A Two-cohort, Open-label, Single-arm, Multicenter Study to Evaluate Efficacy, Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of Emapalumab in Children and Adults with Macrophage Activation Syndrome (MAS) in Still's Disease (Including Systemic Juvenile Idiopathic Arthritis and Adult Onset Still's Disease) or with MAS in Systemic Lupus Erythematosus

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Type of Study: Phase 2/3

Clinical Science Leader

Sponsor's Study Physician
[redacted]

Sobi, Basel, Switzerland
[redacted]

Signature Date

Investigator statement

I have read the protocol entitled “A Two-cohort, Open-label, Single-arm, Multicenter Study to Evaluate Efficacy, Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of Emapalumab in Children and Adults with Macrophage Activation Syndrome (MAS) in Still’s Disease (Including Systemic Juvenile Idiopathic Arthritis and Adult Onset Still’s Disease) or with MAS in Systemic Lupus Erythematosus” and the accompanying current investigator’s brochure. I agree to conduct the clinical investigation in compliance with the Final Protocol, Version 3.0 date 19-October-2023, the International Council for Harmonisation (ICH) harmonised guideline E6(R2): Guideline for Good Clinical Practice (GCP) [1], applicable regulatory or government regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki [2]. I will not implement any changes to study procedures or conduct without prior approval from the Sponsor and, when applicable, the Independent Ethics Committee or Institutional Review Board/ Research Ethics Board as applicable and Regulatory Authority. I will supervise any individual or party to whom I delegate study-related duties and functions conducted at the study site and ensure qualification of individuals or parties who perform delegated tasks.

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

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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1 Synopsis

STUDY IDENTIFIERS

Title of study:	A Two-cohort, Open-label, Single-arm, Multicenter Study to Evaluate Efficacy, Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of Emapalumab in Children and Adults with Macrophage Activation Syndrome (MAS) in Still's Disease (Including Systemic Juvenile Idiopathic Arthritis and Adult Onset Still's Disease) or with MAS in Systemic Lupus Erythematosus
Clinical study number:	NI-0501-14
Type of study:	Therapeutic confirmatory

STUDY OBJECTIVES

Primary objective: To demonstrate efficacy of emapalumab in the treatment of patients in:

- Cohort 1: Macrophage activation syndrome (MAS) in the context of systemic juvenile idiopathic arthritis (sJIA) and adult onset Still's disease (AOSD).
- Cohort 2: MAS in the context of pediatric and adult systemic lupus erythematosus (SLE).

Secondary objective(s):

- To demonstrate efficacy of emapalumab with respect to tapering of glucocorticoids (GCs).
- To evaluate the time to onset of response to emapalumab treatment.
- To evaluate efficacy of emapalumab with respect to overall response (OR).
- To evaluate the sustained efficacy of emapalumab treatment.
- To evaluate the patient's survival after treatment with emapalumab.
- To evaluate the safety and tolerability of emapalumab.
- To evaluate patient-reported outcome of MAS in patients treated with emapalumab.
- To determine the pharmacokinetic (PK) profile of emapalumab.
- To determine the pharmacodynamic (PD) profile of emapalumab.
- To determine the immunogenicity of emapalumab.

Exploratory objectives:

- [redacted]

STUDY ENDPOINTS

Primary efficacy endpoint:

- Proportion of patients with complete response (CR) at Week 8 after first administration of emapalumab.

Secondary endpoint(s):

- GCs tapering to a dose < 50 % of prednisolone (PDN) equivalent at the time of emapalumab start or to the same (or lower) dose being administered before the occurrence of MAS (in patients already treated for the underlying condition), whichever occurs first at any time during the study.
- GCs tapering to ≤ 1 mg/kg/day of PDN equivalent at any time during the study.
- Time to achieve GCs tapering (as defined in the 2 bullets above).
- Time to first CR.
- Proportion of patients with OR as defined by CR or partial response (PR).
- Time to first OR as defined by CR or PR.
- MAS recurrence at any time after achievement of CR.
- Withdrawal from the study due to lack of response as per Investigator decision.
- Survival time.

Safety endpoints

- Incidence, severity, causality and outcomes of adverse events (AEs) (serious and nonserious).
- Withdrawal from the study treatment due to safety reasons.
- Changes from baseline in relevant laboratory parameters, vital signs, physical examinations and electrocardiograms (ECGs).

Patient-reported outcome endpoints

- Health-related quality of life (QoL): Pediatric Quality of Life Inventory (PedsQL™; Generic Core Scales and Infant Scales, Acute versions) also applicable for adults.
- Global Assessment: Patient/Parent Global Impression of Severity.
- Global Assessment: Clinician Global Impression of Severity.

PK endpoints

- Serum concentrations of emapalumab.

PD endpoints

- Levels of circulating free interferon-gamma (IFN-γ) at predose, and total IFN-γ (free IFN-γ + bound to emapalumab) after initiation of the study drug.
- Levels of the main IFN-γ-induced chemokines (CXCL9, CXCL10).
- Levels of MAS markers (soluble CD25).

Immunogenicity endpoints

- Occurrence of anti-drug antibodies (ADA) and neutralizing antibodies to emapalumab.

Exploratory endpoint(s):

- [redacted]

STUDY DESIGN AND METHODS

Study design:	Study NI-0501-14 is an open-label, 2-cohort, single arm, multicenter, interventional, phase 2/3 study. The study enrolls pediatric and adult patients between 6 months and 80 years of age with different etiologies of MAS. These patients will be assigned to different cohorts as per their underlying disease: • Cohort 1: MAS in the context of sJIA and AOSD. • Cohort 2: MAS in the context of pediatric and adult SLE. Each cohort in this study is designed as a single arm study and will be composed of 2 phases: one Run-in phase and one Interventional phase. The Run-in phase will enroll patients as defined in Cohorts 1 and 2, and requiring treatment with GCs. These patients will be treated as per Investigator decision. Patients will be followed for a maximum of 12 weeks, or until reaching a MAS remission as per Investigator assessment, or until presenting an inadequate response to GCs as assessed by the Investigator, whichever occurs first. Every effort should be taken to enroll patients starting from the Run-in phase (i.e., before starting treatment with GCs). However, it should be noted that this phase is not compulsory, therefore patients can join the study directly in the Interventional phase. Patients who also failed GCs plus other MAS therapies and meet all the eligibility criteria may be enrolled in the Interventional phase. If at any time during the Run-in phase, patients present an inadequate response to GCs and additionally meet all eligibility criteria of the Interventional phase, they will be invited to continue into the Interventional phase of the study. Enrollment in the Run-in phase will be achieved when the last patient of the Interventional phase is enrolled. At the time of completion of enrollment into the Interventional phase, patients completing the Run-in phase will not be denied treatment with emapalumab and enrollment into the Interventional phase if needed, and upon fulfillment of all eligibility criteria. A re-treatment with emapalumab is allowed during the Long-term follow-up period of the study if patients present a recurrence of MAS. An interim analysis assessing efficacy will be performed after 16 treated patients in Cohort 1 have reached 8 weeks after first dose of emapalumab, or earlier if the patients discontinued the study. Enrollment in Cohort 1 may be closed upon results of this interim analysis. Further interim analyses will be performed once all patients in each cohort have completed the follow-up to Week 8 (i.e., patients who reach the Week 8 Assessment Visit or discontinue the study early). The interim CSRs written based on these interim analyses may be used for regulatory submissions. Finally, a full CSR including the safety follow-up period will be prepared once both cohorts reach the EOS.
Number of patients planned:	A total of 41 patients are planned to be enrolled in the Interventional phase: 25 patients (of these at least 16 pediatric patients) in Cohort 1, and 16 patients (of these at least 6 pediatric patients) in Cohort 2.
Criteria for inclusion and exclusion:	**Inclusion criteria** <u>Run-in phase in all cohorts</u>

1. Informed consent provided by the patient or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as required by local law.
2. Male and female patients aged between 6 months and 80 years of age at the time of diagnosis of active MAS.
3. MAS defined as per the criteria defined below for each cohort and requiring treatment with GCs as per standard of care.

Interventional phase in all cohorts

1. Informed consent provided by the patient or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as required by local law.
2. Male and female patients aged between 6 months and 80 years of age at the time of diagnosis of active MAS.
3. Patients who have shown an inadequate response to high dose intravenous (i.v.) GCs administered for at least 3 days according to local standard clinical practice, including but not limited to pulses of 30 mg/kg methylprednisolone (mPDN) on 3 consecutive days. High i.v. GCs dose is recommended not to be lower than 2 mg/kg/day PDN equivalent (or at least 60 mg/day in pediatric patients of 30 kg or more and at least 1 g/day in adult MAS patients). In case of rapid worsening of the patient's condition and/or laboratory parameters, as per Investigator judgment, inclusion may occur within less than 3 days from starting high dose GCs.
4. Diagnosis of active MAS confirmed by the treating rheumatologist, having ascertained the following:
   a. Febrile patients presenting with ferritin > 684 ng/mL.
   b. and any 2 of:
      i. Platelet count ≤ 181 x10^9/L
      ii. Aspartate aminotransferase (AST) level > 48 U/L
      iii. Triglycerides > 156 mg/dL
      iv. Fibrinogen level ≤ 360 mg/dL
5. Female patients of childbearing potential (sexually or nonsexually active). Female patients who are sexually active must be willing to use highly effective methods of contraception from study drug initiation to 6 months after the last dose of study drug.

Specific inclusion criteria for Cohort 1 and Cohort 2

1. Cohort 1:
   a. Confirmed sJIA diagnosis. For patients presenting with MAS in the context of the onset of sJIA, high presumption of sJIA will suffice for eligibility.
   b. Confirmed diagnosis of AOSD as per Yamaguchi criteria (Yamaguchi et al. 1992).
2. Cohort 2:
   a. Confirmed diagnosis of SLE as per Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria.

Exclusion criteria

1. Primary hemophagocytic lymphohistiocytosis (pHLH) documented by either the presence of a known causative genetic mutation or abnormal

perforin expression or CD107a degranulation assay as described with pHLH or by the presence of family history.

2. Confirmed malignancy. Note: patients with a suspected malignancy should have mononuclear cells typed by flow cytometry and/or tissue biopsy, as applicable, to rule out malignancy.
3. Treatment with canakinumab, Janus kinase (JAK) inhibitors, tumor necrosis factor (TNF) inhibitors and tocilizumab at the time of emapalumab initiation.
4. Ongoing treatment with anakinra at a dose above 4 mg/kg/day at time of emapalumab initiation.
5. Patients treated with etoposide for MAS in the last 1 month.
6. Presence of any medical or psychological condition or laboratory result that in the opinion of the Investigator can interfere with the patient's ability to comply with the protocol requirements or makes the patient not appropriate for inclusion to the study and treatment with emapalumab.
7. Foreseeable inability to cooperate with given instructions or study procedures.
8. Clinically active mycobacteria (typical and atypical), Histoplasma Capsulatum, or Salmonella infections.
9. Evidence of leishmania infections.
10. Evidence of latent TB.
11. History of hypersensitivity or allergy to any component of the study drug.
12. Receipt of a Bacillus Calmette-Guerin (BCG) vaccine within 12 weeks prior to Screening.
13. Receipt of a live or attenuated live (other than BCG) vaccine within 4 weeks prior to Screening.
14. Pregnancy or lactating female patients.

Assessments:

Run-in phase and GCs treatment period

After a screening period of up to 1 week, patients as defined in Cohorts 1 and 2 and requiring treatment with GCs will be enrolled in the Run-in phase. These patients must meet the specific inclusion criteria for the cohorts and the Run-in phase inclusion criteria.

After signing a specific informed consent form (ICF) for this phase, a thorough review of inclusion and exclusion criteria will be performed. Previous and concomitant medications including any previous MAS and any underlying disease treatment will be collected. Patients will undergo clinical assessment, laboratory assessment, and search for infection. During treatment with GCs all concomitant MAS treatments, concomitant medications for underlying diseases and QoL assessments will be collected. Patients will undergo regular laboratory and clinical assessments. During this phase, AEs, serious adverse events (SAEs), and MAS clinical activity as per Investigator assessment should be collected.

Patients will be followed until they reach a MAS remission as per Investigator assessment, or until they present an inadequate response to GCs, or up to 12 weeks after the start of GCs, whichever occurs first.

If, at any time during this phase, patients present an inadequate response to GCs, they may continue into the Interventional phase of the study.

	Every effort should be taken to enroll patients in the Run-in phase (i.e., before starting treatment with GCs). However, it should be noted that this phase is not compulsory, therefore patients can join the study directly in the Interventional phase. **Interventional phase screening and emapalumab treatment period** Patients fulfilling the eligibility criteria will be enrolled in the Interventional phase. After a screening period of up to 1 week, patients will start treatment with emapalumab. Patients will be treated with emapalumab for 4 weeks. After signing a specific ICF for the Interventional phase, a thorough review of inclusion and exclusion criteria will be performed. Previous and concomitant medications including any previous MAS and any underlying disease treatment will be collected. Patients will undergo clinical and laboratory assessments, search for infections, as well as ECG and imaging assessments prior to enrollment. After starting treatment with emapalumab, current medication for MAS and underlying disease, as well as background GCs treatment and any background treatment for the underlying disease will be collected. Patients will undergo laboratory assessments, clinical and imaging assessments. PK, PD, and immunogenicity samples, and QoL information will be collected. During this phase, AEs, SAEs and MAS clinical activity as per Investigator`s assessment should be recorded. **Interventional phase follow-up period** These patients will then enter a follow-up period up to Week 8 (SD56) followed by a long-term follow-up period which continues for 1 year after last dose of emapalumab**.** During this period concomitant medications including the treatment of underlying disease and any new treatment(s) for MAS will continue to be collected. Patients will undergo clinical, laboratory and imaging assessments. The search for infections will continue as clinically indicated. PK, PD, and immunogenicity as well as QoL information will be collected. During this phase, AEs, SAEs, and MAS clinical activity as per Investigator assessment and survival data should be reported.
Test product; dose and mode of administration:	Patients enrolled in the Interventional phase will receive emapalumab. Emapalumab will be administered by i.v. infusion at an initial dose of [redacted] over a period of 1 to 2 hours, depending on the volume to be infused. Emapalumab treatment will be continued at the dose of [redacted] every 3 days until Study Day 16 (SD16), and then twice-a-week for additional 2 weeks, i.e., until SD28.
Reference product; dose and mode of administration:	Not applicable

Duration of treatments:	Patients in each of the cohorts in the Interventional phase will be treated with emapalumab for 4 weeks. However, it is not expected that treatment duration will be the same across the study population of each cohort. Treatment shall continue until a MAS remission as per Investigator assessment is achieved. In the case of MAS remission met prior to 4 weeks, treatment may be shortened, as per Investigator assessment. However, at least 3 infusions of emapalumab must be administered before study drug discontinuation, except in the case of a major safety concern. In case treatment is stopped before SD28, the patient will continue with the assessments as required per the schedule of assessments in the protocol. In the absence of a trend of improvement in the key MAS clinical and laboratory parameters (including but not limited to ferritin, lactate dehydrogenase [LDH], AST, alanine aminotransferase [ALT], and platelet count) suggestive of a lack of response, the emapalumab regimen may be adapted by shortening the interval (from every 3 days to every 2 days and subsequently if judged further necessary from every 2 days to each day) between the infusions, or by increasing the dose level up to a maximum dose corresponding to [redacted] every 3 days. The treatment could also be prolonged beyond 4 weeks upon Investigator confirmation of a favorable benefit/risk profile in that patient.

Determination of sample size:	The 2 cohorts will be analyzed separately, a sample size for the Interventional phase has been calculated for each cohort. **Cohort 1:** In this cohort, patients intolerant or with inadequate response to GCs will receive other treatments, which occur in 60 to 70 % (Minoia et al. 2014 and Aytac et al. 2016). A successful treatment with GCs, when patients achieve response, can be expected in a proportion of patients up to 40 %. For a fixed study design, the sample size required for Cohort 1 (MAS in the context of sJIA and AOSD) to achieve a power of 80 % using a 1-sided exact binomial test at significance level of 2.5 % to test the null hypothesis: the proportion of CR is ≤ 40% versus alternative hypothesis: the proportion of CR is > 40%, if the truth is 70 % complete responders (De Benedetti et al. 2020), is 25 patients (nQuery 8, version 8.6.0.0). The NI-0501-14 study design is a group sequential design that includes an interim analysis assessing efficacy after the enrollment and treatment of 16 patients in Cohort 1. If efficacy is demonstrated at the time of the interim analysis, then the enrollment in this cohort will be stopped by the Sponsor; otherwise the enrollment will continue up to 25 treated patients Using clinical trial simulations, the overall type 1 error rate for the group sequential design described above is less than 2.5 % and the power is estimated to be 81.7 %. The type 1 error rate spent in the interim analysis (N=16 patients) is 0.5 % based on the 1-sided exact binomial test. The probability of type 1 error in the final efficacy analysis (N=25 patients), given that the study continues after the interim analysis, is 2.0 %. **Cohort 2:** An article by Liu et al. 2018, demonstrated that only 21.9 % of SLE patients with MAS received corticosteroids alone and did not require any other treatments. The assumption was made that patients in this cohort responded less frequently than in the other cohort: expected CR rate of at least 30 %. An exact binomial test at a 1-sided significance level of 2.5 % will have 82 % power to reject the null hypothesis CR rate of 30 %, if the truth is 70 % complete responders, when the sample size is 16 (nQuery 8, version 8.6.0.0).
Statistical methods:	The analysis of the primary endpoint, proportion of patients with CR at Week 8 after first administration of emapalumab, will be performed at Week 8 using an exact binomial test, separately for each cohort. For the Interventional phase: safety, PK, PD, immunogenicity will be summarized separately for each cohort and overall using descriptive statistics. PK and PD data will be evaluated as applicable using population modelling, potentially combining data from other studies. In such case, any PK or PK/PD modelling will be reported separately from the study. QoL data will be analyzed descriptively.

An interim clinical study report (CSR) will be prepared and submitted for the planned interim efficacy analysis once 16 treated patients in Cohort 1 have completed the Week 8 Assessment Visit, or earlier if patients have discontinued the study.

Further interim CSRs will be prepared once all patients in each cohort have completed the follow-up to Week 8 (i.e., patients who reach the Week 8 Assessment Visit or discontinue the study early). These interim CSRs may be used for regulatory submissions..

Finally, a full CSR including the safety follow-up period will be prepared once both cohorts reach the EOS.

2 Abbreviations and definition of terms

2.1 List of abbreviations and definitions

Term	Definition
ACR	American College of Rheumatology
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AOSD	Adult onset Still's disease
aPTT	Activated partial thromboplastin time
AS	Ankylosing spondylitis
AST	Aspartate aminotransferase
BCG	Bacillus Calmette-Guerin
BLA	Biologics license application
BMD	Bone mineral density
BMI	Body mass index
CBC	Complete blood count
CDASH	Clinical Data Acquisition Standards Harmonization
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CMV	Cytomegalovirus
CNS	Central nervous system
COVID-19	Coronavirus disease-19
CpG-ODN	CpG oligodeoxynucleotide
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CsA	Ciclosporin A

CSF	Cerebrospinal fluid
CSR	Clinical study report
CU	Compassionate use
CXCL9	Chemokine (C-X-C Motif) ligand 9
CXCL10	Chemokine (C-X-C Motif) ligand 10
CXCL11	Chemokine (C-X-C Motif) ligand 11
D	Day
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
EOT	End of treatment
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GC	Glucocorticoid
GCP	Good clinical practice
G-CSF	Granulocyte-colony-stimulating factor
GGT	Gamma-glutamyl transpeptidase
HbA1C	Glycated hemoglobin
HLH	Hemophagocytic lymphohistiocystosis
HV	Healthy volunteer
HZ	Herpes zoster
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
iDMC	Independent data monitoring committee
IDO	Indolamine 2,3-dioxygenase
IEC	Independent ethics committee
IFN-γ	Interferon-gamma

IL	Interleukin
ILAR	International League Against Rheumatism
IMP	Investigational medicinal product
IRB	Independent review board
IRR	Infusion-related reaction
i.v.	Intravenous
IVIG	Intravenous immunoglobulin
JAK	Janus kinase
KO	Knockout
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
M	Month
mAb	Monoclonal antibody
MAA	Marketing authorization application
MAS	Macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mPDN	Methylprednisolone
MRI	Magnetic resonance imaging
NAb	Neutralizing antibody
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
OR	Overall response
ORR	Overall response rate
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PDN	Prednisolone
PedsQL™	Pediatric Quality of Life Inventory™
pHLH	Primary hemophagocytic lymphohistiocytosis
PK	Pharmacokinetic
PLT	Platelets

PPD	Purified protein derivative
PR	Partial response
QoL	Quality of life
RBC	Red blood cell count
REB	Research ethics board
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sCD25	Soluble CD25 (i.e., soluble IL-2 receptor)
SD	Study day
sHLH	Secondary hemophagocytic lymphohistiocytosis
sJIA	Systemic juvenile idiopathic arthritis
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
Sobi	Swedish Orphan Biovitrum
SSC	Scientific steering committee
STAT1	Signal transducer and activator of transcription 1
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TLR9	Toll-like receptor 9
TNF	Tumor necrosis factor
ULOQ	Upper limit of quantification
UV	Unscheduled visit
VAS	Visual analog scale
WBC	White blood cell count
UV	Unscheduled visit

3 Data protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the participant identifiable will not be transferred.

The patient must be informed that his or her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.

