Study title: A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of emapalumab, an anti-interferon gamma (anti- IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) or Adult-onset Still's Disease (AOSD) developing Macrophage Activation Syndrome/secondary HLH (MAS/sHLH)

ClinicalTrials.gov ID: NCT03311854

Protocol and protocol amendments

Final protocol, version 2.0 US, dated 07 January 2020

Final protocol, version 1.0 US, dated 19 October 2017

sobi

Clinical Study Protocol

A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) or Adult-onset Still's Disease (AOSD) developing Macrophage Activation Syndrome/secondary HLH (MAS/sHLH)

Protocol number:	NI-0501-06
Version:	2.0 US – Final
Date:	7 January 2020
P-IND Number:	111015
Sponsor:	Swedish Orphan Biovitrum AG 12 Chemin des Aulx 1228 Plan-les-Ouates Switzerland
Sponsor Address for Study-Related Correspondence:	Swedish Orphan Biovitrum AG Messeplatz 10 4058 Basel Switzerland
Study Principal Investigator	[redacted]
Senior Clinical Science Leader	[redacted]
Chief Medical Officer Immunology	[redacted]

INVESTIGATOR AGREEMENT

Protocol Number: NI-0501-06

Protocol date and version: 7 January 2020 – VERSION 2.0 US

Study drug: emapalumab, also referred to as NI-0501

Study title: A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) or Adult-onset Still's Disease (AOSD) developing Macrophage Activation Syndrome/secondary HLH (MAS/sHLH).

Investigator endorsement:

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

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

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

_____ _____

Site Investigator's Signature Date

_____

Site Investigator's Name

CONTACT LIST

Study Location:	Multicenter in North America
Study Principal Investigator:	[redacted]
Sponsor:	Sobi AG 12 Chemin des Aulx 1228 Plan les Ouates Switzerland [redacted]
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Sr. Clinical Science Leader:	[redacted]
Clinical Operations Manager:	[redacted]
Clinical Pharmacologist:	[redacted]
Data Protection Officer	[redacted]

NI-0501-06 SYNOPSIS

Title:	A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) or Adult-onset Still's Disease (AOSD) developing Macrophage Activation Syndrome/ secondary HLH (MAS/sHLH)
Sponsor:	Sobi AG, Switzerland
Study Type, Phase and Design:	• Interventional Phase 2 study • Open-label, single arm, international, multicenter study. ***Please note***: any reference made to MAS in this protocol should be intended as referring to the secondary form of HLH occurring in patients with sJIA/AOSD.
Study Objectives:	The main objectives of the study are: • To describe the pharmacokinetics (PK) profile of emapalumab • To confirm the proposed dosing regimen of emapalumab. • To evaluate the safety and tolerability profile of intravenous (i.v.) administrations of emapalumab • To assess the efficacy of emapalumabTo assess the levels of relevant pharmacodynamic markers, such as IFNγ and main IFNγ-induced chemokines (CXCL9, CXCL10). • To assess other potential disease markers (e.g. sCD25, sCD163, IL-10, IL-6, IL-18, TNFα). • To assess the immunogenicity of emapalumab
Study Population:	• sJIA and AOSD patients with MAS having shown inadequate response to high dose glucocorticoid treatment.
Inclusion Criteria:	• Patients of both genders • sJIA patients: confirmed sJIA diagnosis. For patients presenting with MAS in the context of the onset of sJIA, high presumption of sJIA (as per Appendix A) will suffice for eligibility • AOSD patients: confirmed AOSD diagnosis as per Yamaguchi criteria (Appendix E) • Diagnosis of active MAS confirmed by the treating rheumatologist, having ascertained the followings: *Febrile patient presenting with:* - Ferritin > 684 ng/mL *and any two of:* - Platelet count ≤ 181 x10^9/L - AST levels > 48 U/L - Triglycerides > 156 mg/dL - Fibrinogen levels ≤ 360 mg/dL. (see Appendix B) • Patient presenting an inadequate response to high dose i.v.

