and no IRR required a permanent discontinuation of emapalumab or prevented administration of the full dose of emapalumab.

  No IRR has been reported to date in the NI-0501-06 study (6 patients having completed treatment).

  No anaphylactic/anaphylactoid reactions or delayed hypersensitivity reactions have been observed.

- Immunogenicity:

  Immunogenic responses to antibody therapeutics can impact both safety and pharmacokinetic properties of a drug. The analyses performed so far on HLH patients treated in the NI-0501-04/05/06 studies have detected the presence of ADAs in 3 of 38 patients (7.9%). In none of the patients was

the presence of ADA associated with any adverse event or significant changes in the pharmacokinetics profile, and ADA titers were generally low.

More details on the safety profile of emapalumab as currently known are available in the latest Investigator`s Brochure.

9.8.2.3 Risk minimization measures

The above listed risks are considered to be fully manageable in HLH patients, with adequate minimization measures as follows:

- The ongoing study has been designed with HLH experts;
- Inclusion/exclusion criteria: patients with malformations or severely altered organ functions (due to a concomitant disease), as well as patients with active or latent (in case of TB) infection by *Mycobacteria*, *Histoplasma, Leishmania*, known to be potentially favored by IFNγ neutralization, are not to be included in emapalumab studies;
- Patients are managed in specialized centers for the treatment of HLH, and therefore equipped with all necessary emergency assistance devices;
- Prophylaxis for *Herpes Zoster* virus is mandatory to avoid occurrence of this infection which might be favoured by IFNγ neutralisation;
- Close monitoring for potential infections through careful physical examination, laboratory parameters, active search for EBV, CMV, *Adenoviruses*, and *M. Tuberculosis* at Screening and when clinically indicated, are required per protocol;
- The ongoing study is performed under the surveillance of an iDMC.

10 STUDY, AND SITE DISCONTINUATION

10.1 PATIENT DISCONTINUATION

Patients have the right to voluntarily withdraw from 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.

Reasons for withdrawal from the study may include, but are not limited to, the following:

• Patient withdrawal of consent at any time

• Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study

• Investigator or Sponsor determines it is in the best interest of the patient.

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.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn.

10.2 STUDY TREATMENT DISCONTINUATION

Patients must discontinue study treatment permanently if they experience the following:

- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

All patients who discontinue from the study treatment shall return for all scheduled visits until the end of the study.

10.3 STUDY DISCONTINUATION

Recruitment may be temporarily suspended in case of occurrence of unexpected fatal adverse reactions.

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

The suspension will allow the Sponsor and/or the iDMC to analyze the data already generated and to formulate recommendations (e.g. resuming recruitment with no changes to the protocol, implementing risk minimization measures).

10.4 MANAGEMENT OF TREATMENT DISCONTINUATION

All patients who discontinue emapalumab treatment will be treated according to the standard care at the site and they will continue in the study for long-term follow-up.

11 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

Full details of all statistical issues and planned statistical analyses will be specified in a separate Statistical Analysis Plan (SAP), which will be finalized before 10 patients with a specific HLH etiology completed treatment (i.e. before the first analyses of data for a specific etiology, please see Section 11.3.2). This section contains an overview of the planned methods of analysis.

11.1 SAMPLE SIZE

Initial Planned Sample Size

The primary analysis will evaluate the Overall Response (OR) rate at 4 weeks and use a binomial test with a one-sided significance level of 5% to calculate the p-value. The initial sample size planned for each etiology is 10.

Final Sample Size

The sample size for each of the two etiologies (i.e. M-HLH and non-malignancy-associated HLH) will be reviewed in an ongoing way. Recruitment to particular etiologies may be stopped for futility while recruitment to other etiologies may be expanded up to a sample size of 25 patients for a particular etiology.

11.2 ANALYSIS SETS

Analysis sets will be defined in the SAP. In conjunction with the analysis set listed below, further exploratory analyses may be performed using certain subgroups of patients. In particular, there will be separate consideration of the different etiologies.

11.2.1 All Treated Analysis Set

The All Treated Analysis Set will include all patients entering the study who receive any part of an infusion of study drug.