The patient must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB or IEC members, and by inspectors from regulatory authorities.

4 Ethics

4.1 Independent ethics committee and institutional review board

It is the responsibility of the Investigator to obtain approval of the study protocol, possible amendments, and the written patient information and ICF from the IEC or IRB. The Investigator should file all correspondence with the IEC or IRB. Copies of IEC or IRB correspondence and approvals should be forwarded to Sobi.

4.2 Ethical conduct of the study

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

4.3 Patient information and consent

It is the responsibility of the Investigator to give each patient and the patient's acceptable representative prior to any study-related activities, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The patients must be informed about their right to withdraw from the study at any time. The written patient information and/or ICF must not be changed without prior discussion with the Sponsor. Before any revisions are implemented, the revised written patient information and/or ICF must be approved by the IEC, IRB, or REB as applicable.

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

5 Introduction

Study NI-0501-14 is a 2-cohort study that enrolls patients who are diagnosed with MAS and who are presenting an inadequate response to high doses of GCs. These patients will be enrolled in 2 cohorts as per their background disease. The cohorts are defined as follows:

- Cohort 1: MAS in the context of sJIA and AOSD.
- Cohort 2: MAS in the context of pediatric and adult SLE.

The study has the objectives to investigate the efficacy, safety and tolerability, PK and PD, and immunogenicity of emapalumab (an anti-IFN-γ mAb) in these 2 cohorts.

5.1 Background

HLH is a severe, potentially life-threatening, hyperinflammatory disorder caused by excessive activation and expansion of T lymphocytes and macrophages [3]. The uncontrolled expansion of these immune cells results in marked hypercytokinemia and a hyperinflammatory state characterized by fever, cytopenias, hepatosplenomegaly, liver dysfunction, coagulation abnormalities and hyperferritinemia, and may progress to multiple organ failure and death [4, 5]. There are 2 forms of HLH: primary or hereditary (caused by mutations in known genes) and secondary (reactive or acquired). sHLH can present at any age and may be associated with an infectious trigger, an underlying autoimmune rheumatic disease, or with an underlying malignancy, or can be idiopathic (i.e., present in the absence of identifiable infectious triggers or previously mentioned underlying diseases) [6].

5.1.1 HLH in the context of rheumatic diseases

sHLH presenting on an underlying rheumatic or autoimmune disease is usually referred to with the term MAS. It affects children and can also affect adults with various disorders. MAS is reported in Still's disease; it has also been observed in patients with other rheumatic diseases such as SLE.

The clinical presentation of MAS is typically acute and may become rapidly life-threatening with development of multiorgan failure. It can be as severe as pHLH and could lead to ICU admission in approximately one-third of MAS patients [7]. Clinical features at the onset of MAS include unremitting fever, hepatosplenomegaly, and lymphadenopathy. CNS involvement occurs in almost one-third of the patients and includes a wide spectrum of severity ranging from headache, lethargy, and irritability to disorientation, seizures, or coma. Hemorrhagic manifestations, from easy bruising and purpura to severe mucosal bleeding, are reported in approximately 20 % of cases. Characteristic laboratory features include marked hyperferritinemia, severe cytopenia, liver dysfunction with high levels of serum transaminases and coagulopathy with hypofibrinogenemia. Additional typical laboratory alterations are increased levels of triglycerides, LDH and D-dimer [8]. The 2016 MAS criteria were also tested in AOSD and were found to have an overall sensitivity of 100 %, and specificity of 70.0 % in discriminating between AOSD patients with and without MAS [9].

Approximately 7 to 17 % of patients with sJIA develop overt MAS [10]. Some evidence suggests that subclinical MAS may be seen in as many as one-third of patients with active systemic disease [11].

AOSD is considered the equivalent of sJIA with onset in adulthood [12]. Importantly, clinical similarities include a clear predisposition to develop MAS in both sJIA and AOSD [13] with as many as 20 % of AOSD patients developing MAS [14].

One of the largest available, retrospective, multicenter surveys has investigated the clinical, laboratory, and histopathological characteristics as well as current practice treatment and outcome of MAS in a total of 362 patients [15]. In approximately half of the patients, MAS occurred in the context of active sJIA, with a median time interval between the onset of sJIA and MAS of approximately 4 months. However, in about 25 % of patients MAS occurred at sJIA onset with the diagnosis of MAS and sJIA being done simultaneously. In about one-third of the patients, an infectious trigger was identified, most commonly EBV.

Because MAS is potentially fatal, a timely diagnosis and immediate therapeutic intervention are essential for appropriate management of the disease. Different sets of criteria have been proposed for MAS in patients with sJIA. The most recent and most used classification criteria are the EULAR/ACR approved criteria. These criteria were based on a combination of expert consensus, available evidence from the medical literature and analysis of real patient data. In the validation analyzes, these diagnostic criteria had a very high specificity [16].

MAS has been also increasingly reported to occur in patients with juvenile SLE, with a reported incidence ranging from 0.9 to 4.6 % [17].

MAS is most likely to develop concomitantly to the onset of childhood SLE [18]. In MAS with SLE, similarly to MAS in sJIA, fever has been reported as the most common clinical feature, followed by splenomegaly. Hyperferritinemia, hypoalbuminemia and increase in LDH are among the most common laboratory abnormalities [19-21]. In children, MAS on underlying SLE tends to be very severe; patients require more cardiovascular support and tend to have a higher need for an ICU care and for mechanical ventilation when compared to MAS in sJIA patients [7].

The clinical laboratory characteristics, treatment, and outcome of MAS complicating SLE were reported in 32 pediatric and young adult patients presenting MAS in a context of SLE [19]. In this study, MAS occurred in the setting of active underlying SLE in almost all patients. As an inciting factor, an infectious agent was detected in more than half of the patients. As in MAS with sJIA, EBV was the top causative pathogen identified.

Similarly to what is reported in pediatrics, MAS often occurs at the same time as the first adult SLE flare. In these patients, fever was observed in 100 % of the MAS episodes, increased serum levels of AST, LDH, and ferritin were frequently observed. These patients also tend to require a high rate of ICU admission [17].

As far as the diagnosis of MAS in patients with SLE, no criteria for classification or diagnosis of MAS in the setting of this disease has been developed. In this context, some papers have

reported that the sJIA-related EULAR/ACR criteria for MAS may be useful in guiding a timely diagnosis of MAS [22].

Treatment of MAS occurring on underlying rheumatic diseases

To the best of our knowledge, no prospective studies have been conducted to evaluate safety and efficacy of drugs currently used for the treatment of MAS, and no drug is approved for the treatment of MAS. The presently used approaches are based on data derived from case reports, retrospective surveys, or expert opinion.

High dose GCs are used as the cornerstone treatment for MAS. Indeed, in the large retrospective series from Minoia et al. nearly all patients were given GCs [15]. In patients failing to respond to GCs, CsA has been proposed as additional treatment since the early 2000 [23]. In the same large series mentioned above, ciclosporin was indeed the second most commonly used drug (61 % of patients) [15]. The mainstay treatment is represented by high dose GCs, which are effective in managing the disease in the majority of patients with or without CsA [24].

For patients failing treatment with GCs and CsA, a variety of treatments are typically applied, with none of them supported by more than some case reports or small case series. No data from prospective studies are available in the literature. In the large series mentioned above, other approaches used included IVIGs (36 % of the patients), various cytokine targeted biologics (15 % of the patients), including IL-1, IL-6, and TNF blockers, plasmapheresis and various immunosuppressant and chemotherapies [15].

Although IVIGs have been widely used in the past with the theoretical goal to deactivate macrophages, their efficacy appears to be very limited. The experience with drugs used to treat pHLH (e.g., etoposide) is also limited in patients with MAS. Because of their potential toxicities (cytopenia, immunosuppression, and secondary malignancy), etoposide has been reserved for refractory severe patients, for whom also hematopoietic stem cell transplantation has been reported as a potential therapeutic option. A reduced etoposide regimen has been proposed with the results available being limited to very few cases [25].

During the last decade, cytokine targeted therapy has become available and IL-1 and IL-6 inhibitors have been proven to be highly effective in the treatment of sJIA [26, 27]. Cytokine targeted approaches have been used, however, their role in the treatment of MAS remains unclear.

In the large clinical trials of biologics drugs inhibiting either IL-1 or IL-6, the reported rates of MAS were in the range to those described in the era before biologic agents and MAS presented even in patients with well controlled inactive sJIA [7, 26-31]. These observations demonstrated inhibition of IL-1 or IL-6 as not being fully protective against the development of MAS, and suggested that other factors and other cytokine pathway are involved in the pathogenesis of MAS.

Anakinra, a recombinant IL-1 receptor antagonist, has been used more commonly and data are described in some retrospective cohorts. Similarly to the 2 large trials mentioned above, MAS developed in many patients while receiving anakinra. Efficacy has indeed been reported in at least some of the patients, often associated with an increase in dose, varying from study to study

(up to and above 10 mg/kg/day in some cases) [24, 30, 32-36]. In some of these patients a recurrence of MAS episodes was observed when anakinra dose was reduced, making the cause-effect relationship difficult to be established [33, 36].

In MAS during SLE, data on treatment are scarce. This confirmed the absence of a standard treatment approach except for the use of GCs. In fact, similarly to MAS in sJIA, the treatment of MAS in SLE is primarily based on the parenteral administration of high doses of GCs. Early introduction of cyclophosphamide and ciclosporin have been used as soon as GCs seem to be insufficient, however no differences in outcome have been observed between patients who did or did not receive such additional treatments [20]. In the biggest published series on MAS in SLE, other additional approaches were considered, including IVIGs in 58 % of patients, oral calcineurin inhibitor, anti-IL-1, etoposide or other chemotherapy as well as plasmapheresis [18, 20]. Similarly to pediatric patients diagnosed with MAS in SLE, the treatment of adult MAS in SLE is mainly based on GCs as first line treatment with a MAS remission achieved in about two-thirds of cases. In this patient population, etoposide was used only in severe uncontrolled cases [17].

MAS remains a potentially fatal disease with a very dismal outcome. Overall, the mortality rate ranges between 8 % and 30 % [6, 19, 21, 23, 34].

Around 27 % of patients with MAS in sJIA required an ICU admission [7]. In this patient population, the mortality rate varied between 8 % and 22 % [6, 15].

In a recent report of patients treated with anakinra in MAS on a background of rheumatic or autoimmune diseases other than sJIA, mortality rate was 26 % [34]; 40 to 60 % of patients with MAS in SLE had been admitted to the ICU [7, 18, 20], and the mortality rate in this patient population varied between 5 % and 11.4 % [17, 18, 20].

More than 60 % of patients with MAS in rheumatological disease do not respond to systemic GCs when used alone. In these patients, the course of MAS may become rapidly irreversible leading to a fatal outcome, with about one-third of the patients still requiring ICU admission. Therefore, considering the absence of therapeutic options proven to be effective in all patients, and in the light of the dismal outcome of MAS, there is a high unmet medical need to develop a new drug for the treatment of these patients.

5.1.2 Emapalumab

5.1.2.1 Mode of action

Emapalumab (previously referred to as NI-0501, trade name Gamifant®) is a fully human immunoglobulin G1 (IgG1) anti-IFN-γ mAb that binds to and neutralizes IFN-γ. Emapalumab binds to both soluble and receptor (IFN-γ-R1)-bound IFN-γ.

5.1.2.2 Nonclinical data

5.1.2.2.1 Nonclinical pharmacology

Emapalumab is a high affinity mAb that potently neutralizes human IFN-γ. Emapalumab has shown similar binding affinity and blocking activity for IFN-γ in nonhuman species, including Rhesus and Cynomolgus monkeys, but not from dogs, cats, pigs, rabbits, rats, or mice.

No abnormalities in ECGs, histopathology of organs, and behavior of the animals were observed throughout the preclinical development of emapalumab. More details are available in the current IB.

5.1.2.2.2 Toxicology

Binding and functional data demonstrated that Rhesus and Cynomolgus monkeys were relevant species for evaluating the safety of emapalumab. No off-target toxicity was attributed to emapalumab when it was administered to Cynomolgus monkeys in 13 weekly doses of up to 200 mg/kg. Shigella and Campylobacter infections were observed at all dose levels (10 to 200 mg/kg/week) in animals originally harboring gastrointestinal pathogens (Shigella, Salmonella, Campylobacter) prior to emapalumab administration. These findings were assessed to be in line with the expected pharmacological effect of emapalumab (i.e., neutralization of IFN-γ), given the role played by IFN-γ 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 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.

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 IFN-γ 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 estrus 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 current IB.

5.1.2.3 Clinical data

5.1.2.3.1 Phase 1 experience

Emapalumab was evaluated in a randomized, double-blinded, placebo-controlled, single ascending dose phase 1 study (protocol NI-0501-03) in 20 HVs; 6 HVs received placebo and 14 received emapalumab i.v. at single ascending doses of [redacted].

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

The infusions of emapalumab were well tolerated. The monitoring after drug infusion did not reveal any serious or unexpected off-target safety or immunogenicity concerns. An HZ infection in a patient who was not receiving prophylaxis with acyclovir was reported as a serious adverse reaction in the highest dose group ([redacted]); the event resolved with conventional treatment.

Emapalumab was also evaluated in a phase 1, randomized, double-blinded, placebo-controlled, single center Japanese study (Study Sobi.EMAPALUMAB-102) to evaluate PK, PD, and safety of this drug after a single i.v. administration of emapalumab at 1 mg/kg. This study enrolled Japanese HVs. The PK profile of emapalumab in Japanese HVs appeared to be comparable to the profile in Caucasian HVs (see Section 7.2.5).

More details are available in the current IB.

5.1.2.3.2 Phase 2/3 experience

Study NI-0501-04 was an open-label, single arm, international, multicenter phase 2/3 study that evaluated the efficacy, safety, and PK/PD profiles of multiple i.v. administrations of emapalumab in pediatric patients with pHLH.

The dosing regimen in this study consisted of an initial emapalumab dose of [redacted] administered every 3 days during the first 2 weeks of treatment and subsequently twice-a-week, with the possibility of a dose increase to [redacted] and [redacted] and, if needed, to [redacted], based on clinical and laboratory criteria.

At the BLA/MAA cut-off date of 20 July 2017, 34 patients had been treated, of whom 7 patients had received emapalumab as front-line therapy. The primary efficacy endpoint was ORR at the EOT, defined as achievement of either a CR or PR or HLH improvement based on prespecified objective criteria. This pivotal trial showed that emapalumab was an efficacious targeted therapy. Accordingly, emapalumab received an approval by the FDA for the treatment of adult and pediatric (newborn and older) patients with pHLH with refractory, recurrent or progressive disease, or intolerance to conventional HLH therapy.

Study NI-0501-05 was a long-term surveillance study in which outcome data were collected for patients who had received at least one infusion of emapalumab in either Study NI-0501-04 or Study NI-0501-06. The protocol included a follow-up period of 1 year after HSCT or 1 year after last emapalumab infusion for patients not undergoing HSCT. No safety concerns emerged from the long-term safety surveillance.

Study NI-0501-06 was an open-label, single arm, multicenter phase 2 to evaluate the efficacy and safety of emapalumab in pediatric sJIA or in AOSD patients developing active MAS. The dosing regimen in this study consisted of an initial dose of [redacted] and continuation at the dose of [redacted] every 3 days (until SD15) and then twice-a-week afterwards.

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

Study NI-0501-10 was an open-label, single arm, multicenter phase 2/3 study to evaluate the efficacy, safety, and PK of emapalumab in adult patients with sHLH. The dosing regimen in this study consisted of an initial dose of [redacted] and continuation at the dose of [redacted] every 3 days (until SD15) and then twice-a-week afterwards. This study was prematurely terminated.

For more details on the clinical experience with emapalumab, please refer to the most recent version of the IB.

5.2 Study rationale

Rationale for developing emapalumab in sHLH

All forms of HLH, including MAS, are characterized by T cells and macrophage activation and expansion with overproduction of proinflammatory cytokines. Evidence has been accumulating in support of the pivotal role of IFN-γ in the development of pHLH [37] and in recent years in the development of sHLH, including MAS.

A mouse model of sHLH, in which the infectious trigger is mimicked by repeated stimulation of TLR9 with CpG-ODN, showed the salient features of the human disease, as well as elevated IFN-γ levels. When such stimulation is carried out in IFN-γ KO mice, anemia, thrombocytopenia, and splenomegaly are reduced, and hepatic inflammation is eliminated [38]. Furthermore, IFN-γ KO mice were recently shown to develop sHLH only following administration of CpG in combination with IFN-γ, providing evidence that cooperation between TLR9 and IFN-γ-dependent signals is both necessary and sufficient to cause sHLH: this cooperation involves expansion and activation of cells of the myeloid lineage [39]. Another study using the same model, based on repeated TLR9 stimulation, showed that tissue levels of IFN-γ were closely associated with hypercytokinemia and that antibody-mediated neutralization of the high rate of tissue production of IFN-γ was required for a significant reduction in inflammatory cytokines and of CXCL9 release and improvement in syndrome parameters [40].

Mice transgenic for human IL-6 (IL-6TG mice) mimic a chronic inflammatory condition, similar to sJIA, which is indeed characterized by high levels of pathogenic IL-6 [26, 41]. When challenged with lipopolysaccharide, as a mimicker of an infectious bacterial trigger, IL-6TG mice develop salient features of MAS, including hyperferritinemia, cytopenia and increased liver

function tests [42]. This model replicates the events leading to the occurrence of MAS in patients with sJIA often triggered by infection in the presence of active disease. In this model the syndrome is associated with a significant upregulation of the IFN-γ pathway, reflected by increased levels of IFN-γ mRNA, phosphorylated STAT1 in liver and spleen, and elevated expression of IFN-γ-inducible chemokines CXCL9 in liver, spleen and blood [43]. Administration of an anti-IFN-γ antibody to LPS-challenged IL-6TG mice improved survival and caused reductions in ferritin, fibrinogen, ALT and pro-inflammatory cytokine levels, including IL-1 β, IL-6, and TNF-α, as well as CXCL9 [43].

Overproduction of IL-18 has also been involved in the development of MAS, based on the observations that high levels of IL-18 are a risk factor for the development of MAS and that patients with active MAS have very high levels of IL-18 [44-46]. IL-18 appears to act upstream of IFN-γ, as signs and symptoms of HLH induced by TLR9 stimulation in IL-18 binding protein (a protein that binds to and inhibits the activity of IL-18) KO mice are blocked by an anti-IFN-γ antibody.

These data in models of sHLH and of MAS, together with the data obtained in models of pHLH, in which susceptibility is provided by the presence of mutations in the murine homologue of the causative genes in humans [37, 47, 48], all point to IFN-γ as a common final mediator of several different forms of HLH, independently of the genetic, environmental factors involved in the initial pathogenesis and triggering of the syndrome.

Data from patients with sHLH and MAS supported the pathogenic role of IFN-γ:

- Initial studies on small number of patients with pHLH have shown elevated levels of IFN-γ [5, 49]. This finding was also reported later in patients with sHLH, either triggered by infections or with MAS occurring in the context of sJIA or SLE.

  In 14 patients with sHLH (in 7 of whom a triggering infection was identifiable), serum samples were analyzed during active full-blown disease and during disease remission. Levels of IFN-γ, CXCL9, and CXCL10 (2 IFN-γ-induced chemokines) were markedly higher in the active phase compared to disease remission. The levels of IFN-γ and chemokines (and particular CXCL9) correlated significantly with parameters of disease severity, such as neutrophil and platelet counts, ferritin and ALT, further supporting the pathogenic role of IFN-γ in sHLH [40].

- Serum levels of IL-1β, IL-6, IFN-γ, CXCL9, CXCL10, and CXCL11 were assessed in 20 patients with MAS and 54 patients with sJIA. Levels of IFN-γ, but not of IL-1β or IL-6 were higher in patients with MAS compared to those with active sJIA, but without MAS. During MAS, ferritin and ALT levels, and neutrophil and platelet counts were significantly correlated with serum levels of IFN-γ [50]. In particular, in patients with MAS, CXCL9 levels are strictly correlated with laboratory parameters that reflect disease severity, including ferritin levels, cytopenia, and ALT and LDH levels [50, 51]. Incidentally, CXCL9 has also been found to be elevated in adults with MAS during AOSD [52]. As CXCL9 production appears to be induced only by IFN-γ stimulation

[53], these strong correlations with parameters of MAS severity further support the role of IFN-γ.