	glucocorticoid treatment administered for at least 3 days as per local standard of care (including but not limited to pulses of 30 mg/kg methylprednisolone (mPDN) on 3 consecutive days). High i.v. glucocorticoid dose should not be lower than 2 mg/kg/ day of PDN equivalent in 2 divided doses (or at least 60 mg/day in patients of 30 kg or more). In case of rapid worsening of the patient's condition and/or lab parameters, inclusion may occur within less than 3 days from starting high dose i.v. glucocorticoids. • Tocilizumab, TNF inhibitors and canakinumab, if administered, have to be discontinued before emapalumab initiation. • Informed consent provided by the patient (as required by local law), or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as applicable. • Having received guidance on contraception for both male and female patients sexually active and having reached puberty: Females of child-bearing potential require use of highly effective contraceptive measures (failure rate of less than 1% per year) from screening until 6 months after receiving last dose of the study drug. Highly effective contraceptive measures include: o Sexual abstinence o Hormonal contraceptives: combination or progesterone only o Intrauterine methods: intrauterine devices or systems o Bilateral tubal occlusion o Vasectomised partner Males with partners(s) of child-bearing potential must agree to take appropriate precautions (such as sexual abstinence, barrier contraception, vasectomy) to avoid fathering a child from screening until 6 months after receiving last dose of the study drug.
Exclusion Criteria:	• Diagnosis of suspected or confirmed primary HLH or HLH consequent to a neoplastic disease. • Active mycobacteria (typical and atypical), *Histoplasma Capsulatum*, *Shigella*, *Salmonella*, *Campylobacter* and *Leishmania* infections. • Clinical suspicion of latent tuberculosis. • Positive serology for HIV antibodies. • Presence of malignancy. • Patients who have another concomitant disease or malformation severely affecting the cardiovascular, pulmonary, CNS, liver or renal function that in the opinion of the Investigator may significantly affect likelihood to respond to treatment and/or assessment of emapalumab safety. • History of hypersensitivity or allergy to any component of the study drug. • Receipt of a BCG vaccine within 12 weeks prior to screening. • Receipt of live or attenuated live vaccines (other than BCG) within 6 weeks prior to screening.

	• Pregnant or lactating female patients.
Study Drug:	• Emapalumab, previously referred to as NI-0501, is a fully human IgG1 monoclonal antibody (mAb) directed against human IFNγ.
Dosing Regimen, Frequency of Administration & Treatment Duration:	• Emapalumab will be administered at the initial dose of 6 mg/kg by infusion. • Emapalumab treatment will be continued at the dose of 3 mg/kg, every 3 days until SD15, and then twice-a-week for additional 2 weeks, i.e. until SD28. • Treatment may be shortened upon achievement of complete clinical response (i.e. MAS remission), however at least two infusions of emapalumab at the dose of 3 mg/kg have to be administered (i.e. after SD6). • In the absence of a trend of improvement in key MAS parameters (including, but not limited to ferritin, LDH, AST/ALT and PLT count) suggestive of lack of response, the emapalumab regimen may be adapted (the frequency between infusions shortened, the dose increased or the treatment prolonged beyond 4 weeks) upon assessment of a favorable benefit/risk profile.
Background Therapy & Concomitant Medication:	• Emapalumab will be administered on a background of at least 2 mg/kg/day of PDN equivalent (or at least 60 mg/day in patients of 30 kg or more), which can be tapered during the treatment depending on patient conditions. Cyclosporine A (CsA) may be continued if started at least 3 days prior to initiation of emapalumab treatment. CsA dose adjustments are allowed in order to maintain therapeutic levels. CsA can be withdrawn at any time during the study, upon judgment of the Investigator. CsA should not be introduced once emapalumab treatment has started. • Patients must receive prophylactic treatment for *Herpes Zoster* infections starting preferably the day before (and in any case prior to initiation of emapalumab treatment), and treatment must continue until serum emapalumab levels are no longer detectable. • If being administered and if started (at any dose) at least 3 days before initiation of emapalumab treatment, anakinra may be continued at a maximum dose of 4mg/kg. • Tocilizumab, canakinumab or TNF inhibitors as sJIA/AOSD treatment must be discontinued at the latest before the first emapalumab infusion. • Methotrexate may be continued if ongoing as treatment for the underlying disease. • In the case of an acute inflammatory flare of the underlying sJIA/AOSD during treatment with emapalumab, anakinra may be introduced at a dose of 1 to 4 mg/kg (max. daily dose 100 mg). Such episodes shall be adjudicated by at least two members of the SSC (excluding the treating physician, if applicable), in order to ascertain their nature (i.e. sJIA/AOSD versus MAS flare). • If the patient is receiving intrathecal therapy (e.g. methotrexate and glucocorticoids) at the time of emapalumab treatment initiation, this treatment will be continued until clinically indicated. • Vaccination with a live or attenuated-live (including BCG) vaccine must be avoided during the whole study until serum emapalumab