11.2.2 Per Protocol Analysis Set

The Per Protocol Analysis Set will be the subset of the All Treated Analysis Set excluding major protocol violators. The criteria for identifying 'major violations' will be set down in detail in the SAP.

The All Treated Analysis Set will be the primary analysis set for all efficacy evaluations. Each of the efficacy endpoints will also be analysed in the Per Protocol Analysis Set.

11.3 STATISTICAL AND ANALYTICAL METHODS

11.3.1 Efficacy Data

The primary analysis of the primary endpoint will evaluate the null and alternative hypotheses defined as follows:

$$H_0: ORR \leq 40\% \qquad H_1: ORR > 40\%$$

The analysis will be based on a binomial test with a one-sided significance level of 5%. Descriptive statistics and graphical methods will be used for the evaluation of the secondary efficacy endpoints.

Overall Survival (OS), time to response and duration of response will be summarised in Kaplan-Meier curves. For OS, patients still alive at the end of the study or lost-to-follow-up will be censored at the last known time alive. For time to response, patients without a response at the end of the study or lost-to-follow-up will be censored at the last known time known to not have had a response. The Kaplan-Meier curve for duration of response will be constructed only for those patients who are responders. Summary statistics (namely estimated value, standard error with 95% confidence interval) will be obtained at key time points for OS and time to response. Best response on treatment and HLH response will be summarized with counts and associated 95% confidence intervals. The secondary endpoints are considered to be exploratory and no statistical testing has been planned.

11.3.2 Adaptive Evaluation of the Overall Response Rate

This study recruits patients with different HLH etiologies, namely M-HLH and non malignancy-associated HLH. Emapalumab may not be equally effective across these etiologies, therefore it is proposed to analyse the accumulating data periodically, in order to assess each of the 2 etiologies for futility and efficacy. In this adaptive design, the first analysis for each etiology will occur after 10 patients with that etiology reached the primary endpoint time point, and further reviews for each etiology will take place after every subsequent 5 patients. The decision rule for stopping for futility shall be based on a one-sided p-value looking to see whether the OR rate was significantly below 60%, while the decision rule for considerations for efficacy shall be based on a one-sided p-value looking to see whether the OR rate was significantly above 40%.

For example, with 10 patients, the probability of seeing 2 or fewer ORs is 0.0123 if the true OR rate is 60% and such evidence may result in a decision to stop recruitment for that etiology. In contrast, the probability of seeing 8 or more ORs is 0.0123 if the true OR rate is 40% and this may result in a decision to consider interacting with regulators to discuss the potential for an indication in that etiology. These decision rules are based on the one-sided p-values being below 0.05.

The table below provides the cut-offs for both futility and efficacy based on these same considerations for various sample sizes in multiples of 5 from n=10 through to n=25.

Thresholds for Futility and Efficacy as a Function of Sample Size

Sample size (by etiology)	Threshold for consideration of futility #ORs ≤ this value	Threshold for consideration of efficacy #ORs ≥ this value
10	2 (20%)	8 (80%)
15	5 (33%)	10 (67%)
20	7 (35%)	13 (65%)
25	10 (40%)	15 (60%)

These thresholds provide a guide for the decision making for futility and efficacy.

To support regulatory interactions on the confirmatory strategy, a descriptive evaluation of the efficacy and safety results will be made after a small number of patients, i.e. no more than 10 patients overall (irrespectively of etiology), have completed 4 weeks of treatment.

11.3.3 **Safety Data**

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

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

11.3.4 **Pharmacokinetic Data**

Population PK and PKPD analyses using non-linear mixed effects modelling will be performed and reported separately. A specific PK and PKPD modelling analysis plan will be prepared.

11.3.5 **Pharmacodynamic Data**

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

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

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

11.3.6 Missing Data

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

11.4 REPLACEMENT POLICY

11.4.1 For Patients

Additional patients may be recruited into the study if patients are withdrawn from the study for reasons other than safety or lack of efficacy.

11.4.2 For Centers

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

12 ETHICAL AND LEGAL ASPECTS

12.1 GOOD CLINICAL PRACTICE

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Sobi AG, its authorized representatives, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles rooted in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB)/Independent Ethics Committee (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.