- In SLE patients, the levels of CXCL9 were found to be significantly elevated in the MAS phase compared with those in the active phase of SLE. Elevated serum levels of CXCL9 during the MAS phase were strongly correlated with other inflammatory markers, reflecting the disease activity of MAS associated with SLE, supporting the conclusion that also in SLE associated MAS the IFN-γ pathway is activated [54].

In addition to data from peripheral blood, some studies have reported activation of the IFN-γ pathway in tissue targeted by the disease. Overexpression of IFN-γ was found in liver tissues taken from 5 children with various sHLH [55]. A marked staining for the IFN-γ-inducible proteins CXCL10 and indolamine 2,3-dioxygenase was observed in a lymph node from a patient with active MAS [56]. Moreover, markedly increased mRNA expression of IFN-γ and IFN-γ-inducible genes and high levels of phosphorylated STAT1 were observed in liver biopsies from patients with sHLH [57]. These results show increased expression of IFN-γ and of IFN-γ-inducible proteins within tissues targeted by the disease, and are consistent with the findings in the sHLH TLR9 model, as well as in the MAS IL6TG model, in which high tissue expression was observed and in which neutralization of IFN-γ or genetic deletion of IFN-γ were associated with significantly decreased liver inflammatory infiltrate [38, 40, 43].

Altogether, the data in animal models and in patients with MAS and sHLH point to the key role of overproduction of IFN-γ in driving signs and symptoms of these diseases. Initial experience with emapalumab in the treatment of MAS in the context of sJIA are indeed consistent with this key role of IFN-γ. Data from Study NI-0501-06 demonstrated that emapalumab allowed rapid and permanent tapering of GCs and led to rapid neutralization of IFN-γ, as demonstrated by a rapid decrease in CXCL9 levels. The data also documented the efficacy of emapalumab in patients presenting with different patterns of MAS (during disease course, at onset, and persisting-relapsing). In this study disease remission was achieved in 11/14 patients at Week 8. These results supported the hypothesis of a role of IFN-γ in MAS, demonstrating that IFN-γ is pathogenic in MAS patients. Treatment with emapalumab in this clinical study, at the investigated dose and regimen, was safe and well tolerated. One CMV reactivation reported by the Investigator as an SAE possibly related to emapalumab resolved with standard treatment (De Benedetti et al, 2021 [unpublished abstract]).

Some single case reports have been recently published in which emapalumab was administered on a CU regimen. Lounder and colleagues reported on a patient with refractory EBV-associated HLH, who was successfully treated with emapalumab, despite severe pre-existing comorbidities, including multiple active life-threatening infections at baseline [58]. Furthermore, one patient with AOSD and MAS was reported to be successfully treated with emapalumab following failure of GC pulses and anakinra [59].

All together these observations support the development of emapalumab in MAS patients who responded inadequately to high dose GCs and who are expected to benefit from a targeted therapy aiming at IFN-γ neutralization.

5.3 Potential risks and benefits

5.3.1 Potential benefits

More than 60 % of patients presenting MAS may not respond to systemic GCs and have limited alternative therapeutic options. These options are represented by prolonged treatment with high doses of GCs, administration of CsA or chemotherapy such as etoposide, and off-label biologics (such as anakinra or tocilizumab), with a carried risk of additional toxicity. For patients not responding to available treatments, alternatives should aim to obtain remission of MAS with no or limited safety issues.

Targeted neutralization of IFN-γ with emapalumab represents a promising treatment. In fact:

- In an animal model of MAS, administration of an anti-IFN-γ showed the recovery and/or remission of the signs and symptoms associated with hypercytokinemia. For more details please refer to Section 5.2.
- Observational studies in MAS and sHLH have shown a strong correlation of biomarkers of activation of the IFN-γ pathway (IFN-γ as well as IFN-γ induced chemokines) with disease parameters at onset and during disease evolution in MAS and sHLH. For more details please refer to Section 5.2.
- Having shown efficacy in pHLH, emapalumab was approved by the FDA in November 2018 for the treatment of patients with pHLH who have refractory, recurrent or progressive disease or intolerance with conventional HLH therapy [60].
- The targeted neutralization of IFN-γ by emapalumab in Study NI-0501-06 is presenting a promising response in patients with MAS occurring in the context of sJIA. For more details please refer to Section 5.2.

5.3.2 Potential risks

Infections:

As emapalumab neutralizes IFN-γ activity, emapalumab may increase the risk of infections caused by some specific pathogens potentially favored by IFN-γ neutralization including mycobacteria (typical and atypical), Salmonella, and Histoplasma capsulatum. Study specific requirements should be followed for infection screening, prophylaxis, and monitoring.

The impact on the immune defense caused by the neutralization of IFN-γ is known from patients with inborn errors of the IL-12/23-IFN-γ circuit, particularly patients with complete or partial IFN-γ receptor deficiency, and patients developing neutralizing anti-IFN-γ auto-antibodies. Patients with IFN-γ R deficiency are prone to develop mycobacterial infections and, although to a lesser extent, Salmonella infections [61].

Individuals with anti-IFN-γ auto-antibodies are also susceptible to develop mycobacterial infections, particularly atypical mycobacterial infections, but also opportunistic infections, caused by for example, Histoplasma capsulatum, and Salmonella [62].

Toxicological studies carried out with emapalumab have shown an increased susceptibility to enteral pathogen infections in monkeys having received emapalumab, when the enteral pathogen was present in the intestinal tract prior to emapalumab administration.

As to the development of infections caused by pathogens known to be favored by the absence of IFN-γ biological activity, cumulatively, among the 131 patients that have received emapalumab in completed or ongoing clinical trials up to the safety data cut-off point of 24 August 2021, the following serious events related to emapalumab treatment have been reported:

- A case of HZ infection was reported in a HV, and recovered with antiviral treatment.
- One pHLH patient developed disseminated histoplasmosis, which resulted in treatment discontinuation. The infection resolved with adequate antifungal therapy while emapalumab was still at measurable concentrations in the blood.
- One previously vaccinated pHLH patient developed BCG adenitis that resolved with appropriate therapy.
- A MAS/sJIA patient had a CMV infection reactivation.

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

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

For further information on the occurrence of infections under emapalumab, please refer to the most recent IB.

Infusion-related reactions and hypersensitivity:

IRRs are commonly associated with mAb infusions and are defined as signs or symptoms with a temporal relationship to the administration of an infusion and assessed as related, typically occurring soon after the start of the infusion, although symptoms may be delayed for up to 24 hours. They might be limited, e.g., local skin reactions, or systemic reactions, such as anaphylaxis.

Cumulatively, 131 patients have received emapalumab in completed or ongoing clinical trials up to the safety data cut-off point of 24 August 2021, no patient experienced anaphylactic or anaphylactoid reactions:

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

For further information on IRRs occurring with emapalumab, please refer to the most recent IB.

Immunogenicity:

The immunogenicity of emapalumab has been evaluated in all clinical studies.

In completed studies in the emapalumab development program, ADAs against emapalumab were detected in a small number of patients (approximately 5%) with no impact on safety or efficacy parameters.

For further information on the immunogenicity of emapalumab, please refer to the most recent IB.

5.3.3 Risk minimization measures

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

- The ongoing study has been designed in consultation with MAS scientific experts.
- The study patients are managed in specialized centers for the treatment of MAS. The centers are equipped with all necessary emergency assistance devices.
- Patients with clinically active or latent (in case of TB) infection by mycobacteria, Histoplasma, and/or Salmonella are excluded from the study.
- Close monitoring for HZ infection; prophylaxis for HZ virus infection should be considered according to the Investigator's own benefit-risk assessment. A prompt initiation of anti-HZ therapy is crucial in case of any clinical signs and symptoms, or in case of any confirmed HZ infection.
- Close monitoring for potential infections through careful physical examination, laboratory parameters, active search for infections at Screening, during the treatment period and when clinically indicated are required per protocol.
- The study will be performed under the surveillance of an iDMC.

5.4 Considerations for patients during the COVID-19 pandemic

MAS is a fatal disease with an overall mortality ranging between 8 and 30 %. In the patient population enrolled in Study NI-0501-14, MAS is typically acute, its onset is unpredictable, and it may become rapidly life-threatening with development of multiorgan failure; around one-third of MAS patients require an ICU admission. Therefore, treatment of MAS must be initiated as soon as possible and the benefit/risk of using specific drugs intended to either treat MAS or COVID-19 must be assessed considering the life-threatening nature of the disease.

In the light of the emapalumab safety profile and given that emapalumab has been investigated in pHLH and sHLH with a positive benefit-risk observed so far, Sobi is of the opinion that the benefits of treating with emapalumab in the context of COVID-19 infection outweigh the risks.

In regards to vaccination, the protocol prohibits receipt of live and live attenuated vaccines (Section 7.1.3.2). However, patients enrolled in Study NI-0501-14 have an underlying chronic

rheumatological condition that might lead to the recommendation to vaccinate. The decision to vaccinate against SARS-CoV-2 and the timing of the vaccination are at the discretion of the Investigator and should preferably be in accordance with the approved vaccines product information and official recommendations. This should not preclude treatment of an acute life-threatening disease with emapalumab, the latter having shown promising efficacy and a favorable safety profile in the pilot study NI-0501-06.

6 Study objectives and endpoints

Given the absence of validated endpoints, the experience accumulated to date in MAS in Still's disease, the input from recognized experts in the field of pediatric rheumatology and the data in the scientific literature have all been used to compile the response criteria.

Therefore, in patients with MAS, a CR (i.e., MAS remission) should be anticipated. Accordingly, criteria for efficacy response in this study are defined as presented in Table 1 for Cohorts 1 and 2.

Data from literature has shown that the Week 8 response is a highly predictive factor in the long-term disease outcome [63, 64]. Accordingly, Week 8 has been chosen as the time point to evaluate the primary endpoint in this study. The clinical course of medical conditions triggering HLH, the mechanism of action of emapalumab and the experience accumulated to date in pHLH and MAS in sJIA were additional factors in defining the timepoint of the primary analysis.

Given that patients diagnosed with MAS may require recurrent or prolonged treatment at high doses of GCs with an associated significant morbidity, the tapering of GCs is considered as an important outcome.

Table 1 Response criteria definition – Cohort 1 and Cohort 2

CR (i.e.,. MAS remission)	Resolution of clinical signs and symptoms present at baseline: MAS clinical activity will be measured on a 10 cm VAS. Clinical signs will be considered resolved if VAS is below or equal to 1/10. And Normalization of laboratory parameters relevant to MAS, as follows: • WBC > LLN • Platelet count > LLN • LDH < 1.5 ULN • ALT < 1.5 ULN • AST < 1.5 ULN • Fibrinogen > 100 mg/dL • Ferritin levels decreased by at least 80 % from values at Screening or baseline (whichever is higher) or < 2000 ng/ml, whichever is lower.
PR	Resolution or improvement in clinical signs and symptoms measured by the MAS clinical activity on the VAS. The patient will be classified as PR if he or she presents a VAS < 4/10 And Normalization of at least 3 of the abnormal baseline laboratory parameters relevant to MAS, as defined above.

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CR, Complete response; LDH, Lactate dehydrogenase; LLN, Lower limit of normal; MAS, Macrophage activation syndrome; PR, Partial response; ULN, Upper limit of normal; VAS, Visual analog scale; WBC, White blood cell.

Please refer to Section 7.3.3 for more information on the clinical signs and symptoms to be considered for the evaluation of the MAS clinical activity.

6.1 Primary objective

- To demonstrate efficacy of emapalumab in the treatment of patients in:
  - Cohort 1: MAS in the context of sJIA and AOSD.
  - Cohort 2: MAS in the context of pediatric and adult SLE.

6.1.1 Primary efficacy endpoint

- Proportion of patients with CR at Week 8 after first administration of emapalumab.

6.2 Secondary objectives

- To demonstrate efficacy of emapalumab with respect to tapering of GCs.
- To evaluate the time to onset of response to emapalumab treatment.
- To evaluate efficacy of emapalumab with respect to OR.
- To evaluate the sustained efficacy of emapalumab treatment.

- To evaluate the patient's survival after treatment with emapalumab.
- To evaluate the safety and tolerability of emapalumab.
- To evaluate patient-reported outcome of MAS in patients treated with emapalumab.
- To determine the PK profile of emapalumab.
- To determine the PD profile of emapalumab.
- To determine the immunogenicity of emapalumab.

6.2.1 Secondary endpoints

- GCs tapering to a dose < 50 % of PDN equivalent at the time of emapalumab start or to the same (or lower) dose being administered before the occurrence of MAS (in patients already treated for the underlying condition), whichever occurs first at any time during the study.
- GCs tapering to ≤ 1 mg/kg/day of PDN equivalent at any time during the study.
- Time to achieve GCs tapering (as defined in the 2 bullets above).
- Time to first CR.
- Proportion of patients with OR as defined by CR or PR.
- Time to first OR as defined by CR or PR.
- MAS recurrence at any time after achievement of CR.
- Withdrawal from the study due to lack of response as per Investigator decision.
- Survival time.

6.2.1.1 Safety endpoints

- Incidence, severity, causality and outcomes of AEs (serious and nonserious).
- Withdrawal from the study treatment due to safety reasons.
- Changes from baseline in relevant laboratory parameters, vital signs, physical examinations, and ECGs.

6.2.1.2 Patient-reported outcome endpoints

- Health-related QoL: Pediatric QoL Inventory (PedsQL™; Generic Core Scales and Infant Scales, Acute versions). Link to examples of questionnaires also applicable to adults is provided in Appendix 1.
- Global Assessment: Patient/Parent Global Impression of Severity. Example is provided in Appendix 1.
- Global Assessment: Clinician Global Impression of Severity (see Appendix 1).

6.2.1.3 PK endpoints

- Serum concentrations of emapalumab.

6.2.1.4 PD endpoints

- Levels of circulating free IFN-γ at predose, and total IFN-γ (free IFN-γ + bound to emapalumab) after initiation of the study drug.
- Levels of the main IFN-γ-induced chemokines (CXCL9, CXCL10).
- Levels of MAS markers (sCD25).

6.2.1.5 Immunogenicity endpoints

- Occurrence of ADAs and NAbs to emapalumab.

6.3 Exploratory objectives

[redacted]

6.3.1 Exploratory endpoints

[redacted]

7 Investigational plan

7.1 Overall study design and plan

7.1.1 Discussion of study design

7.1.1.1 Overall study design

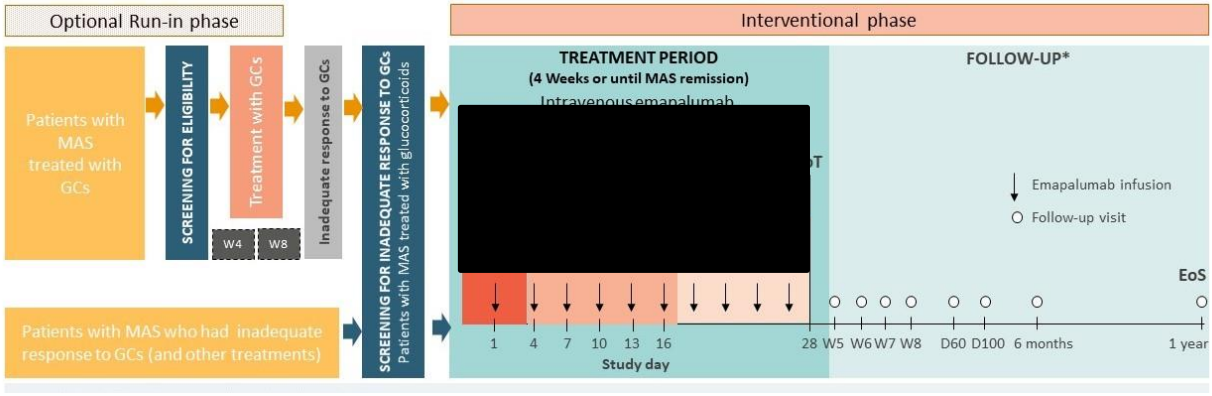
Study NI-0501-14 is an open-label, 2-cohort, single arm, multicenter, interventional, phase 2/3 study.

The study enrolls pediatric and adult patients between 6 months and 80 years of age with different etiologies of MAS. These patients will be assigned to different cohorts as per their underlying disease:

- Cohort 1: MAS in the context of sJIA and AOSD.
- Cohort 2: MAS in the context of pediatric and adult SLE.

Each cohort in this study is designed as a single arm study and will be composed of 2 phases; one Run-in phase and one Interventional phase, see Figure 1.

Figure 1 Overview of study design for study NI-0501-14



Abbreviations: D, Day; EOS, End of study; EOT, End of treatment; GCs, Glucocorticoids; MAS, Macrophage activation syndrome; SD, Study day; W, Week.

The Run-in phase will enroll patients as defined in Cohorts 1 and 2, and requiring treatment with GCs. These patients will be treated as per Investigator decision. Patients will be followed for a maximum of 12 weeks, or until reaching a MAS remission as per Investigator assessment, or until presenting an inadequate response to GCs as assessed by the Investigator, whichever occurs first.

The Interventional phase enrolls patients fulfilling the eligibility criteria as described in the inclusion/exclusion criteria, Section 7.1.3. It should be noted that patients meeting eligibility criteria of the Interventional phase could be enrolled directly without having to undergo the Run-in phase.

A total of 41 patients are planned to be enrolled in the Interventional phase: 25 patients (of these at least 16 pediatric patients) in Cohort 1, and 16 patients (of these at least 6 pediatric patients) in Cohort 2.

Every effort should be taken to enroll patients starting from the Run-in phase (i.e., before starting treatment with GCs). However, it should be noted that this phase is not compulsory, therefore patients can join the study directly in the Interventional phase. Patients who also failed GCs plus other MAS therapies and meet all the eligibility criteria may be enrolled in the Interventional phase. If at any time during the Run-in phase, patients present an inadequate response to GCs and additionally meet all eligibility criteria of the Interventional phase, they will be invited to continue into the Interventional phase of the study.

Enrollment in the Run-in phase will be achieved when the last patient of the Interventional phase is enrolled. At the time of completion of enrollment into the Interventional phase, patients completing the Run-in phase will not be denied treatment with emapalumab and enrollment into the Interventional phase if needed, and upon fulfillment of all eligibility criteria.

For Cohort 1, the design and execution of the study is intended to recruit an adequate proportion of patients (at least 5) who had no prior treatment with biological agents or had undergone washout for such drugs (i.e., 5 half-lives must have elapsed from the last dose of the biologic).

A re-treatment with emapalumab is allowed during the Long-term follow-up period of the study if patients present a recurrence of MAS.

An interim analysis assessing efficacy will be performed after 16 treated patients in Cohort 1 have reached 8 weeks after first dose of emapalumab, or earlier if the patients discontinued the study. Enrollment in Cohort 1 may be closed upon results of this interim analysis. The data from the interim analysis will be used for regulatory submission purposes.

An extension study to provide post-study access to emapalumab is not planned. Access to emapalumab for patients who completed the study will be considered upon request of the Investigator. The Sponsor will assess the evidence of benefit with the Investigator, on a case by case basis. If a positive individual benefit risk assessment is confirmed, and if applicable per national regulatory requirements, emapalumab may be provided to individual patients, and administered under the Investigator`s responsibility.

7.1.1.2 Rationale of the study design

The study is designed mainly to address the rarity of MAS forms under evaluation for which clinical data on the possible therapeutic options for patients who failed to respond to high dose GCs are limited.

The Run-in phase of this study is designed to provide data on MAS response to standard GC therapy; the data will support the characterization of the evolution of MAS under GCs treatment and provide data on the incidence of inadequate response to GCs. This phase will also support the identification of patients naïve to treatment with biologic agents.

The Interventional phase of this study is designed to gather evidence on emapalumab and to generate efficacy and safety data that could potentially support a marketing approval for emapalumab as a treatment of MAS.

The choice of the 2 cohorts in this study is mainly based on the similarities and differences that would exist between the different underlying diseases and to MAS with regard to the clinical presentation, the treatment, and the outcome.