	levels are no longer detectable. • Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, i.v. parenteral nutrition, inotropic support, antibiotics, anti-fungal and anti-viral treatments, ultrafiltration or hemodialysis, as well as general supportive care are permitted.
Sample Size:	• Approximately 12 patients (and a minimum of 10 sJIA patients) will be enrolled in North America and Europe in total.
Number of Sites and Recruitment Duration:	• International, multi-center. • The recruitment period, in this rare population, is estimated to be approximately 2 years. A twin protocol NI-0501-06 EUDRACT 2016-004223-23 is running in Europe. • Patients enrolled under these two protocols will be analyzed jointly and data reported in a single CSR.
Study Duration and Study End Definition:	• The duration of the study will be at least 8 weeks for each patient (*plus* up to 1 week screening period). A short-term follow-up of 4 weeks follows SD28 or the last emapalumab infusion whichever occurs later [***Note***: If emapalumab treatment is prolonged beyond 4 weeks in a given patient, additional visits will be performed weekly until completion of a 4-week follow-up after the last emapalumab infusion, short-term follow-up that should occur under the present protocol]. • End of the study is defined as last patient last visit. • All patients who have received at least one dose of emapalumab will be asked to enter a long-term follow-up study.
Study Scientific Oversight/ Study Safety Monitoring :	• A Scientific Steering Committee (SSC) composed of international experts in pediatric rheumatology as well as in HLH has been involved in the preparation of study design and will continue to play an advisory role throughout the course of the study, to support the iDMC in the study oversight, and the Sponsor in the interpretation of the study results. • An independent Data Monitoring Committee (iDMC) composed of relevant experts (pediatric rheumatologist, hemato-oncologist with experience in HLH, pediatric immune deficiency/infectious disease specialist, bio-statistician and a specialist in ethics) will oversee the safety management of the study, reviewing all data generated on an ongoing basis with the aim to ensure that patients are not exposed to unnecessary risks.
Study Endpoints:	**Pharmacokinetics and Pharmacodynamics** • PK profile of emapalumab. • Levels of circulating free IFNγ at pre-dose, and total IFNγ (free IFNγ+bound to emapalumab) after initiation of emapalumab. • Levels of the main IFNγ-induced chemokines (CXCL9, CXCL10). • Correlation between chemokine levels (CXCL9, CXCL10) and levels of free emapalumab, free IFNγ (pre-dose) and total IFNγ

(*exploratory analysis*).

- Correlation of chemokine and total IFNγ levels, and laboratory parameters of MAS severity, e.g. ferritin, platelet count, LFTs (*exploratory analysis*).
- Levels of other potential disease markers (e.g. sCD25, sCD163, IL-10, IL-6, IL-18, TNFα).
- Levels (if any) of circulating antibodies against emapalumab to determine immunogenicity (ADA).

In particular, based on:

- levels of circulating emapalumab
- levels of total IFNγ
- levels of IFNγ–induced chemokines (namely CXCL9 and CXCL10)

a PK/PD modelling will be used to confirm that the proposed dose regimen is adequate in relation to the IFNγ production in this patient population.

Safety

The tolerability and safety of emapalumab treatment will be assessed as follows:

- Incidence, severity, causality and outcomes of AEs (serious and non-serious), with particular attention being paid to infections.
- Evolution of laboratory parameters, in particular CBC, LFTs, inflammatory markers (ferritin and CRP) and coagulation parameters.
- Number of patients withdrawn from the study due to safety reasons.

Efficacy

An assessment of emapalumab efficacy in this patient population will be based on the following variables:

- Number of patients achieving MAS remission by Week 8 after initiation of emapalumab treatment.
- Time to MAS remission.
- Number of patients for whom at any time during the study glucocorticoids can be tapered *i)* to the same (or lower) dose being administered before the occurrence of MAS (in those patients who are already treated for the underlying condition) or *ii)* by 50% (or less) of the dose administered at emapalumab treatment start (in those patients who present with MAS at disease onset).
- Time to glucocorticoids tapering (as above described).
- Survival time.
- Number of patients withdrawn from the study due to lack of efficacy.