12.2 INVESTIGATOR 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 CRFs and queries.

12.3 INFORMED CONSENT

Before being enrolled in this clinical study, the patient (or the patient's 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 and will specify who obtained informed consent from the patient (or the patient's legally authorized representative), and when the informed consent was obtained.

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 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. In the event that the patient's legally authorized representative signed the ICF due to the patient's condition at the time of consent, the subject's personal consent should be pursued, should his/her condition allow to personally consent. If the patient is not capable to personally consent, this should be clearly documented in the patient's medical file.

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

12.4 CONFIDENTIALITY AND DATA PRIVACY

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 medical records and copies thereof used for conducting the study or regulatory purposes 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.

12.5 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.

12.6 APPROVAL OF THE CLINICAL STUDY PROTOCOL AND AMENDMENTS

Before the start of the study, the study protocol, informed consent document, any subject-facing documents (e.g. patient card) and any other documents (as appropriate) will be submitted to the IRB/IEC with a cover letter or a form listing the documents submitted, their version and date 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 ICH 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 an IRB/IEC committee member. 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 and/or any other documents (as appropriate) should also be revised.

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

All documents handed over to patients or their legally authorized 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 IRB/IEC and in accordance with local legal requirements by the regulatory authorities. This includes but is not limited to the Informed Consent Form, Patient Information Sheet, assent form, advertisements, training materials.

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

12.8 CLOSURE OF THE STUDY

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 ICH GCP non-compliance
- Inaccurate, incomplete or delayed data collection
- Failure to adhere to the study protocol
- Failure to provide requested follow-up information for data queries.

12.9 RECORD RETENTION

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

- Signed informed consent documents for all subjects
- Subject identification code list, screening log and enrolment log (if applicable)
- Record of all communications between the Investigator and the IRB/IEC and/or regulatory authorities
- 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 shipments, returns, destruction and accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (subject records, hospital records, laboratory records, etc.)
- All other documents, as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, the Investigator must ask Sobi AG for permission to make alternative arrangements. Details of these arrangements should be documented and archived both at the clinical trial center and in the Trial Master File (TMF). These may include but are not limited to notifications to the IRB/IEC and/or regulatory authorities (as applicable).

12.10 LIABILITY AND INSURANCE

Liability and insurance provisions for this study are provided in the Investigator/Investigational site/Other site personnel or facility contract as applicable.

12.11 FINANCIAL DISCLOSURE

Investigators and study site staff listed on the Delegation of Authority Log 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 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.

12.12 DISCLOSURE OF PROTOCOL AND STUDY RESULTS AND PUBLICATION POLICY

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

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 prior to the start of the trial.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements. Any formal publication of the study in which contribution of Sobi AG personnel exceeded that of conventional monitoring 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.

13 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 ICH GCP and applicable standard operating procedures/working instructions. Direct access to the on-site study documentation and medical records must be ensured.

13.1 STUDY MONITORING AND SOURCE DATA VERIFICATION

As part of the responsibilities commensurate with participating in the study, the Investigator agrees to maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the patients treated under this protocol. In addition, the Investigator agrees to maintain all administrative documents (e.g., IRB/IEC 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/institution should maintain a record of the location(s) of the essential documents. The storage system (irrespective of the media used) should provide for document identification, search and retrieval.

13.2 ON-SITE AUDITS

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

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

13.3 SERIOUS GCP BREACHES

Sobi AG is required to report a serious ICH 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. an important protocol deviation, or non-reporting of critical safety information that has the potential of jeopardizing patients' safety, Sobi AG must be notified within 24 hours.

14 DOCUMENTATION AND USE OF STUDY FINDINGS

14.1 DOCUMENTATION OF STUDY RESULTS

An electronic CRF (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. Sobi AG will not have exclusive control of those data.

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 CRF copies left with the Investigator (print-outs and/or pdf exports) are an exact copy of the data maintained in the database.

14.2 USE OF COMPUTERIZED SYSTEMS AT THE CLINICAL TRIAL CENTRE

When clinical information of patients are entered directly into an investigational site's computerized medical record system (electronic Health Records System; i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with

health authority requirements pertaining to computerized systems used in clinical research. An acceptable electronic Health Records System allows preservation and integrity of the original entry of data by ongoing review, change control processes and audit trails. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, 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.