AOSD is a rare autoinflammatory disorder sharing the same clinical manifestations and laboratory findings of sJIA [12]. Although traditionally they have been viewed as separate disease entities, there is growing recognition that sJIA and AOSD represent a disease continuum with different ages of onset, based on a number of shared clinical, genetic, and laboratory features, as well as a strikingly similar response to IL-1 and IL-6 inhibitors [65-68]. Numerous reports are suggesting that, at least for the cardinal features, (spiking) fevers, arthritis, arthralgia, skin manifestations and leukocytosis, neutrophilia, sJIA and AOSD cohorts show clear similarities [12, 66]. Also the overall disease course and prognosis have been reported to be similar for sJIA and AOSD [69, 70]. Importantly, clinical similarities include a clear predisposition to develop MAS in both sJIA and AOSD [13]. AOSD and sJIA being considered as one disease (Still’s disease) with MAS in this indication having the same mechanism,

treatment, and treatment outcome. Therefore, it appears justifiable to allow the inclusion of this population together with the sJIA patients, in order to optimize the potential collection of data in these patients and to potentially gather information on the utility of emapalumab in this population.

SLE is a lifelong autoimmune disease that does not share any clear similarities with Still's disease. Data from the literature would allude that SLE patients presenting MAS behave slightly different from the sJIA patients [7]. MAS patients with an underlying SLE diagnosis appear to have more organ system dysfunction at their index MAS episode than children with sJIA. They also seem to have a higher rate of ICU admission and a higher CNS involvement rate. These patients are reported with a mortality rate reported up to 22 % in MAS in Still's disease [15] and up to 11 % in MAS in SLE [17].

Due to the clinical differences that are reported between MAS in Still's disease and MAS in SLE, to the absence of any published data supporting the biological similarities between MAS in SLE and MAS in Still's disease, and considering the outcome of these patients when they fail the standard treatment, this study was designed to include these patients presenting MAS and failing GCs in 2 different cohorts.

7.1.2 Study periods

The patient's participation in the Run-in phase of the study comprises 2 parts: Screening, and GCs treatment period.

The patient's participation in the Interventional phase of the study comprises 3 parts: Screening, emapalumab treatment period, and follow-up, as shown in Table 2.

Table 2 Overview of the Interventional phase design in study NI-0501-14

Screening Up to 1 week prior to VIP 1	Treatment period (4 weeks)		Follow-up					
	Initial dose [redacted]	Subsequent doses [redacted]	Follow-up to Week 8 (4 weeks)[b]		Long-term follow-up (after last dose of emapalumab)[c,d]			
	VIP 1 (SD1)	VIP 2 (SD4) and onwards	Weeks 5, 6, 7 visits (SD35-42-49)	Week 8 visit (SD56)	D60	D100	M6	Y1

Abbreviations: CR, Complete response; D, Day; EOS, End of study; M, Month; MAS, Macrophage activation syndrome; SD, Study day; VIP, Visit Interventional phase; Y, Year.
Note: The dose of [redacted] will be administered every 3 days until SD16, and then twice-a-week for an additional 2 weeks, i.e., until SD28. Treatment can be stopped before SD28 if the patient reached a CR.
Note: In the absence of a trend of improvement in key MAS clinical and laboratory parameters suggestive of a lack of response, the emapalumab regimen may be adapted by shortening the interval between the infusions (from every 3 days to every 2 days and subsequently if judged further necessary from every 2 days to each day), or by increasing the dose level up to a maximum dose corresponding to [redacted] every 3 days. The treatment could also be prolonged beyond 4 weeks upon Investigator confirmation of a favorable benefit/risk profile in that patient.
Note: D60 and D100 are 60 days and 100 days after last dose of emapalumab, respectively. M6 is 6 months after last dose of emapalumab, and Y1 is 1 year after last dose of emapalumab.
[a]Additional MAS treatments allowed in case of unsatisfactory MAS control after 3 doses of emapalumab. It is expected that VIP 2 will occur on SD4, however if the Investigator chooses to reduce the interval between doses, this visit may occur on another study day, which should be noted in the eCRF.
[b]In the treatment period up to Week 8 the patient will be followed up to SD56. The count starts from SD1.
[c]In the Long-term follow-up (D60 up to EOS) the count starts from last dose of emapalumab.
[d]Patients who relapse during the Long-term follow-up period of the study can be re-treated with emapalumab following the same dosing regimen.

7.1.2.1 Screening period

Each of the study phases (the Run-in phase and the Interventional phase) will have its own screening period.

Written informed consent for participation in the study must be obtained before study specific screening tests are performed for either of the study phases.

Note: the Run-in phase is not mandatory; patients can join the study directly in the Interventional phase.

Evaluations performed before ICF signature, as per routine care, will be accepted for screening purposes if done in the 15 days prior to the first dose of study drug. This will be explicitly explained in the ICFs. In the event where tests are older than 15 days prior to first dose or in a case of any new clinical signs suggestive of infection or brain involvement, abnormal or old assessments will have to be repeated.

The Investigator should keep a log of the patients screened and the reasons for noneligibility. ICFs for enrolled patients in each of the study phases and for patients who are not subsequently enrolled will be maintained at the study site.

In each of the study phases, after giving written informed consent, patients who are willing to participate in the study will undergo screening assessments within 1 week prior to Visit 1 at SD1. Patients must fulfill all the study entry criteria and the eligibility criteria evaluation must be available prior to the first visit.

In rare cases of unexpected delay due to logistical or technical reasons, it may be necessary to extend the screening period by 1 week. Extending the screening period beyond 1 week must be prospectively approved by the Sponsor, and should be in exceptional circumstances only; careful scheduling should remain a priority.

Patients may only be rescreened once if there is a substantial change in the patient's condition (e.g., a prohibited medication was stopped). 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.

In case a patient is enrolled in the Interventional phase and if medical condition warrants rapid treatment initiation, availability of the results for infection assessment at 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, in this case, samples for infection screening need to be collected for analysis prior to first administration of emapalumab according to the protocol requirements.

Patients enrolled in the Run-in phase and presenting an inadequate response to GCs must sign a new ICF and undergo the screening assessment of the Interventional phase form prior to start treatment with emapalumab.

7.1.2.2 Treatment period

7.1.2.2.1 Glucocorticoid treatment period - Run-in phase

Patients in each of the cohorts enrolled in the Run-in phase must be treated with GCs for MAS. The dose of GCs should be administered as per Investigator decision. Patients will be followed as per Table 4 for a maximum of 12 weeks, or until reaching a MAS remission as per Investigator assessment, or until presenting an inadequate response to GCs, as assessed by the Investigator, whichever occurs first. Patients presenting an inadequate response to GCs can join the Interventional phase.

7.1.2.2.2 Emapalumab treatment period - Interventional phase

Patients in each of the cohorts enrolled in the Interventional phase will be treated with emapalumab for 4 weeks. However, it is not expected that treatment duration will be the same across the study population of each cohort.

Treatment shall continue until a MAS remission as per Investigator assessment is achieved. In the case of MAS remission met prior to 4 weeks, treatment may be shortened, as per Investigator

assessment. However, at least 3 infusions of emapalumab must be administered before study drug discontinuation, except in the case of a major safety concern.

In the absence of a trend of improvement in the key MAS clinical and laboratory parameters (including but not limited to ferritin, LDH, AST, ALT and PLT count) suggestive of a lack of response, the emapalumab regimen may be adapted by shortening the interval (from every 3 days to every 2 days and subsequently if judged further necessary from every 2 days to each day) between the infusions, or by increasing the dose level up to a maximum dose corresponding to [redacted] every 3 days. The treatment could also be prolonged beyond 4 weeks upon Investigator confirmation of a favorable benefit/risk profile in that patient. The clinical and laboratory data guiding the Investigator's decision on dose adaptation or treatment prolongation should be reported on the eCRF.

Patients will undergo an EOT assessment at the Week 4 assessment visit, 3 days after the last Week 4 infusion of emapalumab. In case treatment is shortened, an 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 EOT visit should be performed.

If MAS recurs or reactivates after a satisfactory response during the off-drug Long-term follow-up period (i.e., after Week 8), re-treatment with emapalumab can be reinstated. In such a case the patient can be treated with the same treatment schedule.

7.1.2.3 Follow-up period

The follow-up period will be applicable only for patients treated with emapalumab.

This follow-up period is divided into 2 phases. One follow-up period where patients will be followed weekly for 4 weeks up to Week 8 (SD56), followed by Long-term follow-up.

At the end of the follow-up to Week 8, patients will undergo a follow-up assessment. This visit is expected to take place at Week 8 from first dose of emapalumab and will serve to assess the primary efficacy endpoint of the study. The Week 8 visit should occur regardless of when the patient completed their study treatment.

The Long-term follow-up will start after treatment discontinuation or treatment completion, and will continue up to 1 year after last emapalumab administration.

Patients re-treated with emapalumab will be followed up to 1 year from the last dose of emapalumab received during the re-treatment, or until the EOS (Section 12), whichever occurs first. In either case, these patients should have a minimum of 4 weeks of follow-up.

7.1.3 Study population

Patients eligible in this study are male and female pediatric and adult patients diagnosed with either Still's disease or SLE and developing MAS as per the MAS diagnosis criteria [16].

These patients should have been treated with GCs for MAS and should be presenting an inadequate response to GCs before starting treatment with emapalumab.

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

7.1.3.1 Inclusion criteria

Run-in phase in all cohorts

1. Informed consent provided by the patient or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as required by local law.
2. Male and female patients aged between 6 months and 80 years of age at the time of diagnosis of active MAS.
3. MAS defined as per the criteria defined below for each cohort and requiring treatment with GCs as per standard of care.

Interventional phase in all cohorts

1. Informed consent provided by the patient or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as required by local law.
2. Male and female patients aged between 6 months and 80 years of age at the time of diagnosis of active MAS.
3. Patients who have shown an inadequate response to high dose i.v. GCs administered for at least 3 days according to local standard clinical practice, including but not limited to pulses of 30 mg/kg mPDN on 3 consecutive days. High i.v. GCs dose is recommended not be lower than 2 mg/kg/day PDN equivalent (or at least 60 mg/day in pediatric patients of 30 kg or more and at least 1 g/day in adult MAS patients). In case of rapid worsening of the patient's condition and/or laboratory parameters, as per Investigator judgment, inclusion may occur within less than 3 days from starting high dose GCs.

4. Diagnosis of active MAS confirmed by the treating rheumatologist, having ascertained the following (Appendix 3):
    a. Febrile patients presenting with ferritin > 684 ng/mL
    b. and any 2 of:
        i. Platelet count ≤ 181 x10^9/L
        ii. AST-level > 48 U/L
        iii. Triglycerides > 156 mg/dL
        iv. Fibrinogen level ≤ 360 mg/dL
5. Female patients of childbearing potential (sexually or nonsexually active). Female patients who are sexually active must be willing to use highly effective methods of contraception from study drug initiation to 6 months after the last dose of study drug (see Section 7.1.3.1.1).

Specific inclusion criteria for Cohort 1 and Cohort 2

1. Cohort 1:
    a. Confirmed sJIA diagnosis. For patients presenting with MAS in the context of the onset of sJIA, high presumption of sJIA (Appendix 4) will suffice for eligibility.
    b. Confirmed diagnosis of AOSD as per Yamaguchi criteria (Appendix 5).
2. Cohort 2:
    a. Confirmed diagnosis of SLE as per SLICC 2012 criteria (Appendix 6).

7.1.3.1.1 Pregnancy and breastfeeding

Sexually active female patients of childbearing potential* are expected to use highly effective methods of contraception during dosing and for 6 months after last dose of study drug.

Highly effective contraception methods include:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral.
    - Intravaginal.
    - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral.
    - Injectable.
    - Implantable.
- Intra-uterine device.
- Intra-uterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomised partner.

- Sexual abstinence.

*Please note: a woman is considered to be of childbearing potential, i.e., fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

7.1.3.2 Exclusion criteria

1. pHLH documented by either the presence of a known causative genetic mutation or abnormal perforin expression or CD107a degranulation assay as described with pHLH or by the presence of family history.
2. Confirmed malignancy. Note: patients with a suspected malignancy should have mononuclear cells typed by flow cytometry and/or tissue biopsy, as applicable, to rule out malignancy.
3. Treatment with canakinumab, JAK inhibitors, TNF inhibitors, and tocilizumab at the time of emapalumab initiation.
4. Ongoing treatment with anakinra at a dose above 4 mg/kg/day at time of emapalumab initiation.
5. Patients treated with etoposide for MAS in the last 1 month.
6. Presence of any medical or psychological condition or laboratory result that in the opinion of the Investigator can interfere with the patient's ability to comply with the protocol requirements or makes the patient not appropriate for inclusion to the study and treatment with emapalumab.
7. Foreseeable inability to cooperate with given instructions or study procedures.
8. Clinically active mycobacteria (typical and atypical), Histoplasma capsulatum, or Salmonella infections.
9. Evidence of leishmania infection.
10. Evidence of latent TB.
11. History of hypersensitivity or allergy to any component of the study drug.
12. Receipt of a BCG vaccine within 12 weeks prior to Screening.
13. Receipt of a live or attenuated live (other than BCG) vaccine within 4 weeks prior to Screening.
14. Pregnancy or lactating female patients.

7.1.4 Withdrawal of patients from treatment or study

7.1.4.1 Withdrawal from treatment

Study drug must be permanently discontinued in the following situations:

- Any treatment emergent adverse reaction (including infections), (i.e., assessed as related), which is considered as life-threatening.
- Any medical condition that the Investigator or Sponsor determines may jeopardize the patient's safety.
- Pregnancy.

A patient might be also withdrawn from the study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient.

When a patient is withdrawn, the date of last emapalumab dose and the date and reason for treatment withdrawal should be clearly described in the relevant sections of the eCRF.

All patients who permanently discontinue treatment will be treated according to local medical practice. A patient who prematurely discontinues study treatment is NOT considered as withdrawn from the study. All assessments relevant to the EOT Visit must be performed and the patient will enter the follow-up period.

7.1.4.2 Withdrawal from study

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.
- 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.

If a patient withdraws from the study, every effort should be made to obtain information on the reason for consent withdrawal. Patients should be encouraged to attend the EOS Visit. 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.

7.1.4.3 Study suspension

The study may be temporarily suspended in case of the occurrence of unexpected fatal adverse reactions related to emapalumab or at the iDMC's own request as an outcome of their regular or ad hoc study data review.

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

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

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

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

7.1.5 Replacement of withdrawn patients

Withdrawn patients will not be replaced.

7.2 Treatments

7.2.1 Treatments administered

Details on the investigational medicinal product are provided in Table 3.

Table 3 Investigational medicinal product

Treatment	Investigational product	Dosage form	Route	Daily dose	Dosage regimen
Emapalumab	NI-0501	Solution	Intravenous infusion	[redacted] at SD1 then [redacted] at SD4 and onwards	[redacted] at SD1, then [redacted] every 3 days until SD16 and then [redacted] twice-a-week until SD28 with a possibility to change the dose (decrease the dose intervals or increase the dose level up to a maximum dose corresponding to [redacted] every 3 days) as described in Section 7.2.6 and 7.1.2.2.

Abbreviations: SD, Study day.

7.2.2 Description of investigational medicinal product

Emapalumab (previously referred to as NI-0501) is a fully human anti-IFN-γ mAb that binds to and neutralizes human IFN-γ.

Emapalumab is manufactured by a third-party manufacturing facility duly qualified by Sobi AG and is supplied as described in the IMP Manual. Vials are filled single-use glass vials which require a dilution prior to administration. The nominal composition of the emapalumab sterile concentrate for infusion (per mL) is as follows:

Ingredient	Quantity (per mL)
Emapalumab	5 mg or 25 mg/mL
L-Histidine	1.55 mg
L-Histidine monohydrochloride, monohydrate	3.14 mg
Sodium Chloride (NaCL)	7.31 mg
Polysorbate 80	0.05 mg
[redacted]	[redacted]

The solution contains no antimicrobial preservative, and therefore each vial must be used only once. Emapalumab should be stored between 2 and 8 °C in a secure area at the study site. Further instructions on handling and storage of emapalumab are available in the Pharmacy manual.

7.2.3 Investigational medicinal product handling

7.2.3.1 Packaging and labeling

Emapalumab will be supplied to study sites in glass vials containing 2, 10, or 20 mL solution at a concentration of 5 or 25 mg/mL. Labeling and packaging will be prepared to meet local regulatory requirements. The Pharmacy manual provides further details.

7.2.3.2 Investigational medicinal product supply, preparation, and administration

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

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

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.

Further information on the preparation and administration of emapalumab are available in the Pharmacy manual.

7.2.4 Method of assigning patients to treatment groups

Not applicable.

7.2.5 Selection of dosing regimen

Emapalumab will be administered by i.v. infusion at an initial dose of [redacted] over a period of 1 to 2 hours depending on the volume to be infused. Emapalumab treatment will be continued at the dose of [redacted] every 3 days until SD16, and thereafter twice-a-week for an additional 2 weeks, i.e., until SD28. Treatment may be shortened upon achievement of MAS remission as per Investigator assessment, however at least 3 infusions of emapalumab must be administered, except in the case of a major safety concern.

In the PK study in Japanese HVs (Study Sobi.EMAPALUMAB-102), the same dose was administered (1 mg/kg) as in Study NI-0501-03 in Caucasian HVs to allow comparison of the PK profiles between these 2 ethnic groups.

Preliminary data from Study Sobi.EMAPALUMAB-102 (Phase 1, Japanese) and final data from Study NI-0501-03 (Phase 1, Caucasian) indicate that the PK of emapalumab are comparable between Japanese and Caucasian HVs. In these studies, the infusion of emapalumab was well tolerated and the effects during the 8 weeks monitoring after the drug infusion did not reveal any off-target safety or immunogenicity concerns.

Emapalumab is an anti-IFN-γ mAb that binds and neutralizes IFN-γ. Concentration-time profiles of emapalumab, total IFN-γ, CXCL9, and sCD25 from Study NI-0501-04 in patients with pHLH

and Study NI-0501-06 indicate that the proposed dosing scheme results in a rapid initial neutralization of IFN-γ and a normalization of CXCL9 and sCD25 levels. The acute onset and rapid worsening of MAS also suggest the need for a higher initial emapalumab dose to achieve a prompt and complete neutralization of IFN-γ in all patients. In essence, a loading dose of [redacted] circumvents possible target-mediated drug disposition effects even in patients who temporarily show high total IFN-γ concentrations (as expected in MAS patients, and a faster onset of action). The maintenance dose of [redacted] every 3 days for 2 weeks followed by twice-a-week for 2 weeks maintains the emapalumab concentration at levels demonstrating neutralization of IFN-γ activity.

The rationale for dose selection in Study NI-0501-14 is further supported by observations from Study NI-0501-06 in sJIA patients diagnosed with MAS (where also an initial dose of [redacted] followed by [redacted] every 3 days until SD15 and then twice weekly until SD28 were used), with a rapid decrease of CXCL9 levels, indicating a fast neutralization of circulating IFN-γ activity. The decrease in CXCL9 was followed by a decrease and/or normalization in sCD25 levels and other markers such sCD163 or ferritin. In Study NI-0501-06, the proposed dosage scheme foresaw that upon achievement of CR, treatment could be shortened, which occurred in 7 patients. The proposed dosage scheme also foresaw the possibility to increase exposure to emapalumab by increasing the dose or shortening the dosing interval. For critically ill patients, the dosing interval was transiently shortened to 2 days in 3 patients. In one of these patients, treatment was prolonged to 38 days (i.e., 17 infusions) based on the clinical status of that patient. These limited dosing adaptations indicated that the proposed dosing scheme covered the majority of the treated population and provided the flexibility to address certain variability in the response observed in the patients.

Emapalumab has shown a good safety profile to date and has been given in doses up to [redacted] In 1 patient with pHLH in Study NI-0501-04, [redacted] was administered daily for 16 infusions with no relevant safety or tolerability concerns.

In conclusion, based on the expected high IFN-γ activity in MAS patients, the data from Study NI-0501-06 and the benign safety profile of emapalumab; an initial dose of [redacted] followed by repeated administrations of [redacted] is deemed appropriate to achieve rapid and maintained neutralization of IFN-γ activity and consequently MAS remission.

7.2.6 Selection and timing of doses for each patient

If not already hospitalized, patients will be in the treatment unit from the day before the first administration of emapalumab. Patient discharge should be as per the Investigator's decision.

Emapalumab will be administered by i.v. infusion at an initial dose of [redacted] over a period of 1 to 2 hours depending on the volume to be infused.

Emapalumab treatment will be continued at the dose of [redacted], every 3 days until SD16, and then twice-a-week for additional 2 weeks, i.e., until SD28. Treatment may be shortened upon achievement of MAS remission as per Investigator assessment. However at least 3 infusions of

emapalumab must be administered before study drug discontinuation, except in the case of a major safety concern.