Statistical Analysis:	• All study variables are considered to be exploratory in this study, and no hierarchy of endpoints has been specified, as the objective of this pilot study is to collect and analyze data to confirm that the proposed dose regimen is adequate in this patient population. Statistical methods will therefore focus on summarizing the data collected using descriptive statistics and on appropriate graphical

	presentations. • For binary endpoints (MAS remission by Week 8, number of patients who taper glucocorticoids, number of patients who discontinue due to lack of efficacy), 95% confidence intervals will be calculated for proportions. • For time to event endpoints (time to MAS remission, time to achievement of glucocorticoids tapering and time to death), Kaplan-Meier curves will be calculated and summary statistics, such as medians, proportions event-free at various time points will be calculated and presented, and 95% confidence intervals calculated where possible. • Data relating to safety will be listed and summarised using descriptive statistics.

LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-drug-antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AOSD	Adult-onset Still's Disease
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BCG	Bacillus Calmette-Guérin
BSA	Body Surface Area
CBC	Complete blood cell count
CDC	Complement Dependent Cytotoxicity
CL	Systemic drug clearance
C_{max}	Peak drug plasma concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CpG	Cytosine-phosphate-guanine
CRF	Case report form
CRP	C-reactive protein
CsA	Cyclosporin A
CSF	Cerebrospinal fluid
C_{trough}	Plasma drug concentration immediately prior next dosing
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
EBV	Epstein-Barr virus
EoT	End of treatment
EoS	End of study
γGT	Gamma Glutamyl Transferase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
HSCT	Hematopoietic stem cell transplantation

HSV	Herpes simplex virus
HZ	Herpes Zoster
HZV	Herpes Zoster virus
ICMJE	International Committee of Medical Journal Editors
iDMC	Independent Data Monitoring Committee
IFNγ	Interferon gamma
IFNγ-R1	Interferon gamma receptor chain 1
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IgG1	Immunoglobulin G1
IL	Interleukin
ILAR	International League of Associations for Rheumathology
IMP	Investigational medicinal product
ITT	Intention-to-treat
i.v.	Intravenous
KD	Dissociation constant
KM	Michaelis-Menten constant
KO	Knock Out
LCMV	Lymphocytic choriomeningitis virus
LDH	Lactate dehydrogenase
LFTs	Liver function tests
LLN	Lower limit of normal
mAb	Monoclonal antibody
MAS	Macrophage activation syndrome
mPDN	Methylprednisolone
MRI	Magnetic resonance imaging
NK	Natural killer
NaCl	Sodium chloride
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PDG	Preliminary diagnostic guidelines (Ravelli *et al.*, 2005)
PDN	Prednisone
pHLH	Primary HLH
PK	Pharmacokinetic
PLT	Platelets
PPD	Purified protein derivative
PT	Prothrombin Time
SAE	Serious adverse event
SAP	Statistical analysis plan

SAD	Single ascending dose
sCD25	soluble CD25 (i.e. soluble IL-2 receptor)
SD(n)	Study Day number (e.g. Study day 1 = SD1)
sJIA	Systemic Juvenile Idiopathic Arthritis
SoA	Schedule of assessments
SSC	Scientific steering committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
$t_{1/2}$	Elimination half-life
Tmax	Time when plasma concentration is at peak
TMDD	Target mediated drug disposition
TMF	Trial Master File
TNFα	Tumor necrosis factor alpha
ULN	Upper limit of normal
US	Ultrasonography
Vss	Volume of distribution at steady state

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PART I

1 BACKGROUND INFORMATION

1.1 EMAPALUMAB

1.1.1 Description and mode of action

Emapalumab is a fully human IgG1 anti-interferon gamma (IFNγ) monoclonal antibody (mAb) which binds and neutralizes IFNγ. emapalumab binds to soluble and receptor (IFNγR1)-bound forms of IFNγ.

Since emapalumab is a human IgG1, it retains the characteristics of this immunoglobulin isotype.

After binding to its receptor, IFNγ acts to produce a variety of physiological and cellular responses. Numerous studies over the last 20 years have associated IFNγ with the pathogenesis and the maintenance of inflammatory diseases (Billiau A 1996, Schoenborn JR 2007, Zhang SY 2008), and most recently, in the pathogenesis of HLH.