15 REFERENCES

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16 APPENDIX 1

NI-0501-10: ELIGIBILITY REVIEW FORM

How to use this form

1. This form is used to guide the review of patient's eligibility (by Site and Sponsor).
2. It should be completed after the patient has been consented, and before the joint eligibility review call, if scheduled.
3. Please send the completed form to NI-0501-10@sobi.com

Institution

Institution name and location:	
Treating physician:	

Patient information

Patient ID*:* *assigned sequentially*	
Age:	
Gender	☐ Male ☐ Female
If the patient is a female, is she pregnant or lactating?	☐ Yes ☐ No

HLH initial diagnosis

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

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

☐ Fever	
☐ Splenomegaly	
☐ Cytopenias affecting 2 of 3 lineages (hemoglobin < 90 g/L; platelets <100 x 109/L; neutrophils < 1 x 109/L)	

☐ Hypertriglyceridemia (fasting triglycerides ≥ 3 mmol/L or ≥ 265 mg/dL) and/or hypofibrinogenemia (≤ 1.5 g/L)	
☐ Hemophagocytosis in bone marrow, spleen or lymph nodes	
☐ Low or absent NK-cell activity	
☐ Ferritin ≥ 500 µg/L	
☐ Soluble CD25 ≥ 2400 U/mL	

Trigger of secondary HLH:

☐ Rheumatic disease *Please indicate any known or suspected rheumatic conditions*	
☐ Infectious disease *Please indicate any known or suspected infections*	
☐ Neoplastic disease *Please indicate any known or suspected neoplastic diseases*	
☐ Other	

Did the patient already receive any therapy for HLH?

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

Overall patient's condition and infectious status

Patient's general condition	
Cardiovascular function	
Pulmonary function	
CNS function	
Liver function	
Renal function	
Other important concomitant diseases	☐ Yes (specify):
	☐ No
• recently resolved and ongoing infections (indicate duration and severity)	☐ Yes (specify):
	☐ No
Treatments / procedures ongoing at the time of request (other than HLH treatments)	
☐ Biologics	
☐ Transfusions	
☐ G-CSF	
☐ Antibioticotherapy	
☐ Antifungal treatments	
☐ Antiviral treatments	
☐ Cardiorespiratory support	
☐ Renal replacement therapy	
☐ Other	

Current (within 60 days from SD0) or scheduled administration of therapies known to trigger the cytokine release syndrome	☐ Yes (specify):
	☐ No
Current (within 60 days from SD0) or scheduled administration of PD-1/PD-L1/CTLA-4 inhibitors	☐ Yes (specify):
	☐ No
Current JAK-inhibitors administration	☐ Yes (specify):
	☐ No
Life-expectancy associated with the underlying disease (triggering HLH) < 3 months	☐ Yes (specify):
	☐ No

Ongoing participation in an investigational trial, or administration of any investigational treatment within 30 days from Screening	☐ Yes (specify):
	☐ No
Vaccinations within prior 12 weeks:	☐ Yes (specify):
	☐ No
Has the presence of active or latent TB infection been excluded?	☐ Yes (specify):
	☐ Waiting for test results. There are no clinical findings suggestive of this infection.
	☐ No
Has the presence of atypical mycobacterial infection been excluded?	☐ Yes (specify):
	☐ Waiting for test results. There are no clinical findings suggestive of this infection.
	☐ No
Has the presence of *Histoplasma capsulatum* infection been excluded?	☐ Yes (specify):
	☐ Waiting for test results. There are no clinical findings suggestive of this infection.
	☐ No
Has the presence of *Leishmania* infection been excluded?	☐ Yes (specify):
	☐ Waiting for test results. There are no clinical findings suggestive of this infection.
	☐ No
Is infection with HIV (HIV ELISA or PCR positive), hepatitis B (HBsAg positive), hepatitis C (anti-HCV positive) present?	☐ Yes (specify):
	☐ No

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

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

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

Enter date

Investigator's name and signature *Date*