In the absence of a trend of improvement in the key MAS clinical and laboratory parameters (including but not limited to ferritin, LDH, AST, ALT and PLT count) suggestive of a lack of response, the emapalumab regimen may be adapted by shortening the interval (from every 3 days to every 2 days and subsequently if judged further necessary from every 2 days to each day)between the infusions, or by increasing the dose level up to a maximum dose corresponding to [redacted] every 3 days. The treatment could also be prolonged beyond 4 weeks upon Investigator confirmation of a favorable benefit/risk profile in that patient. The clinical and laboratory data guiding the Investigator's decision on dose adaptation or treatment prolongation should be reported on the eCRF.

It is recommended that the i.v. central line remains in place to ensure venous access during the treatment period. Infusion via a central line is preferred, however infusion via a peripheral line is acceptable only if no central line is available. Since no data are available on the compatibility of emapalumab with other i.v. substances or additives, other medications/substances should not be added to the infusion material or infused simultaneously through the same i.v. line. If the same i.v. line is used for subsequent infusions of other drugs, the line should be flushed appropriately with saline before and after infusion of emapalumab.

7.2.7 Blinding and unblinding

This is an open-label study with no level of blinding.

7.2.8 Background and concomitant therapy

7.2.8.1 Glucocorticoids

For a patient to be eligible for the study, an inadequate response to high dose i.v. GCs administered for at least 3 days as per local standard of care (including but not limited to pulses of 30 mg/kg mPDN on 3 consecutive days) must be documented. Inclusion into the Interventional phase can however occur within less than 3 days from starting high dose i.v. GCs, in case the patient's condition and/or laboratory parameters are rapidly worsening.

At the time of emapalumab start, high dose i.v. GCs is recommended not to be lower than 2 mg/kg/day of PDN equivalent in 2 divided doses (or at least 60 mg/day in pediatric patients of 30 kg or more and at least 1 g/day in adult MAS patients).

During the study, emapalumab must be administered on a background of GCs. The choice of GCs before entering the study will follow the local standard of care in each form of MAS.

GCs tapering may be initiated as soon as the patient's condition allows, according to the Investigator's assessment. The tapering scheme can be selected by the Investigator with the objective of reaching the same (or lower) dose being administered before the occurrence of MAS (in patients already on treatment for the underlying disease) or decreasing by 50 % (or more) the

GCs dose administered at initiation of emapalumab treatment (in patients presenting with MAS as first manifestation of the underlying disease).

In the event of underlying disease worsening after GCs tapering, a higher dose can be re-introduced and maintained until a satisfactory response is achieved according to the Investigator.

7.2.8.2 Prophylactic treatment

Herpes Zoster prophylaxis

Based on the pathophysiological link between lack of IFN-γ biological activity and intracellular infections, patients treated with emapalumab are at increased risk for certain infections including HZ infection.

Therefore, close monitoring of patients for signs and symptoms of infection, including HZ, is of utmost importance. Of note, laboratory testing may be useful in cases with less typical clinical presentation and high suspicion for HZ infection. Equally important, when the diagnosis of HZ is apparent from the clinical presentation, or after confirming cases of suspected HZ, the treating physician should consider the prompt initiation of antimicrobial therapy according to local practice. In addition, the Investigator should consider using HZ prophylaxis according to his/her own benefit-risk assessment. Worthy of mention, antiviral medications used either to treat an overt HZ infection or to prevent its occurrence can be administered together with emapalumab. Also, the treating physician may decide to stop HZ prophylaxis at any time. Finally, nonadmitted patients, i.e., study participants that are followed on an outpatient basis, should be instructed to seek medical advice if signs or symptoms of clinically significant infection occur.

Anti-microbial prophylaxis

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

7.2.8.3 Anakinra

In sJIA and AOSD patients, if anakinra is ongoing and if it has been started (at any dose) at least 3 days before initiation of emapalumab treatment, it may be continued at a maximum daily dose of 4 mg/kg. In the case of an acute inflammatory flare of the underlying Still's disease during treatment with emapalumab, anakinra may be introduced at a dose of 1 to 4 mg/kg/day (maximum daily dose of 100 mg). Such episodes shall be adjudicated by at least 2 members of the SSC (excluding the treating physician, if applicable), in order to ascertain their nature (i.e., sJIA/AOSD versus MAS flare). To note, the adjudicated data will not be part of the clinical database and a separate report containing a summary of the adjudication will be prepared by the SSC.

7.2.8.4 Ciclosporin, mycophenolate mofetil, and methotrexate

In all cohorts, CsA may be continued, if already started at least 3 days prior to initiation of emapalumab treatment. CsA dose adjustments are allowed in order to maintain therapeutic levels. CsA should not be introduced once emapalumab administration has started.

When it is used as a treatment of the underlying disease, methotrexate may be started during the study.

Mycophenolate mofetil is also allowed for SLE patients if started at least 2 weeks before the MAS diagnosis and continuing at a stable dose. This drug should not be introduced once emapalumab administration has started.

7.2.8.5 Belimumab

When used as a treatment for SLE, belimumab can be continued if administered at a stable dose (i.e., after completion of the loading dose period).

7.2.8.6 Other MAS therapies

If the patient is receiving intrathecal therapy (e.g., methotrexate and/or GCs) at the time of emapalumab treatment initiation, this treatment will be continued if clinically indicated.

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

The unsatisfactory control in this case is defined as follows:

- Patients who present a clinically relevant worsening.

In this circumstance, the Investigator must fully document the worsening of the clinical situation in the patient's medical file and in the eCRF. The Investigator will decide whether to stop emapalumab or not.

7.2.8.7 Other concomitant medication

Intravenous immunoglobulin is allowed if used as replacement treatment (i.e., 400 mg/kg) 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 eCRF (dose, date of administration).

G-CSF is permitted in case of prolonged neutropenia.

Concomitant treatment for SLE, i.e., azathioprine and hydroxychloroquine can be continued.

Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, i.v. parenteral nutrition, inotropic support, antibiotics, antifungal and anti-viral treatment, ultrafiltration or hemodialysis, as well as general supportive care (e.g., gastroprotective agents, antihypertensives etc.) are permitted during the study. Other therapy considered necessary for the patient's welfare may be given at the discretion of the Investigator. All such therapies must be recorded in the eCRF.

7.2.9 Prohibited medication

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

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

Tocilizumab, canakinumab, TNF inhibitors, or JAK inhibitors must be discontinued before initiation of emapalumab treatment. No washout period is required between last dose of tocilizumab, canakinumab, TNF inhibitors, or JAK inhibitors and the first dose of emapalumab.

In the case of an acute inflammatory flare of the underlying disease, tocilizumab, canakinumab, TNF inhibitors, or JAK inhibitors (as approved in the applicable country for the treatment of the underlying disease) can be restarted more than 44 days after the last dose of emapalumab (i.e., after 2 half-lives of emapalumab have elapsed), but never before Week 8 (SD56).

7.2.10 Treatment compliance

Administrations of emapalumab will be recorded in the eCRF as described in Section 7.2.3. Product accountability records will be kept. The pharmacy and Investigator must maintain accurate records demonstrating date and amount of emapalumab received, to whom and by whom administered or dispensed (patient-by-patient accounting), and accounts of returned emapalumab and any emapalumab accidentally or deliberately destroyed.

7.3 Efficacy, safety, pharmacokinetic, pharmacodynamic, and pharmacogenetics assessments

7.3.1 Study schedule

7.3.1.1 Schedule of events

The visit schedule and the study assessments for patients enrolled in the Run-in phase are described in Table 4. The visit schedule and the study assessments for patients enrolled in the Interventional phase are described in Table 5 (screening, treatment period, and follow-up to Week 8) and in Table 6 for the Long-term follow-up.

The assessment schedule is the same for Cohorts 1 and 2.

Table 4 Schedule of assessments – Run-in phase

Assessment		Screening RI visit SD-7 to SD-1	Visit 1 RI (start of MAS treatment) SD1	Visit 2 RI[a] (Week 1 from first MAS treatment) SD7	Visit 3 RI[a] (Week 4 from first MAS treatment) SD28	Visit 4 RI[a] (Week 8 from first MAS treatment) SD56	EOS/study withdrawal or SD84 (Week 12)[b]	UV[c]
Informed consent		x						
Review of inclusion exclusion criteria		x	x					
Demography and medical history		x						
pHLH genetical test, perforin level, and degranulation tests[d]		x						
GCs		x	x	x	X	x	x	x
Previous and concomitant medication including any previous MAS and any underlying disease treatment		x	x	x	X	x	x	x
Clinical assessment	Vital signs[e]	x	x	x	X	x	x	x
	Physical exam[f]	x	x	x	X	x	x	x
	Underlying disease assessment	x	x	x	X	x	x	x
	MAS clinical signs and symptoms including MAS clinical activity[g]	x	x	x	X	x	x	x
Laboratory assessment	CBC[h]	x	x	x	X	x	x	x
	Biochemistry[h]	x	x	x	X	x	x	x
	Coagulation[h]	x	x	x	X	x	x	x
	Urinalysis[h]	x						
	Pregnancy test (serum or urine) (if applicable)	x						

Table 4 Schedule of assessments – Run-in phase

Assessment		Screening RI visit SD-7 to SD-1	Visit 1 RI (start of MAS treatment) SD1	Visit 2 RI[a] (Week 1 from first MAS treatment) SD7	Visit 3 RI[a] (Week 4 from first MAS treatment) SD28	Visit 4 RI[a] (Week 8 from first MAS treatment) SD56	EOS/study withdrawal or SD84 (Week 12)[b]	UV[c]
Infection	CMV	x	x	x	X	x	x	
	Adenovirus, EBV	x		**If clinically indicated**				
	Histoplasma capsulatum, Salmonella leishmania	x		**If clinically indicated**				
	Typical/Atypical mycobacteria	x	**If clinically indicated**					
Current MAS treatment		x	x	x	X	x	x	x
QoL assessment[i]		x				x	x	
AE reporting			x	x	X	x	x	

Abbreviations: AE, Adverse event; ALP, Alkaline phosphatase, ALT, Alanine aminotransferase; aPTT, Activated partial thromboplastin time; AST, Aspartate aminotransferase; CBC, Complete blood cell count; CMV, Cytomegalovirus; CR, Complete response; CRP, C-reactive protein; EBV, Epstein-Barr virus; EOS, End of study; GC, Glucocorticoid; GGT, Gamma-glutamyl transpeptidase; HLH, Hemophagocytic lymphohistiocytosis; LDH, Lactate dehydrogenase; MAS, Macrophage activation syndrome; pHLH, Primary hemophagocytic lymphohistiocytosis; PLT, platelets; QoL, Quality of life; RBC, Red blood cell count; RI, Run-in phase; SD, Study day; UV, Unscheduled visit; VAS: Visual analog scale; WBC, White blood cell count.

a Visit 2 should occur at SD7 ± 2 days from the MAS treatment with GCs start. Visit 3 should occur at SD28 ± 3 days from the MAS treatment with GCs start. Visit 4 should occur at SD56 ± 3 days from the MAS treatment with GCs start.

b Patients who do not reach MAS remission (as per Investigator assessment), and do not have an inadequate response to GCs by Week 8 will have their EOS Visit 12 weeks after start of GCs. All other patients will combine the Week 8 and EOS Visit.

c UV to be reported when remission or inadequate response to GCs is detected outside of the scheduled assessments. Assessments performed at the UV are per the Investigator's decision.

d The genetical and functional tests relevant to HLH diagnosis are not mandatory. They should be reported if available.

e Vital signs include body temperature, heart rate, blood pressure, and oxygen saturation. More frequent measurements will be done if medically indicated.

f The physical examination should include as a minimum the patient's weight, and should assess the MAS clinical activity as described in Section 7.3.3.

g MAS clinical signs and symptoms will include the evaluation of MAS clinical activity by VAS and the assessment of clinical signs and symptoms as indicated in Section 7.3.3.

h **CBC** includes hematocrit, hemoglobin, PLT, RBC, and WBC. Hematology differential: lymphocytes, monocytes, neutrophils. **Biochemistry** includes glucose, CRP, sodium, potassium, calcium, AST, ALT, GGT, ALP, LDH, bilirubin (total, direct and indirect), triglycerides, albumin, creatinine, urea, and ferritin. **Coagulation** includes aPTT, prothrombin time, D-dimers, and fibrinogen. **Urinalysis** includes glucose, blood, protein, leukocytes, ketones, and pH (test to be performed at screening visits only).
i Quality of life assessments will be collected at MAS remission (as per Investigator assessment) if it occurs after Week 8.

Table 5 Schedule of assessments – Interventional phase – screening, emapalumab treatment, and follow-up to Week 8 (from SD-1 to SD56)

Visit	Screening for Interventional phase	Interventional phase (emapalumab treatment period)				Follow-up to Week 8	
		Week 1 and Week 2 (SD2 to SD16)[a]		Week 3 to Week 4 (SD17 to SD27)[a,b]	Week 4 (SD28)/EOT visit[c]	Weekly follow-up visits[d]	
	Screening visit (SD-7 to SD-1)	VIP 1 (SD1)	VIP 2 VIP 3 VIP 4 VIP 5 VIP 6	VIP 7 VIP 8 VIP 9	VIP 10	Week 5-6-7 (SD35-42-49) (± 2 days) VIP Week 5, VIP Week 6, VIP Week 7	Week 8 Follow-up Visit SD56[e] VIP Week 8
Informed consent	x						
Review of inclusion exclusion criteria	x	x					
Demography and medical history	x						
pHLH genetical tests, perforin level and degranulation tests[f]	x						
GCs	x	x	x	x	x	x	x
Previous and concomitant medication including any previous MAS and any underlying disease treatment[g]	x	x	x	x	x	x	x
Emapalumab infusion		x	x	x	x (if applicable)		

Table 5 Schedule of assessments – Interventional phase – screening, emapalumab treatment, and follow-up to Week 8 (from SD-1 to SD56)

Visit		Screening for Interventional phase	Interventional phase (emapalumab treatment period)				Follow-up to Week 8	
			Week 1 and Week 2 (SD2 to SD16)[a]		Week 3 to Week 4 (SD17 to SD27)[a,b]	Week 4 (SD28)/EOT visit[c]	Weekly follow-up visits[d]	
		Screening visit (SD-7 to SD-1)	VIP 1 (SD1)	VIP 2 VIP 3 VIP 4 VIP 5 VIP 6	VIP 7 VIP 8 VIP 9	VIP 10	Week 5-6-7 (SD35-42-49) (± 2 days) VIP Week 5, VIP Week 6, VIP Week 7	Week 8 Follow-up Visit SD56[e] VIP Week 8
Clinical assessment	Vital signs[g]	x	x(pre/postinf.)	x(pre/postinf.)	x(pre/postinf.)	x(pre/postinf.)	x	x
	Physical examination[h]	x	x(pre-inf)	x(pre-inf)	x(pre-inf)	x(pre-inf)	x	x
	Underlying disease assessment	x	x	x	x	x	x	x
	MAS clinical signs and symptoms including MAS clinical activity[i]	x	x	x	x	x	x	x
	Tuberculosis clinical examination[j]	x				x		x
	Clinical monitoring for HZ infection	x	x	x	x	x	x	x
Laboratory assessment	CBC[k]	x	x(pre-inf)	x(pre-inf)	x(pre-inf)	x(pre-inf)	x	x
	Biochemistry[k]	x	x(pre-inf)	x(pre-inf)	x(pre-inf)	x(pre-inf)	x	x

Table 5 Schedule of assessments – Interventional phase – screening, emapalumab treatment, and follow-up to Week 8 (from SD-1 to SD56)

Visit		Screening for Interventional phase	Interventional phase (emapalumab treatment period)				Follow-up to Week 8	
			Week 1 and Week 2 (SD2 to SD16)[a]		Week 3 to Week 4 (SD17 to SD27)[a,b]	Week 4 (SD28)/EOT visit[c]	Weekly follow-up visits[d] Week 5-6-7 (SD35-42-49) (± 2 days) VIP Week 5, VIP Week 6, VIP Week 7	Week 8 Follow-up Visit SD56[e] VIP Week 8
		Screening visit (SD-7 to SD-1)	VIP 1 (SD1)	VIP 2 VIP 3 VIP 4 VIP 5 VIP 6	VIP 7 VIP 8 VIP 9	VIP 10		
	Coagulation[k]	x	x(pre-inf)	x(pre-inf)	x(pre-inf)	x(pre-inf)	x	x
	Urinalysis[k]	x						
	Pregnancy test (serum or urine) if applicable	x				x		
Infection[l]	Adenovirus, EBV	x	If clinically indicated					
	CMV	x	CMV every 2 weeks (± 2 days) if clinically possible					x
	Atypical mycobacteria Histoplasma Salmonella, leishmania	x	If clinically indicated					
	Tuberculosis	x						x

Table 5 Schedule of assessments – Interventional phase – screening, emapalumab treatment, and follow-up to Week 8 (from SD-1 to SD56)

Visit		Screening for Interventional phase	Interventional phase (emapalumab treatment period)				Follow-up to Week 8	
			Week 1 and Week 2 (SD2 to SD16)[a]		Week 3 to Week 4 (SD17 to SD27)[a,b]	Week 4 (SD28)/EOT visit[c]	Weekly follow-up visits[d] Week 5-6-7 (SD35-42-49) (± 2 days) VIP Week 5, VIP Week 6, VIP Week 7	Week 8 Follow-up Visit SD56[e] VIP Week 8
		Screening visit (SD-7 to SD-1)	VIP 1 (SD1)	VIP 2 VIP 3 VIP 4 VIP 5 VIP 6	VIP 7 VIP 8 VIP 9	VIP 10		
Imaging	Chest X-ray[m]	x	If clinically indicated					x
	Abdominal ultrasound	x				x		x
	Brain MRI	x (if clinically indicated)						x (if brain involvement at baseline)
ECG		x						x
AE reporting			x	x	x	x	x	x
PK[n]			x (pre- and postinf)	x (pre- and postinf)	x (pre- and postinf)	x (pre- and postinf)	x	x
PD[n]			x (pre- and postinf)	x (pre-inf)	x (pre-inf)	x (pre-inf)	x	x
Immunogenicity (ADA and NAb)			x (pre-inf)					x
QoL assessment[o]		x						x

Abbreviations: ADA, Anti-drug antibodies; AE, Adverse event; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; aPTT, Activated partial thromboplastin time; AST, Aspartate aminotransferase; BMD, Bone mineral density; CBC, Complete blood cell count; CMV, Cytomegalovirus; CRP, C-reactive protein; CXCL9, Chemokine (C-X-C Motif) ligand 9; CXCL10, Chemokine (C-X-C Motif) ligand 10; EBV, Epstein-Barr virus; ECG, Electrocardiogram; eCRF, Electronic case report form; EOT, End of treatment; GC, Glucocorticoid; GGT, Gamma-glutamyl transferase; HLH, Hemophagocytic lymphohistiocytosis; HZ, Herpes zoster; IFN-γ, Interferon-gamma; inf, Infusion; LDH, Lactate dehydrogenase; MAS, Macrophage activation syndrome; MRI, Magnetic resonance imaging; NAb, Neutralizing antibodies; PCR, Polymerase chain reaction; PD, Pharmacodynamics; pHLH, Primary hemophagocytic lymphohistiocytosis; PK, Pharmacokinetics; PLT, platelets; QoL, Quality of life; RBC, Red blood cell count; sCD25, Soluble CD25 (i.e., soluble IL-2 receptor); SD, Study day; TB, Tuberculosis; VAS, Visual analog scale; VIP, Visit interventional phase; WBC, White blood cell count.

a During treatment with emapalumab, visits for infusion will occur concomitantly to emapalumab infusion on SD1 every 3 days until SD16, and twice weekly thereafter (not more than 4 days apart) until Week 4 or until a MAS remission (as per Investigator assessment), is achieved. It is expected that VIP 2 will occur on SD4, VIP 3 will occur on SD7, VIP 4 will occur on SD10, VIP 5 will occur on SD13, and VIP 6 will occur on SD16, however if the Investigator chooses to reduce the interval between doses, these visits may occur on other study days, which should be noted in the eCRF.

b These visits will occur at each emapalumab infusion. If treatment continues above VIP Week 4, VIP 9 assessments should be performed and the visit should be named subsequentially.

c The EOT assessment should be performed 3 days (± 1 day) after the last emapalumab infusion. If emapalumab treatment is shortened, an EOT Visit must be performed 3 days (± 1 day) after the last emapalumab infusion. If emapalumab treatment continues beyond the Week 4 assessment visit, an additional EOT Visit must be performed 3 days (± 1 day) after the last emapalumab infusion.

d Patients that complete their study treatment earlier than SD28 should complete an EOT visit 3 days (±1 days) after the last emapalumab infusion. After the EOT visit, three weekly follow-up visits should be completed with the assessments outlined for week 5, 6 and 7. Following the third weekly follow-up visit, the patient will complete the week 8 visit at SD56 (±3 days).

e The Week 8 assessment should be performed at SD56 (± 3 days) from first emapalumab infusion. This assessment should be performed in all patients regardless of when they complete the study treatment.

f The genetical and functional tests relevant to HLH diagnosis are not mandatory. They should be reported if available. In case a patient enrolled in the Run-in phase agrees to continue in the Interventional phase, genetic and functional testing do not have to be repeated.
Previous and concomitant medication including any previous MAS and any underlying disease treatment

g Vital signs include body temperature, heart rate, blood pressure, and oxygen saturation. 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, which is to be taken only pre-infusion. More frequent measurements will be done if medically indicated (Section 7.3.4.3).

h Physical examination should include as a minimum the patient's height at Screening, weight before each emapalumab infusion then every 2 weeks, the assessment of MAS clinical activity as described in Section 7.3.3 and footnote h, and the guided TB clinical exam as described in Section 7.3.4.2.2 and footnote i.

i MAS clinical signs and symptoms will include the evaluation of MAS clinical activity by VAS and the assessment of clinical signs and symptoms as indicated in Section 7.3.3. Assessment of MAS clinical signs and symptoms including activity by VAS should be performed pre-infusion.

j A TB guided clinical examination should be performed at the baseline visit then every 4 weeks. If a patient is presenting any unexplained fever, cough, a skin lesion suggestive of TB or any other clinical signs and symptoms suggestive of TB infection as per Investigator discretion, a PCR testing should be performed.

k **CBC** includes hematocrit, hemoglobin, PLT, RBC, and WBC. Hematology differential: lymphocytes, monocytes, neutrophils. **Biochemistry** includes glucose, CRP, sodium, potassium, calcium, AST, ALT, GGT, ALP, LDH, bilirubin (total, direct and indirect), triglycerides, albumin, creatinine, urea, and ferritin. **Coagulation** includes aPTT, prothrombin time, D-dimers, and fibrinogen. **Urinalysis** includes glucose, blood, protein, leukocytes, ketones, and pH (test to be performed at Screening only).

l 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. Only patients who have been in regions where leishmania is endemic during the 6 months prior to screening, or are living in an endemic country at the time of screening, are required to be actively screened for leishmania. The search for infections will be repeated if was done more than 30 days prior to the presumed emapalumab treatment start or if any clinical symptoms suggestive of infection. CMV testing is mandated every 2 weeks during the treatment phase of the study: the number of samples collected will take into consideration the weight and health status of the patient.

m Chest X-ray will be performed as a measure for detection of pulmonary infections, or to check for MAS lung involvement at Screening and at Week 8. Chest X-ray should be done more frequently in case of clinical suspicion of a pulmonary infection.

n PK will serve to measure the emapalumab concentration and PD to test sCD25, total IFN-γ, CXCL9, and CXCL10. PK samples should be taken preferably within 30-60 min post-infusion, but not earlier than 30 min. If the post-infusion sample must be collected from the same line as emapalumab has been administered through, the line must be flushed with 0.9% saline before the sample collection.
In case of children weighing < 12 kg, the Investigator has the possibility to reduce the PK/PD sampling to every second visit between VIP 3 and VIP 9.

o In some countries QoL will also be assessed in an Exit Interview (see Appendix 2). The Exit Interview will be performed separately by phone a few weeks (2-4 weeks) after the EOT.