1.1.2 Preclinical Data

1.1.2.1 Non-clinical Pharmacology

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

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

1.1.2.2 Toxicology

Binding and functional data demonstrated *Rhesus* or *Cynomolgus* monkeys to be relevant species to evaluate the safety of emapalumab. No off-target toxicity was attributed to the drug when administered to *Cynomolgus* monkeys in 13 weekly doses of up to 200 mg/kg. An enhanced susceptibility to infections due to the pharmacological effect of the drug was observed at all dose levels (10 to 200 mg/kg/week) in animals originally harboring gastrointestinal pathogens (*Shigella, Salmonella, Campylobacter*) prior to emapalumab administration. In a study where *Cynomolgus* monkeys were not initially found to be harboring gastrointestinal pathogens, weekly administrations of emapalumab for 8 consecutive weeks at doses up to 30 mg/kg were well tolerated, without the need for antibiotic prophylaxis.

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

1.1.2.3 Safety pharmacology

There were no abnormal findings in ECGs taken periodically during treatment and recovery periods in the 8 week and 13 week repeated dose toxicology studies in *Cynomolgus* monkeys, where animals were exposed to doses up to 200 mg/kg of emapalumab weekly. No abnormal findings were observed in the histopathological investigations of the hearts and lungs in these animals compared to untreated

animals. Histopathological analysis of kidneys from these animals revealed no abnormal findings and the periodic urinalysis readings were also normal, indicating no abnormal effects on renal function. There were no histopathological findings in brains in both studies. Furthermore, no abnormal behavior of the animals was observed throughout the study periods, suggesting no effects on CNS.

1.1.3 Clinical Data

Note to the reader: in order to reflect the information available at the time the study was initiated this section is not being updated. Please refer *to the most current Investigator`s Brochure to ensure awareness of the data that served as basis for the approval of emapalumab in the US for the treatment of adult and pediatric (newborn and older) patients with pHLH with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy and to ensure awareness of all available clinical data.*

A Phase 1 randomized double-blinded placebo-controlled single ascending dose study in 20 healthy adult volunteers investigating the safety, tolerability and pharmacokinetic profiles of single intravenous (i.v.) administrations of emapalumab was conducted between September 2011 and April 2012. During this study a total of 14 subjects received increasing doses of 0.01, 0.1, 1, and 3 mg/kg emapalumab (3, 3, 4, and 4 subjects, respectively), while 6 subjects received placebo.

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

All emapalumab infusions were uneventful.

A similar incidence of commonly reported infections (e.g., upper respiratory tract infections) was observed after administration of emapalumab and in subjects who had received placebo.
A Herpes Zoster (HZ) infection was reported in one subject ([redacted]), 14 days after his infusion of 3 mg/kg of emapalumab. This event was assessed as related to the emapalumab infusion and considered as serious (medically significant) in the context of a Phase 1 study in healthy volunteers (HVs). Its intensity was moderate and its course normal under antiviral therapy. The subject recovered with no sequelae.
An increased susceptibility to HZ infections in patients having developed auto-antibodies against IFNγ (Browne SK 2012) or having received ustekinumab (a mAb which decreases IFNγ production by inhibiting the p40 subunit of IL-12) has been described in the literature (Failla V 2011).

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

A study to evaluate the efficacy and safety of emapalumab treatment in patients with primary HLH (protocol NI-0501-04) has been completed. The protocol allows for inclusion of patients either treatment-naïve (first line patients) or reactivating after initial response to conventional therapy or not achieving a satisfactory response or showing intolerance to conventional therapy (second line patients). Based on preliminary efficacy and safety evidence, and on the positive benefit/risk profile observed so far, the study, which originated as Phase 2 trial, has been recently amended to continue as Phase 2/3 study with the inclusion of the same study population (i.e., first and second line pHLH patients). Thirty-one patients have been enrolled as of September 15th 2016, of whom 18 received transplantation. Five patients received emapalumab as 1st line therapy. More than 500 emapalumab infusions have been performed in the study patients who have received a median of 7 weeks of therapy (range 4 days-31 weeks; continuation of emapalumab treatment beyond 8 weeks can occur

under the long-term follow-up protocol NI-0501-05). Infusions have been well tolerated with no premedication needed, and no safety concerns after emapalumab administration have emerged to date. Based on data gathered so far, emapalumab treatment has shown the potential to improve relevant clinical and laboratory features of HLH such as fever, splenomegaly, cytopenia, hyperferritinemia, hypofibrinogenemia, and also CNS signs and symptoms. Early tapering of glucocorticoids has been possible in the majority of patients.