Please refer to Table 6 for any unscheduled visit to be performed under this treatment period.

Table 6 Schedule of assessments – Long-term follow-up

Assessment		Long-term follow-up up to 1 year from last dose of emapalumab				
		Day +60 visit (± 1 week)	**Day +100 visit (± 1 week)**	**6-month visit (± 2 weeks)**	**1-year visit/EOS Visit/WD visit (± 2 weeks)[a]**	**UV[b]**
GCs		x	x	X	x	
Concomitant medication including treatment of underlying disease and any additional MAS treatment (if applicable)		x	x	X	x	
Clinical assessment	Vital signs[c]	x	x	X	x	
	Physical exam[d]	x	x	X	x	
	Underlying disease assessment	x	x	X	x	
	Survival	x	x	X	x	
	MAS clinical signs and symptoms including MAS clinical activity[e]	x	x	X	x	
	TB clinical exam[f]	x	x	X	x	
	Clinical monitoring of HZ infection	x	x	X	x	x
Laboratory assessment	CBC[g]	x	x	X	x	
	Biochemistry[g]	x	x	X	x	
	Coagulation[g]	x	x	X	x	
	Pregnancy test (serum or urine) if applicable	If indicated			x	

Table 6 Schedule of assessments – Long-term follow-up

Assessment		Long-term follow-up up to 1 year from last dose of emapalumab				
		Day +60 visit (± 1 week)	**Day +100 visit (± 1 week)**	**6-month visit (± 2 weeks)**	**1-year visit/EOS Visit/WD visit (± 2 weeks)[a]**	**UV[b]**
Infection	Other infection as clinically indicated[h]	x	x	X	x	
	Mycobacterium TB[i]				x	
Imaging	Abdominal ultrasound			X	x	
	Chest X-ray	When clinically indicated				
	Brain MRI				x (if brain involvement at baseline)	
ECG					x	
AE reporting		x	x	X	x	x
PK[j]		x	x	X	x	x
PD[j]		x	x	X	x	x
Immunogenicity (ADA and NAb)				X	x	
QoL assessment				X	x	

Abbreviations: ADA, Anti-drug-antibodies AE, Adverse event; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; aPTT, Activated partial thromboplastin time; AST, Aspartate aminotransferase; BMD, Bone mineral density; CBC, Complete blood cell count; CMV, Cytomegalovirus; CXCL9, Chemokine (C-X-C Motif) ligand 9; CXCL10, Chemokine (C-X-C Motif) ligand 10; EBV, Epstein-Barr virus; EOS, End of study; GC, Glucocorticoid; GGT, Gamma-glutamyl transferase; HZ, Herpes zoster; IFN-γ, Interferon-gamma; LDH, Lactate dehydrogenase; MAS, Macrophage activation syndrome; MRI, Magnetic resonance imaging; NAb, Neutralizing antibodies; PCR, Polymerase chain reaction; PD, Pharmacodynamics; PK, Pharmacokinetics; PLT, platelets; QoL, Quality of life; RBC, Red blood cell count; sCD25, Soluble CD25 (i.e., soluble IL-2 receptor); TB, Tuberculosis; UV, Unscheduled visit; VAS, Visual analog scale; WBC, White blood cell count; WD, Withdrawal.

a The EOS Visit could be combined to the 1-year Follow-up Visit or to the Withdrawal Visit as applicable.

b A UV should be performed whenever it is clinically indicated throughout the study, the assessments to be performed during these visits should be as clinically indicated. Assessments performed at the UV are per the Investigator's decision.

c Vital signs include body temperature, heart rate, blood pressure, and oxygen saturation. More frequent measurements will be done if medically indicated, as described in Section 7.3.4.3.

d The physical examination should include as a minimum the patient's height at Month 6 visit and 1-year visit, and the assessment of MAS clinical activity as described in Section 7.3.3.
e MAS clinical signs and symptoms will include the evaluation of MAS clinical activity by VAS and the assessment of clinical signs and symptoms as indicated in Section 7.3.3.
f A TB guided clinical examination should be performed at the baseline visit then every 4 weeks. If a patient is presenting any unexplained fever, cough, a skin lesion suggestive of TB or any other clinical signs and symptoms suggestive of TB infection, as per Investigator discretion, a PCR should be performed.
g **CBC** includes hematocrit, hemoglobin, PLT, RBC, and WBC. Hematology differential: lymphocytes, monocytes, and neutrophils. **Biochemistry** includes glucose, C-reactive protein (CRP), sodium, potassium, calcium, AST, ALT, GGT, ALP, LDH, bilirubin (total, direct and indirect), triglycerides, albumin, creatinine, urea, and ferritin. **Coagulation** includes aPTT, prothrombin time, D-dimers, and fibrinogen.
h CMV, EBV, and adenovirus as clinically indicated.
i The mycobacterium TB search to be performed by PCR testing.
j PK will serve to measure the emapalumab concentration and PD to test sCD25, total IFN-γ, CXCL9, and CXCL10.

7.3.1.2 Screening visit

Screening will occur up to 1 week prior to the first administration of the study drug if patient is enrolled in the Interventional phase or up to 1 week prior to start of GCs if patient is enrolled in the Run-in phase. The aim of the screening is to collect necessary data to confirm the patient's eligibility.

The ICF must be signed by the patient or by the patient's legally authorized representative(s) (as required by local law) prior to any study-related procedures, with the assent of patients who are deemed suitable to provide it, as applicable. A separate informed consent must be obtained for each of the study phases.

Should the patient be critically ill and unable to sign the ICF, the patient's legally authorized representative(s) can sign the ICF, however the patient's signature should be collected once the patient's condition has stabilized.

In case a patient enrolled in the Run-in phase agrees to continue in the Interventional phase, medical history, MAS history, underlying disease history, and genetic and functional testing do not have to be repeated. The search for infections will be repeated if was done more than 30 days prior to the presumed emapalumab treatment start or if any clinical symptoms suggestive of infection.

Patients who do not meet the criteria for participation in this study (screening failure) may be rescreened if there is a substantial change in the patient's condition (e.g., a prohibited medication was stopped).

7.3.1.3 Study visit – Run-in phase

Effort should be made to adhere to the schedule of assessments as per Table 4.

A window of ± 2 days will be allowed for all assessments scheduled for Visit 2 occurring at 1 week, and a window of ± 3 days will be allowed for all assessments scheduled for Visits 3 and 4 occurring at 4 weeks and 8 weeks from the start of GCs treatment.

When MAS remission as per Investigator assessment is not achieved at any of the scheduled visits, the MAS remission should be reported as a UV [27] when it happens.

If a patient reaches MAS remission as per Investigator assessment before Week 8 and/or outside of Week 4, both the UV (to document the MAS remission) and visit occurring at Week 4 and Week 8 should be performed.

In case a patient presents an inadequate response to GCs at any time outside of any of the scheduled visits, the inadequate response to GCs should be documented as a UV. This patient will be discontinued from the Run-in phase of the study and will be invited to join the Interventional phase of the study for treatment with emapalumab.

If a patient decides to withdraw his or her consent, every effort should be made to collect the reason of consent withdrawal.

Patients enrolled in this phase will be followed for a maximum of 12 weeks, or until reaching a MAS remission as per Investigator assessment, or until presenting an inadequate response to GCs as assessed by the Investigator, whichever occurs first.

7.3.1.4 Study treatment visits (Visit 1 up to Week 8 visit) - Interventional phase

Every effort should be made to adhere to the schedule of assessments as per Table 5.

During treatment with emapalumab, visits for infusion will occur on SD1 and every 3 days until SD16, and thereafter twice-a-week (not more than 4 days apart).

If emapalumab treatment is shortened, an EOT visit must be performed 3 days (± 1 day) after the last emapalumab infusion. If emapalumab treatment continues beyond the Week 4 assessment visit, an additional EOT visit must be performed 3 days (± 1 day) after the last emapalumab infusion. Independently from when the study treatment is completed (i.e., before or after SD28) the scheduled visits as described in Table 5 and Table 6 have to be performed.

The Week 8 assessment should be performed 8 weeks (SD56 ± 3 days) after the first emapalumab infusion. This assessment should be performed in all patients regardless of when they complete the study treatment.

If a patient decides to withdraw his or her consent at any time during this first part of the Interventional phase, every effort should be made to collect the reason for consent withdrawal.

7.3.1.5 Long-term follow-up visit – Interventional phase

Every effort should be made to adhere to the schedule of assessments as per Table 6. Long-term follow-up will be conducted after the discontinuation of emapalumab treatment up to 1 year after last administration of emapalumab. The 1-year visit represents the last visit of the study for each patient.

If a patient decides to withdraw his or her consent at any time during this Long-term follow-up period, every effort should be made to collect the reason for consent withdrawal.

7.3.2 Demography, medical history, and other baseline characteristics

Demographics, medical history and other baseline characteristics should include:

- Demographics: year of birth, sex, race and ethnicity (if allowed by local regulations) to be collected at Screening and recorded in the eCRF.
- Relevant medical history as judged by the Investigator will be collected at Screening and recorded in the eCRF. Where possible, diagnosis, not symptoms must be recorded. Any new medical condition occurring after the informed consent signature must be reported as an AE. Should a patient undergo the Run-in phase just before starting any treatment with emapalumab, the medical history will be required prior to Run-in phase only.
- Underlying disease history including initial diagnosis, date of disease onset, any previous history of underlying disease flare (in the last 12 months prior to enrollment)

and current and previous treatment of the underlying disease (including and not limited to GCs) must also be collected and reported in the eCRF. Should a patient undergo the Run-in phase just before starting any treatment with emapalumab, these data will be required prior to Run-in phase only.

- Prior MAS therapy received (when applicable), date of MAS diagnosis, molecular diagnosis, and relevant functional tests performed if available. Should a patient undergo the Run-in phase just before starting any treatment with emapalumab, these data will be collected prior to Run-in phase only.
- If a patient starts the study at the Interventional phase, previous MAS treatment (doses, start date and end date) as well as detailed information on inadequate response to high dose i.v. GCs and to other MAS treatments including clinical signs and symptoms, VAS of MAS clinical activity and MAS laboratory parameters including, but not limited to: blood cell counts, ferritin, AST, ALT, fibrinogen, D-dimer, triglycerides, CRP, and LDH should be collected. These data should be reported since the date of diagnosis of the current MAS episode.

7.3.3 Efficacy assessments

The efficacy assessment in this study is based on a clinical and laboratory assessment. These clinical and laboratory assessments will support the primary endpoints as defined in Table 1.

In Cohorts 1 and 2, the Investigator will be asked to assess MAS clinical activity and document it on a VAS. MAS clinical activity should be reported in the eCRF and in the source document, for patients not having fever greater than 38.0 °C at the time of enrollment, the reason must be clearly defined in the source data. The Investigator will also be asked to assess and document the clinical parameters as listed below as per Table 4, Table 5, and Table 6.

- Fever (greater than 38.0 °C).
- Skin rash.
- Hemorrhagic manifestations:
    - Skin bleeding (petechiae, ecchymosis, purpura) (choose among “stable”, “worsened”, “improved” or “resolved”).
    - Mucosal bleeding (gut, respiratory) (choose among “present” or “absent”).
- Evidence of CNS involvement:
    - Clinical (headache, irritability, seizures, confusion, lethargy, coma) (choose among “stable”, “worsened”, “improved” or “resolved”).
    - CSF abnormalities (cell count) (if lumbar puncture performed based on clinical indication).
- Respiratory function:
    - Oxygen support (choose among “present” or “absent”; if present, indicate how many liters of O_2 are required to maintain O_2 saturation above 93 %).
    - Mechanical ventilation (choose among “present” or “absent”).
- Cardiac:
    - Pericarditis (if echocardiography is performed, results should be reported).

    - Inotropic support.
- Kidney:
    - Ultrafiltration/dialysis.
- Other.

The laboratory features relevant to MAS (i.e., WBC, platelet count, LDH, AST, ALT, fibrinogen, ferritin) are specifically considered to assess the response in Cohorts 1 and 2. They should be collected and reported as described in Section 7.3.4.2.1.

The disease would be considered as recurring or reactivating as per the Investigator's assessment. In such cases the event should be reported on the AE page. Any new MAS related clinical signs and symptoms are considered as a single criterion for reactivation.

7.3.4 Safety assessments

7.3.4.1 Adverse events

7.3.4.1.1 Definitions

Adverse event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A treatment emergent AE is any AE temporally associated with the use of study treatment (from study treatment initiation) whether or not considered by the Investigator as related to the study treatment.

AEs include:

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

- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

AEs diagnosis *versus* signs/symptoms

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

Persistent and recurrent AEs

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

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

Serious adverse event

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

- Results in death.
- Is life-threatening (i.e., at immediate risk of death but it does not refer to an event which could hypothetically have caused a death had it been more severe).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect (i.e., in an offspring to the study patient).
- Is a medically important event.

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

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

Hospitalization

Hospitalization includes transfer within a hospital (e.g., from a psychiatric unit to an ICU) and also includes admissions for less than 24 hours.

Hospitalization in the absence of an AE occurring during the study should not be considered an SAE. For the purpose of the study, the following will not be considered as SAE:

- Elective hospitalizations for surgical procedures that are a result of a patient's pre-existing condition(s) which have not worsened since receiving IMP.
- Protocol specified admission such as hospitalization for infusions and study visits.
- Preplanned admission for a condition specified at baseline for the patient.

7.3.4.1.2 Adverse event reporting period

All AEs occurring after informed consent signature and up to EOS must be collected and recorded in the specific AE forms of the eCRF regardless of seriousness and relationship with IMP.

All AEs should be followed up until they are resolved, or the Investigator assesses them as stable, or the patient's participation in the study ends.

Severity assessment

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

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

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

Causality assessment

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

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

- Temporal relationship of event onset to the initiation of IMP.
- 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 IMP or with similar treatments.
- Known association of the event with the disease under study.

7.3.4.1.3 Serious adverse event reporting

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and investigators.
- An investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB, and will notify the IRB or IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- Any serious COVID-19 infection which has been assessed as related to emapalumab, must be submitted as a SUSAR (as with any other unexpected SAE).

All SAEs must be reported by the Investigator to the Sobi Global Pharmacovigilance & Patient Safety department within 24 hours of the Investigator's first knowledge of the event.

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

The SAE forms must be sent to the Sponsor (e-mail contact details provided on the SAE form). The Investigator must complete the SAE form in English, and must assess the causal relationship of the event to IMP.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it.

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

The reference safety document to assess expectedness of a suspected serious adverse reaction and reported by the Sponsor to Regulatory Authorities, IECs or IRBs and Investigators is the reference safety information section of the current version of the IB.

Follow-up of SAEs

SAEs still ongoing at the EOS must be followed up until resolution or stabilization.

7.3.4.2 Laboratory safety assessments

Clinically significant abnormal laboratory values should be reported as AEs (see Section 7.3.4.1.1 for details).

7.3.4.2.1 Laboratory assessment

Blood and urine laboratory analyzes are part of the routine monitoring of MAS patients, thus samples will be analyzed locally except for PK, PD, ADA, NAb, and infection tests (where these cannot be done locally).

For patients above 20 kg, it is estimated that the blood sample volumes to be drawn over 4 weeks of study will be a maximum of 40.5 mL, which is within the 3 % of total blood volume that is acceptable according to the Recommendations of the Expert Group on Clinical Trials for the Implementation of Regulation (EU) No 536/2014 on Clinical Trials on Medicinal Products for Human Use, September 2017, for the total blood volume to be drawn per age group.

For patients between 12 and 20 kg, analyzes performed on blood samples shall favor as much as possible the use of microsampling techniques. For these patients, where microsampling is used, it is estimated that the blood sample volumes over 4 weeks of study will be a maximum of 36.3 mL, which is within the 3 % of total blood volume that is acceptable according to the Expert Group Recommendations.

For younger patients (between 5 and 12 kg), it is estimated that the blood volume per 4 weeks is 30.8 mL, which is slightly higher than the maximum allowable sample total blood volume to be drawn according to the Recommendations of the Expert Group on Clinical Trials for the Implementation of Regulation (EU) No 536/2014 on Clinical Trials on Medicinal Products for Human Use, September 2017, for the total blood volume to be drawn per age group.

In the case of children <12 kg, the Investigator may reduce the PK/PD sampling to every second visit between Visit 3 and Visit 9, a measure which is expected to reduce the volume by 4 mL. These tests could be also prioritized over the CMV testing mandated every 2 weeks during the first 4 weeks of the study.

If additional safety laboratory samples are required for safety reasons, the number of samples collected will take into consideration the weight and health status of the patient.

Laboratory assessment will be performed at each study visit and will include:

Complete blood count: hematocrit, hemoglobin, PLT, RBC, WBC.

Hematology differential: lymphocytes, monocytes, neutrophils.

Biochemistry: glucose, CRP, sodium, potassium, calcium, AST, ALT, GGT, ALP, LDH, bilirubin (total, direct and indirect), triglycerides (fasting if possible), albumin, creatinine, urea, ferritin.

Coagulation: aPTT, prothrombin time, D-dimers, and fibrinogen.

Urinalysis: includes pH, glucose, blood, protein, leukocytes, ketones: assessment to be done at Screening only.

Pregnancy test: (if applicable).

Interventional phase: pregnancy testing (serum or urine) will be performed at Screening, EOT, and EOS. Additional pregnancy tests will be performed upon suspicion of pregnancy or as mandated by local regulations, as long as emapalumab serum concentrations are detectable.

Run-in phase: pregnancy testing (serum or urine) will be performed at Screening and during the study conduct as per the Investigator's decision.

7.3.4.2.2 Search for infection

Infection search will be performed during the study at the time points detailed in the schedules of assessments in Table 4, Table 5, and Table 6. When applicable, a blood sample is expected to be drawn for the purpose of infection and virus monitoring. PCR or serology are expected to be performed.

Search for infections include the following pathogens:

Atypical mycobacteria, leishmania, Histoplasma capsulatum, Salmonella

Patients with clinical signs and symptoms related to any of these infections at Screening are not eligible and must not be treated with emapalumab.

Patients presenting with only a positive test for infection can still be enrolled, the patient must be treated for this infection as clinically indicated per local guidelines.

If a patient is enrolled and then presents clinical signs and symptoms suggestive of any of these infections, the Investigator has the choice to halt the infusion based on his or her own benefit risk assessment.

Mycobacterium TB

- **At Screening**

  TB testing at Screening will be performed via IFN-γ-release assay or PPD test. In addition, a baseline sample via PCR in any relevant specimen (e.g., urine or blood, or sputum) must be obtained, as this test will be used starting from emapalumab treatment initiation to perform regular TB monitoring. In the case of a patient having received BCG vaccination, a PPD test must be performed and combined with IFNγ-release assay if the PPD result ≥5 mm. Results of the TB testing performed at Screening must be available for eligibility assessment. Patients presenting active or clinical suspicion of latent TB are not eligible to enter the study. Patients with clinical manifestations of TB prior to treatment must not be treated with emapalumab. Should the results of the IFN-γ-release assay be inconclusive and the PPD test not supportive to confirm the diagnosis, the Investigator shall use the results of the PCR and the clinical examination to aid in the determination of the patient`s eligibility. If needed, the opinion of a specialist may be requested to decide the enrollment of the patient. Please note that patients with any clinical signs or symptoms and a positive PCR test will not be treated with study drug.

- **During study treatment period**

  Patients should undergo a TB guided clinical examination to assess if any TB clinical signs and symptoms exist. The TB clinical examination is to be done by the Investigator systematically every 4 weeks until the end of the follow-up period at Week 8 and then at every visit during the Long-term follow-up period. This clinical examination should be completed with a PCR testing in relevant specimen only if there is any clinical suspicion of TB at clinical examination.

- **End of study visit**

  At the EOS Visit TB testing is performed with PCR only.

CMV, EBV, Adenovirus, and HZ

To collect information and to monitor any infection reactivation, EBV and adenovirus will be monitored at baseline and reported when indicated during the study treatment and follow-up periods.

CMV will be monitored at baseline and then every 2 weeks (± 2 days) during the emapalumab treatment period, and then as clinically indicated during the follow-up period.

A clinical examination to assess whether any HZ clinical signs and symptoms exist is required at each visit during the Interventional phase and the Long-term follow-up period. Laboratory testing (e.g., skin PCR) may be performed at the Investigator's discretion in cases of less typical clinical presentation and high suspicion for HZ infection.

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

7.3.4.3 Vital signs

Vital signs include measurement of body temperature, heart rate, systolic and diastolic blood pressure, and oxygen saturation.

During the emapalumab treatment period, heart rate and blood pressure must be measured pre-infusion (within 30 minutes from start of infusion), directly after infusion and at 1 and 2 hours post-infusion. Body temperature can be measured pre-infusion only. More frequent measurements may be done as medically indicated.

Clinically significant abnormal vital signs should be reported as AEs (see Section 7.3.4.1.1 for details).

7.3.4.4 Physical examination

The physical examination will be performed at Screening and at each study visit (before emapalumab infusion during the emapalumab treatment period).

The physical examination should include at a minimum the height (at Screening, 6 months, and 1-year visit), the weight (at Screening, prior to each emapalumab infusion visit and then every 2 weeks up to Week 8), and an assessment of MAS clinical activity as described in Section 7.3.3.

A TB-directed clinical examination should be performed at Screening, at Week 4 visit, at Week 8 visit and then at every dedicated visit during the Long-term follow-up period. In case an Investigator detects any lung, skin, or abdominal clinical signs and symptoms suggesting a TB infection, TB testing by PCR should be performed.

A HZ-focused clinical examination is to be performed at each visit after first dose of emapalumab.

Any abnormalities reported at baseline should be recorded as medical history. New or worsening of abnormalities should be reported as AEs (see Section 7.3.4.1.1 for details).

7.3.4.5 Electrocardiograms

An ECG will be performed at Screening, at Week 8, and at the EOS Visit. The ECG will be interpreted locally by the Investigator or delegate.

Clinically relevant ECG findings that were present prior to Screening must be recorded in the medical history section of the eCRF. Clinically relevant findings found after Screening must be reported as an AE (see Section 7.3.4.1.1 for details).

7.3.4.6 Imaging

Abdominal ultrasound

Abdominal ultrasounds, including spleen (longitudinal) measurements and assessment of hepatomegaly presence, will be performed at Screening, at the end of the emapalumab treatment period (i.e., SD28), at Week 8 visit then at 6 months and 1-year visits.

Chest X-ray

Chest X-ray will be performed as a measure for detection of pulmonary infections, or to check for MAS lung involvement at Screening and at Week 8. Chest X-ray should be done more frequently in case of clinical suspicion of a pulmonary infection.

Brain MRI

Brain MRI should be performed in case of neurological symptoms occurrence, prior to initiation (or at latest by SD6), and repeated at Week 8 and the EOS (if baseline neurological syndrome), whenever possible.

Any observed abnormalities reported prior to baseline should be recorded as medical history. New or worsening of abnormalities should be reported as AEs (see Section 7.3.4.1.2 for details).

7.3.4.7 Pregnancy

Pregnancy testing will be performed as described in Section 7.3.4.2.1.

Any pregnancy occurring during the study up to the EOS (including the Run-in phase and Interventional phase) must be reported within 24 hours of the Investigator's knowledge of the event.

Pregnancies must be reported on the Sobi Pregnancy Notification Form and sent to the Sponsor (e-mail contact details provided on the Pregnancy Notification Form).

Follow-up of pregnancy: Any pregnancy must be followed to its conclusion, and its outcome must be reported to the Sponsor.

7.3.5 Quality of life assessment

The PedsQL is a set of questionnaires that is used to measure generic health-related QoL in pediatric patients. This questionnaire is also applicable to adults. In the Run-in phase this measure will be collected at Screening, Week 8 and at the time of MAS remission as per Investigator assessment, if the remission is achieved after Week 8. In the Interventional phase, this measure will be collected at Screening, Week 8, follow-up visit Month 6, the EOS Visit, and at the time of MAS remission as per Investigator assessment, if remission is achieved after Week 8.

PedsQL will be supported by clinician and patient/parent global impression questionnaires. In the Run-in phase these will be collected at Screening, Week 8, and at the time of remission if the remission is achieved after Week 8. In the Interventional phase, these will be collected at Screening, Week 8, follow-up visit Month 6, the EOS Visit and at the time of remission as per Investigator assessment if remission is achieved after Week 8.

To document disease and treatment specific experience, Exit Interviews with study patients who received emapalumab (or their caregivers) will be conducted by phone a few weeks (2 to 4 weeks) after the EOT Visit. These interviews will be performed with patients who received emapalumab. The Exit Interview will be conducted by an independent CRO in English-speaking countries. Additional information on the conduct of the Exit Interview is provided in Appendix 2.

7.3.6 Pharmacokinetic assessments

7.3.6.1 Sampling procedures

PK blood samples will be collected for all patients receiving active study treatment at the time points as described in Table 5 and Table 6.

PK sampling should be done predose and at end of infusion for all visits of emapalumab infusion. In addition, a PK sample will be collected during follow-up on all visits. It should be noted that a separate i.v. line will have to be used when collecting the PK samples, i.e., not the same i.v. line as used for the i.v. infusion of active study treatment. If a second line is not

possible the same line can be used, however the blood draw must be done at least 30 minutes after infusion. If the post-infusion sample must be collected from the same line as emapalumab has been administered through, the line must be flushed with 0.9% saline before the sample collection.

The date and time of blood sampling will be recorded in the eCRF. Samples will be sent to central laboratory for analysis.

Additional details will be described in a laboratory manual.

7.3.6.2 Bioanalytical method

All the details regarding the PK serum samples analysis will be described in a dedicated bioanalytical plan which will be agreed and signed.

The quantification of emapalumab (NI-0501) in human serum samples will be performed using a validated Sandwich sequential immunoassay on Gyrolab platform, with a quantification range of 62.50 ng/mL (LLOQ) – 8 000.00 ng/mL (ULOQ). All the samples are to be dispatched under frozen conditions to the bioanalytical laboratory and will be analyzed within established timeframe stability.

7.3.7 Pharmacodynamic assessments

Blood samples for determination of CXCL9, CXCL10, sCD25, and total INF-γ, will be collected at the timepoints as detailed in Table 5 and Table 6.

The date and time of sampling will be recorded in the eCRF. It should be noted that a separate i.v. line will have to be used when collecting the PD samples, i.e., not the same i.v. line as used for the i.v. infusion of emapalumab. If a second line is not possible the same line can be used, however the blood draw must be done at least 30 minutes after infusion.

All the details regarding PD and other biomarkers serum samples analysis will be described in dedicated bioanalytical plans.

Additional details will be described in a laboratory manual.

7.3.8 Immunogenicity assessment

A search for ADA and NAbs will be performed during the study at the time points as detailed in Table 5 and Table 6.

All the ADA and any NAb analyzes will be performed at LGC (Newmarket Road, Fordham, Cambridgeshire, CB7 5WW, United Kingdom) using validated methods. All the details regarding these analyzes will be described in a sample analysis plan.

8 Study scientific oversight

Two scientific committees will ensure the scientific oversight of the study.

8.1 Scientific steering committee

An SSC composed of international experts in rheumatology has been involved in the preparation of the study design and protocol writing. They may also take the role of Investigator on the study.

The SSC will continue to play an advisory role throughout the study. Specific details on the role of the SSC will be available in an SSC charter.

8.2 Independent data monitoring committee

The iDMC will be composed of independent international experts who will conduct a review of the data at regular intervals in order to ensure that the safety profile of emapalumab remains favorable and the risk of treating remains positive. Specific details on the role of the iDMC will be available in the iDMC charter.

9 Quality control and quality assurance

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

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

The Sponsor will establish a systematic, prioritized, risk-based approach to monitoring and has chosen a combination of on-site and centralized monitoring.

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

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

It is required that each Investigator together with relevant personnel are available and devote sufficient time during the monitoring visits and possible audits.

10 Statistical plan

An interim CSR will be prepared and serve for regulatory submission using the planned interim efficacy analysis once 16 treated patients in Cohort 1 (MAS in Still's disease cohort) have undergone the Week 8 Assessment Visit or have discontinued the study early.

Further interim interim analyses will be prepared once all patients in each cohort have completed the follow-up to Week 8 (i.e., patients who reach the Week 8 Assessment Visit or discontinue the study early). The interim CSRs written based on these interim analyses may be used for regulatory submissions.

Finally, a full CSR including the safety follow-up period will be prepared once both cohorts reach the EOS.

Complete details of the statistical and analytical methods will be provided in a formal SAP, which will be finalized prior start of treatment in the first patient. Any deviations from the SAP will be noted and explained in the CSRs. PK and PD concentration data will be analyzed descriptively as part of the SAP. Additional work, e.g., correlation, population PK and/or PK/PD analysis may be conducted separately, potentially in combination with other studies. This will be described separately in a PK and PD modelling analysis plan, and will be reported separately from the CSR.

This study is planned to enroll adult and pediatric patients diagnosed with MAS in Still's disease and MAS in SLE.

10.1 Determination of sample size

The 2 cohorts will be analyzed separately, a sample size for the Interventional phase has been calculated for each cohort.

Cohort 1:

In this cohort, patients intolerant or with inadequate response to GCs will receive other treatments, which occur in 60 to 70 % [15, 21]. A successful treatment with GCs, when patients achieve response, can be expected in a proportion of patients up to 40 %.

For a fixed study design, the sample size required for Cohort 1 (MAS in the context of sJIA and AOSD) to achieve a power of 80 % using a 1-sided exact binomial test at significance level of 2.5 % to test the null hypothesis: proportion of CR is ≤ 40 % versus alternative hypothesis: proportion of CR is > 40 % if the truth is 70 % complete responders [71], is 25 patients (nQuery 8, version 8.6.0.0)

The NI-0501-14 study design is a group sequential design that includes an interim analysis assessing efficacy after the enrollment and treatment of 16 patients in Cohort 1. If efficacy is demonstrated at the time of the interim analysis, then the enrollment in this cohort will be stopped by the Sponsor; otherwise the enrollment will continue until 25 patients are treated.

Using clinical trial simulations, the overall type 1 error rate for the group sequential design described above is less than 2.5 % and the power is estimated to be 81.7 %. The type 1 error rate spent in the efficacy interim analysis (N=16 patients) is 0.5 % based on the 1-sided exact binomial test. The probability of type 1 error in the final efficacy analysis (N=25 patients), given that the study continues after the interim analysis, is 2.0 %.

Cohort 2:

An article by Liu et al. [19], demonstrated that only 21.9 % of SLE patients with MAS received corticosteroids alone and did not require any other treatments. The assumption was made that patients in this cohort responded less frequently than in the other cohort: expected CR rate of at least 30 %.

An exact binomial test at a 1-sided significance level of 2.5 % will have 82 % power to reject the null hypothesis CR rate of 30 %, if the truth is 70 % complete responders, when the sample size is 16 (nQuery 8, version 8.6.0.0).

10.2 Definition of study populations

In addition to the analysis sets listed below, further exploratory analyzes may be performed using other subgroups of patients, which will be described in the SAP.

10.2.1 All treated analysis set

The All Treated Analysis Set will include all patients who receive any part of an infusion of study drug, and will be used to evaluate efficacy, safety, PK and PD and immunogenicity endpoints. This population, also called Safety Analysis Set, will be used as the primary population for the efficacy and safety analyses.

10.2.2 Evaluable analysis set

The Evaluable Analysis Set will be a subset of the All Treated Analysis Set patients who received a minimum of 3 consecutive infusions of emapalumab, and for whom the diagnosis of background disease sJIA and AOSD (i.e., Cohort 1) or SLE (i.e., Cohort 2) is confirmed (e.g., no evidence for malignancy-related HLH or pHLH has emerged after enrollment), and excluding major protocol violators (deviations impacting primary efficacy analysis and leading to exclusion of the impacted patients). The criteria for identifying “major violations” will be defined in the SAP.

This population will be used as a sensitivity analysis of the primary efficacy endpoint.

10.2.3 All screened analysis set

The All Screened Analysis Set will include all patients who signed an ICF.

10.2.4 Run-in phase analysis set

The Run-in Phase Analysis Set will include all patients enrolled in the Run-in phase.

10.3 Overall statistical and analytical plan

All analyzes will be presented separately for each cohort with the exception of safety, PD, PK, ADA, and QoL data that will also be displayed overall.

10.3.1 General statistical issues

For measurements of continuous endpoints, summary statistics will include n, mean, median, standard deviation, minimum, lower quartile, upper quartile, and maximum values. For binary data (proportions of patients showing a defined variable) the counts and percentages will be tabulated.

This is a multicenter study, but due to the low number of patients per cohort, no analyzes by individual centers will be performed.

Sections 10.3.2 to 10.3.9 describe statistical analyzes applicable to the data collected during the Interventional phase. Section 10.3.10 describes analyzes for the Run-in phase.

10.3.2 Demographics and baseline characteristics

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

10.3.3 Analysis related to primary objective

The analysis of the primary endpoint, CR at Week 8 after first administration of emapalumab (see Section 6.1.1), will be performed at Week 8 using an exact binomial test, separately for each cohort.

The primary analysis of the primary endpoints will evaluate the null (H_0) and alternative hypotheses (H_1) defined as follows:

H_0: $p \leq 0.4$ H_1: $p > 0.4$, where p is the proportion of patients with CR in Cohort 1.

H_0: $p \leq 0.3$ H_1: $p > 0.3$, where p is the proportion of patients with CR in Cohort 2.

For Cohort 1:

- At the first interim analysis: if a 2-sided 99 % CI is above the alternative hypothesis (i.e., CR rate > 40 %), the null hypothesis (i.e., CR rate ≤ 40 %) will be rejected.
- At the final analysis (if no stop for efficacy at the first interim analysis): if a 2-sided 96 % CI is above the alternative hypothesis (i.e., CR rate > 40 %), the null hypothesis (i.e., CR rate ≤ 40 %) will be rejected.

For Cohort 2, if a 2-sided 95 % CI is above the alternative hypothesis (i.e., CR rate > 30 %), the null hypothesis (i.e., CR rate ≤ 30 %) will be rejected.

10.3.4 Analysis related to secondary objective

Secondary efficacy endpoints mapped to the secondary efficacy objectives are presented in Table 7 divided by cohort (also see Section 6.2.1).

GCs tapering will be summarized using counts, percentages, and 95 % CI. Summary of time to first achievement of GCs tapering will include for each observed time, the estimate rate, failure rate, number of events and the number of noncensored patients remaining (also called population at risk for survival time endpoint). The median, lower quartile, and upper quartile estimates of time-to-event and their 95 % CI will be tabulated in a separate table. All time-to-event endpoints will be summarized and displayed as described for GCs tapering. A Kaplan-Meier (survival time) or Kaplan-Meier failure (e.g., time to first GCs tapering, time to first CR) graph will also be presented.

For binary endpoints, counts and percentages together with 95 % CIs will be tabulated.

Table 7 Secondary objectives and efficacy endpoints

Objectives	Endpoints	Cohort1	Cohort 2
Secondary Efficacy Objectives and Endpoints			
To demonstrate efficacy of emapalumab with respect to tapering of GCs	GCs tapering to a dose below 50 % of PDN equivalent at the time of emapalumab start or to the same (or lower) dose being administered before the occurrence of MAS (in patients already treated for the underlying condition) whichever occurs first at any time during the study. GCs tapering to ≤ 1 mg/kg/day of PDN equivalent at any time during the study.	x	x
	Time to achieve GCs tapering as defined above	x	x
To evaluate the time to onset of response to emapalumab treatment	Time to first CR	x	x
To evaluate efficacy of emapalumab with respect to OR	OR as defined by CR or PR	x	x
	Time to first OR as defined by CR or PR	x	x
To evaluate the sustained efficacy of emapalumab treatment	MAS recurrence at any time after achievement of CR	x	x
	Withdrawal from the study due to lack of response as per Investigator decision	x	x
To evaluate the patients' survival after treatment with emapalumab	Survival time	x	x

Abbreviations: CR, Complete response; GC, glucocorticoid; MAS, macrophage activation syndrome; OR, Overall response; PDN, prednisolone; PR, Partial response.

10.3.5 Analysis of safety and tolerability data

All data relating to safety (see Section 6.2.1.1) will be listed and summarized using descriptive statistics. For each clinical laboratory test, a shift table will be tabulated and patient level data will be listed. In addition, other exploratory analyzes of safety data, including summaries for different subsets of patients, may be conducted.

10.3.5.1 Adverse events

Reported AEs during the study will be coded using MedDRA and summarized in frequency tables by body system organ class (SOC), and by Preferred Terms within each SOC. AEs will also be tabulated by severity and relationship to the study medication. Separate tabulations will

be performed for serious and nonserious AEs. Summaries will also be produced of SAEs and AEs leading to withdrawal from the study.

10.3.6 Analysis of quality of life assessments

The QoL data will be analyzed descriptively. Analysis of the Exit Interview will not be incorporated in the clinical database and the CSR; it will be performed by an external vendor and provided in a separated document.

10.3.7 Analysis of pharmacokinetics, pharmacodynamics, and immunogenicity

PK, PD and immunogenicity data (see Sections 6.2.1.3, 6.2.1.4, and 6.2.1.5) will be analyzed descriptively; as described in the SAP. In addition, population PK and/or PD modelling might be conducted, potentially using data from other studies. This would be described in a separate analysis plan and reported separately from the CSR.

10.3.8 Analysis related to exploratory objectives

To evaluate the correlation between PD parameters and relevant laboratory parameters per cohort, correlations between CXCL9 and total IFN-γ levels, and laboratory parameters of disease severity, e.g., ferritin, platelet count, and liver function tests may be investigated in each cohort. This work may be conducted as part of a population PK/PD analysis combining data from other studies. If so, this work will be described in a separate analysis plan and reported separately from the CSR.

10.3.9 Interim analyses

A first interim analysis, assessing efficacy, will be performed for Cohort 1 (MAS in the context of sJIA and AOSD) after enrollment of 16 treated patients who have reached the Week 8 Assessment Visit or have discontinued the study early. The purposes of the first interim analysis are to terminate enrollment in Cohort 1 if efficacy is shown and to serve for regulatory submission. If the efficacy is demonstrated at the time of the interim analysis, then the enrollment in this cohort will be stopped by the Sponsor; otherwise the enrollment will continue up to 25 treated patients. The overall type 1 error will be controlled: using simulations the formal stopping efficacy boundary will be determined by a 1-sided exact binomial test at a significance level of 0.5 % to test if the CR rate is significantly above 40 % (see Section 10.1). With 16 treated patients at the time of the interim analysis, the threshold for the efficacy consideration will be 12 out of 16 patients (corresponding to a CR rate of 75 %, i.e., 99 % Exact CI: [0.4009; 0.9545] with lower limit above 40 %).

Note that patient recruitment will not be put on hold in this cohort during the performance of the first interim analysis.

A second interim analysis will be performed for Cohort 1 after enrollement of 25 patients treated with emapalumab who have reached the Week 8 Assessment Visit or have discontinued the study early. The second interim analysis may be used for regulatory submission. For Cohort 1, the null hypothesis (i.e., CR rate ≤ 40 %) will be rejected if a 2-sided 96 % CI is above the alternative hypothesis (i.e., CR rate > 40 %). No formal statistical hypothesis testing will be performed for Cohort 2 at the time of the second interim analysis.

A third interim analysis will be performed for Cohort 2 after enrollement of 16 treated patients who have reached the Week 8 Assessment Visit. The third interim analysis may be used for regulatory submission. The null hypothesis (i.e., CR rate ≤ 30 %) will be rejected if a two-sided 95 % CI is above the alternative hypothesis (i.e., CR rate > 30 %).

10.3.9.1 Multiple comparison and multiplicity

Adjustment for multiple testing due to the interim analysis has been considered. The efficacy analyzes of the 2 cohorts will be performed and presented separately (i.e., independent populations), therefore no adjustment due to testing of the 2 cohorts will be performed. No other multiple testing has been done.

10.3.10 Exploratory subgroup analyzes

Descriptive analysis will be provided on data collected in the Run-in phase. The objective of this phase is to measure response when MAS patients are treated with GCs therapy. In this phase, patients will be followed to assess disease response to GCs alone. The descriptive analyzes will present per cohort: the proportion of patients achieving a CR, the proportion of patients achieving a PR, the proportion of patients achieving PR or CR under GCs alone, the times to first response (CR, CR or PR), and the cumulative dose (from MAS diagnosis until first PR or CR of MAS) of GCs needed to achieve a first response.

Other subgroup analyzes may be considered and described in the SAP.

10.3.11 Handling of missing data

Patients who are prematurely discontinued from the study will be classified as nonresponders from the time of their withdrawal in all analyzes of response status, and their data will be censored at time of withdrawal in all time-to-event analyzes.

For continuous endpoints in patients prematurely withdrawn from the study, all available data will be used in the analyzes. Reasons for early study termination will be presented. Patients prematurely discontinued from treatment will not be excluded in the statistical analysis.

11 Data collection, handling, and record keeping

11.1 Data standards

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

11.2 Case report form

A CRF is required and should be completed for each included patient. In this study an eCRF will be used. The completed original eCRFs are the sole property of Sobi and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities, without written permission from Sobi.

It is the responsibility of the Investigator to ensure completion and to review and approve all CRFs. CRFs must be signed electronically by the Investigator. These signatures serve to attest that the information contained on these CRFs is correct. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

11.3 Source data

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

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

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

11.4 Protocol deviations

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

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

For the purpose of this protocol, deviations requiring notification to CRO are defined as any patients who:

- Entered the study even though they did not satisfy entry criteria.
- Developed withdrawal criteria during the study and were not withdrawn.
- Received wrong treatment or incorrect dose.
- Received excluded concomitant treatment.

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

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

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

11.5 Database closure

Prior to database closure, all tasks or criteria defined in the data management plan must be completed and documented. The study database must be locked before generation of any final CSR results. The database lock will be approved by relevant study personnel and all edit accesses will be removed. Database extracts will be performed for analyzes other than the final analyzes (i.e., interim analyzes).

The study database can only be unlocked if data errors are detected which either have a significant impact on the statistical outcome of the analysis, or affects the safety profile of the investigational product. The database can only be unlocked after the approval from the Study Statistician.

11.6 Record retention

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

All documents and data relating to the study will be kept securely by the Investigator in a secure file and/or electronically. The storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version

history, search and retrieval. The data will be available for evaluation and/or audits from Health Authorities, Sobi, or Sobi's representatives.

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

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

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

12 End of study per cohort and overall

The end of the study per cohort is defined as the date of the last patient's last visit or EOS call in that cohort.

The EOS overall is defined when the last patient enrolled in the study (independent of the cohort) will reach the date of last visit or EOS call.

13 Sponsor's discontinuation criteria

Sobi reserves the right to discontinue the study prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating patients within 30 days. All study materials must be collected and all the CRFs completed to the greatest extent possible.

14 Dissemination and publication of results

Sobi will register the study by posting study information and post study results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations, e.g., on www.clinicaltrials.gov and EudraCT.

Sobi is committed to publishing study results in a complete, accurate, balanced, transparent, and timely manner. Sobi follows the principles of the International Committee of Medical Journal Editors recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals including criteria for authorship [72].

The data from this study will be considered for reporting at a scientific meeting or for publication in a scientific journal. Interim analyzes may be published.

The Sponsor will be responsible for these activities and will work with the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues. The results of the study,

or any part thereof, shall not be published without the prior written consent and approval of Sobi, such consent and approval not to be unreasonably withheld.

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Appendix 1 Quality of life questionnaires

PedsQL™, Pediatric Quality of Life Inventory™: [73]

- Infant, version 1.0, Parent Report for Infants (ages 1-12 months).
- Infant, version 1.0, Parent Report for Infants (ages 13-24 months).
- Core, version 4.0, Parent Report for Toddlers (ages 2-4).
- Core, version 4.0, Young Child Report (ages 5-7).
- Core, version 4.0, Parent Report for Young Children (ages 5-7).
- Core, version 4.0, Child Report (ages 8-12).
- Core, version 4.0, Parent Report for Children (ages 8-12).
- Core, version 4.0, Teenager Report (ages 13-18).
- Core, version 4.0, Parent Report for Teenagers (ages 13-18).
- Core, version 4.0, Young Adult Report (ages 18-25).
- Core, version 4.0, Parent Report for Young Adults (ages 18-25).
- Core, version 4.0, Adult Report (ages over 26).

http://www.pedsql.org

Patient/Parent Global Impression of Severity

For patient
Please choose the response below that best describes the severity of your overall health status over the past week.
□ None □ Mild □ Moderate □ Severe

For caregiver
Please choose the response below that best describes the severity of your child's overall health status over the past week.
□ None □ Mild □ Moderate □ Severe

Clinician Global Impression of Severity

Considering your total clinical experience with this particular population, what response below best describes the overall severity of the status of the patient over the past week?

□ None □ Mild □ Moderate □ Severe

Appendix 2 Exit interview

Exit Interview background and objectives

A telephone or web-enabled interview, referred to as the Exit Interview, may be conducted approximately 2 to 4 weeks following the EOT Visit. The interview is not a mandatory procedure in this study; it will be conducted by an independent CRO in English-speaking countries.

The Exit Interview will provide a qualitative summary to support the QoL assessment from the patient or caregiver perspective, of the patient or caregiver experience of MAS and treatment with emapalumab. Analysis of the Exit Interview will not be incorporated in the clinical database and CSR; it will be performed by an external vendor and provided in a separated document.

Interview questions designed to fully assess the participant/caregiver experience in this clinical program will be administered in a semi-structured format. The interview will be conducted by an independent trained qualitative researcher from a third party. A third party will also conduct the analyzes and develop the report.

The interview will be audio-recorded for subsequent transcription and qualitative analysis. Final de-identified transcripts will serve as source data; audio files will be deleted at the completion of data collection for the Exit Interview substudy.

The specific objectives of the interview:

- Understand symptoms and impacts of MAS, including changes experienced during the study.
- Determine which changes during the study are most meaningful to both patients and caregivers.
- Identify potential unanticipated treatment benefits.
- Complement/supplement the interpretation of patient-reported study data (PedsQL, clinician and caregiver/patient global assessment change) and identify gaps where emerging concepts have not been captured by the study patient-reported outcome measures.
- Gather qualitative data pertaining to treatment satisfaction.
- Gather qualitative data pertaining to the experience of participating in the study.

For adult patients, the interview will last up to 60 minutes. The interview may last up to 90 minutes for children aged 6 to 17 years to allow time for discussion with both the child and parent/legal representative. For children under age 6 years, the interview will be conducted with the parent/legal representative only and will last up to 60 minutes.

Informed consent

The site investigator will ask each patient/parent/legal representative to participate in the Exit Interview and will provide the Exit Interview ICF for review before the patient/parent/legal guardian agrees to participate. Consent should be documented prior to transfer of contact information to the interviewer and completion of the interview. Caregivers will also be asked to

confirm their consent at the start of interviews prior to the start of audio-recording. Participants will be identified using a coded number, and the data used in the analyzes will be completely de-identified.

Interview procedures

After consent is documented at the site, the contact information will be provided by the site investigator or staff and securely transferred to the interviewer team, who will contact the caregiver directly to schedule and conduct the interview either by telephone or video-conference. At the start of the interview, participants will be reminded that their involvement in the study is voluntary and that if there are any questions they do not feel comfortable answering, they do not have to answer them. They will also be reminded that they are free to stop the interview at any time. Participants will provide verbal consent to be recorded.

The interviews will start with a series of open-ended questions to explore issues and themes of direct importance to participants. Probes will be used for follow-up lines of questioning or to raise topics/issues of interest that do not emerge organically. The interview guide will also include several closed-ended questions.

Qualitative data transcription & analysis

Audio-recordings will be transcribed, and transcripts de-identified prior to analysis. Methodologically, a thematic approach will be applied to the qualitative data in order to identify patient/caregiver experiences related to the clinical study, including but not limited to natural disease history (signs and symptoms), meaningful treatment benefits, study participation, and other concepts of importance. Closed-ended questions will be summarized with frequency tables and descriptive statistics as appropriate (e.g., means, standard deviations).

Analyzes will use facilitated qualitative data analysis software to manage and organize the transcript data. An initial codebook structure will be developed based on the interview guide, with preliminary code definitions based on initial review of transcripts. Analysts will assign codes to segments of transcripts (quotations), following an inductive approach by adding new codes or refining existing codes based on the data contained within the transcripts. To ensure reliability, a portion of the data (approximately 10% of the transcripts) will be double-coded independently by 2 analysts at the start of the coding process. The transcripts will be compared and any differences will be discussed with a third member of the project team, with the codebook revised accordingly.

Appendix 3 Diagnosis of macrophage activation syndrome

2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: A European League Against Rheumatism/American College of Rheumatology/Pediatric Rheumatology International Trials Organisation Collaborative Initiative [16]

A febrile patient with known or suspected systemic juvenile idiopathic arthritis is classified as having macrophage activation syndrome if the following criteria are met:

- Ferritin > 684 ng/mL

and any two of the following:

- Platelet count ≤ 181 $x10^9$/L
- AST levels > 48 U/L
- Triglycerides > 156 mg/dL
- Fibrinogen levels ≤ 360 mg/dL.

Appendix 4 Operational case definition of new onset sJIA used in development of treatment plans (designed by Childhood Arthritics and Rheumatology Research Alliance) [74]

Patient should have: 1. Age 6 months to 18 years 2. Fever[1] for at least 2 weeks 3. Arthritis[2] in one or more joints (6 weeks duration not required) 4. At least one of the following: a. Evanescent erythematosus rash b. Generalized lymphadenopathy c. Hepatomegaly or splenomegaly d. Pericarditis, pleuritis, and/or peritonitis
Patient should not have any of the following: 1. Infection: including concomitant active or recurrent chronic bacterial, fungal or viral infection at presentation; nor underlying infection which may mimic initial presentation of Sjia[3] 2. Malignancy[3] 3. Positive screening test for TB without documented past treatment 4. Prior treatment for sJIA other than NSAIDs or short-term steroids[4] 5. Immunization with live virus vaccines within the 4 weeks prior to enrollment

Abbreviations: AS, Ankylosing spondylitis; IBD, Inflammatory bowel disease; ILAR, International League Against Rheumatism; IVIG, intravenous immunoglobulin; NSAID, Nonsteroidal anti inflammatory drug, RF, Rheumatoid factor; sJIA, Systemic juvenile idiopathic arthritis; TB, Tuberculosis.

[1] Daily fever is not required, but must at some point exhibit a quotidian fever pattern, defined as fever that rises to ≥ 39 °C at least once a day and returns to ≤ 37°°C between fever peaks.

[2] Swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness, is observed by a physician, and which is not due to primarily mechanical disorders or to other identifiable causes.

[3] Infections, malignancy and other diagnoses which can present with similar symptoms as sJIA should be excluded before initiating treatment plans for new onset sJIA in order to avoid unintended adverse effects of the treatment plans if used for other diagnoses.

[4] Prior treatment with steroids should not exceed 2 weeks of oral steroids, and/or 3 pulses of methylprednisolone. Prior treatment with IVIG for possible Kawasaki Disease is allowed. Duration of NSAIDs is without restriction.

NOTE: The above is not meant to represent diagnostic nor classification criteria for sJIA. The differences between this operational case definition and the ILAR criteria are:

- ILAR specifies that the duration of *quotidian* fever must be 3 days (the total duration of fever is two weeks in both).
- ILAR specifies six weeks' duration of arthritis.
- Psoriasis, positive RF, arthritis in HLA B27 positive male after 6 years of age, family history of AS, IBD with sacroiliitis, acute anterior uveitis and reactive arthritis are listed as exclusions in the ILAR definition.

Appendix 5 Preliminary criteria for classification of adult Still's disease [75]

Classification of adult Still's disease requires 5 or more criteria including 2 or more major criteria[1]. Any disease listed under "Exclusions" should be excluded.

Major criteria: • Fever of 39 °C or higher, lasting 1 week or longer. • Arthralgia lasting 2 weeks or longer. • Typical rash[2]. • Leukocytosis (10.000/mm3 or greater) including 80 % more of granulocytes.
Minor criteria: • Sore throat. • Lymphadenopathy and/or splenomegaly[3]. • Liver dysfunction[4]. • Negative RF and negative ANA[5].
Exclusions: • Infections (especially, sepsis and infectious mononucleosis). • Malignancies (especially, malignant lymphoma). Rheumatic diseases (especially, polyarteritis nodosa and rheumatoid vasculitis with extraarticular features).

Abbreviations: ANA, Antinuclear antibody; IgM. Immunoglobulin M; RF, Rheumatoid factor.

[1] All criteria are applicable only in absence of other clinical explanations.

[2] Macular or maculopapular nonpruritic salmon-pink eruption usually appearing during fever.

[3] Lymphadenopathy is defined as recent development of significant lymph node swelling, and splenomegaly is confirmed on palpation or by an echogram.

[4] Liver dysfunction is defined as an abnormally elevated level of transaminases and/or lactate dehydrogenase, which is attributed to liver damage associated with this disease but not with drug allergy/toxicity or other causes. For the differentiation, it is recommended to see if liver function returns to normal upon discontinuation of hepatotoxic drug or not, before applying this criterion.

[5] RF in serum must be negative by routine test for the detection of IgM RF, and serum ANA must be negative by routine immunofluorescence test.

Appendix 6 Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus [76]

A patient is classified as having SLE if the patient satisfies 4 of the criteria listed in the table below, including at least one clinical criterion and one immunologic criterion. OR The patient has biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies.

Clinical Criteria	Immunological Criteria
1. Acute cutaneous lupus: including lupus malar rash (do not count if malar discoid) bullous lupus toxic epidermal necrolysis variant of SLE maculopapular lupus rash photosensitive lupus rash *in the absence of dermatomyositis* or subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias) 2. Chronic cutaneous lupus: including classical discoid rash localized (above the neck) generalized (above and below the neck), hypertrophic (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap 3. Oral ulcers: palate buccal tongue or nasal ulcers *in the absence of other causes, such as vasculitis, Behcet's, infection (herpes), inflammatory bowel disease, reactive arthritis, and acidic foods* 4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs): *in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia* 5. Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and	1. ANA above laboratory reference range 2. Anti-dsDNA above laboratory reference range, except ELISA: twice above laboratory reference range 3. Anti-Sm: presence of antibody to Sm nuclear antigen 4. Antiphospholipid antibody: any of the following: lupus anticoagulant, false-positive RPR, medium or high titer anticardiolipin (IgA, IgG or IgM), anti-β2 glycoprotein I (IgA, IgG or IgM) 5. Low complement: low C3, low C4, low CH50 6. Direct Coombs test *in the absence of hemolytic anemia*

Clinical Criteria	Immunological Criteria
30 minutes or more of morning stiffness 6. Serositis: typical pleurisy for more than 1 day or pleural effusions or pleural rub, typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day or pericardial effusion or pericardial rub or pericarditis by EKG *in the absence of other causes, such as infection, uremia, and Dressler's pericarditis* 7. Renal: Urine protein/creatinine (or 24-hour urine protein) representing 500 mg of protein/24 hour or Red blood cell casts 8. Neurologic: seizures, psychosis, mononeuritis multiplex (*in the absence of other known causes such as primary vasculitis myelitis*) peripheral or cranial neuropathy(*in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus*) acute confusional state (*in the absence of other causes, including toxic-metabolic, uremia, drugs*) 9. Hemolytic anemia *10.* Leukopenia (< 4000/mm^3 at least once) *in the absence of other known causes such as Felty's, drugs, and portal hypertension* OR Lymphopenia (< 1000/mm^3 at least once) *in the absence of other known causes such as glucocorticoids, drugs and infection* 11. Thrombocytopenia (<100,000/mm^3) at least once *in the absence of other known causes such as drugs, portal hypertension, and TTP*	

Abbreviations: ANA, Antinuclear antibodies; anti-dsDNA, Anti-double stranded DNA; DNA, Deoxyribonucleic acid; ELISA, Enzyme-linked immunosorbent assay; EKG, Electrocardiogram; IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M; RPR, Rapid plasma reagin; SLE, Systemic lupus erythematosus; TTP, Thrombotic thrombocytopenia purpura.

Appendix 7 Study administrative structure

Study center:	Sites in EU, US, Japan, China, and Russia.
Monitoring:	Pharmaceutical Research Associates, Inc., Raleigh, North Carolina, USA (CRO).
SAE reporting:	SOBI AB (publ).
Data management:	Pharmaceutical Research Associates, Inc., Raleigh, North Carolina, USA (CRO).
Statistics:	Pharmaceutical Research Associates, Inc., Raleigh, North Carolina, USA (CRO).
Pharmacokinetics:	SOBI AB (publ).
Investigational products (production):	Emapalumab NI-0501 see Section 7.2.3
Investigational products (packaging and labeling):	See Section 7.2.3.1
Clinical laboratory:	All clinical laboratory safety assessments will be performed at the local hospital.
Pharmacokinetics and Bioanalysis:	The pharmacokinetics and pharmacodynamic biomarkers assessments will be performed in a central laboratory. Details on these laboratories will be provided in a dedicated bioanalytical plan.

Appendix 8 Additional protocol signatures

Sponsor's Clinical Study Manager

[redacted]

Clinical study manager

[redacted]

Signature

Date

Sponsor's Statistician

[redacted]

Program Statistician, emapalumab

[redacted]

Signature

Date

Appendix 9 Summary and rationale for protocol amendment 2

Appendix 9.1 Amendment 2 summary

This non-substantial amendment includes the following changes to the Clinical Study Protocol version 2.0, dated 22 February 2022:

- Updated, schedules of assessment to include the ECG at the End of Study, in Table 6, as required in section 7.3.4.5
- Changed details of Clinical Study Physician
- Changed details of Clinical Study Manager
- Introduction of a third interim analysis and change in timepoint for when the second interim analysis will be performed
- Addition of a footnote to clarify how to manage patients that go into MAS remission earlier than the anticipated 4 weeks of treatment as well as correction of the order of the footnotes in Table 5
- Clarification of timepoint when assessments should be done at baseline
- Clarification that reason for lack of fever at the time of patient enrolment must be explained in patient medical records
- Clarification how to manage PK sampling in case the same line as emapalumab infusion is used for sampling
- Clarification as to when post-infusion PK-samples are expected to be collected
- Removal of the statement that bioanalytical plans will be signed off prior to shipment of any samples to bioanalytical laboratories
- Amended Appendix 9.1 to summarise the changes in the protocol amendment 2 and the reasons for the amendment

In addition to the above mentioned changes, cross-references have been updated, and minor typographical, editorial, grammatical corrections and clarifications have been made.

Appendix 9.2 Reason for amendment 2

This protocol amendment is to accommodate a request from the FDA for additional data and analyses.

Other minor updates were included as they had been identified during the study conduct as inconsistencies or topics requiring further detail for a common understanding of study conduct.