For updated information about the above, please refer to the most recent Investigator`s Brochure.

1.2 HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

HLH is a rare, serious and life threatening disease of pathologic immune activation, characterized by clinical signs and symptoms of extreme inflammation (fever, splenomegaly, cytopenias, coagulopathy), leading to the development of abnormal immune-mediated pathologies which, through tissue damage, ultimately may cause multi-organ failure and death (Henter JI(a) 1991).
HLH comprises primary (genetic/familial) HLH and secondary HLH.

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

The genetic defects in primary HLH affect genes involved in cytotoxic pathway of NK-cells and/or cytotoxic lymphocytes required to eliminate activated macrophages, encoding proteins for perforin synthesis, cytolytic granule maturation, granule exocytosis and release (Filipovich A 2010). In addition, some immunodeficiency syndromes, e.g. Griscelli syndrome type 2 (GS-2) and Chediak-Higashi syndrome (CHS), present frequently with HLH (Janka GE(b) 2013).

Secondary forms of HLH can occur during the course of an infection, an autoimmune/rheumatic disease or in association to a malignancy. Secondary forms present with the same signs and symptoms of primary HLH and can be equally severe.

The presence of signs and symptoms of HLH in patients suffering from a rheumatic disease, such as systemic Juvenile Idiopathic Arthritis (sJIA) and Systemic Lupus Erythematosus (SLE), is often referred to by rheumatologists as Macrophage Activation Syndrome (MAS), as more specifically described in the following section.

Adult-onset Still's disease is a rare autoinflammatory disorder sharing the same clinical manifestations and laboratory findings of sJIA (Jamilloux Y 2015). 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 (Giampietro C 2012, Feist E 2018, Nirmala N 2015).

Importantly, clinical similarities include a clear predisposition to develop MAS in both sJIA and AOSD (Ruscitti P 2017).

In the present protocol, any reference made to MAS should be intended as referring to the secondary form of HLH occurring in patients with sJIA/AOSD.

1.2.1 Macrophage Activation Syndrome (MAS)

MAS is a severe, potentially life-threatening complication of rheumatic diseases which is caused by excessive activation and expansion of T lymphocytes and macrophages. The uncontrolled expansion

of these immune cells results in a marked hypercytokinemia and a hyperinflammatory state associated with fever, cytopenias, hepatosplenomegaly, liver dysfunction, coagulation abnormalities and hyperferritinemia, and may progress to multiple organ failure and death (Schulert GS 2015).

Because of its strong clinical and pathological similarity to HLH, MAS is classified among the secondary or acquired forms of HLH. In fact, it has been recently demonstrated that the majority of patients with MAS have impaired NK and perforin functional tests and that a significant number of MAS patients show polymorphisms or heterozygous mutations in PRF1 and UNC13D (Zhang M 2014).

MAS occurs most frequently in patients with sJIA and AOSD, less often with systemic lupus erythematosus (SLE), but is also described, though more rarely, in patients with vasculitis, particularly with Kawasaki disease. Approximately 7–17% of patients with sJIA develop overt MAS (Moradinejad MH 2011, Sawhney S 2001), some evidence suggests that subclinical MAS may be seen in as many as one third of patients with active systemic disease (Behrens EM(b) 2007).

Because MAS is potentially fatal, a timely diagnosis and immediate therapeutic intervention are essential for appropriate management of the disease. The reported mortality rates in MAS reach 20-30%, and it remains the major source of mortality in pediatric rheumatology (Grom AA(b) 2016).

Different sets of criteria have been proposed for the diagnosis of MAS in patients with sJIA. The HLH-2004 diagnostic guidelines (Henter JI(c) 2007), primarily developed for primary (genetic) forms of HLH, have sometimes been recommended. However, they present several limitations when applied to patients with sJIA. For example, criteria such as cytopenias and hypofibrinogenemia below the thresholds required by HLH-2004 become evident only in the later stages of MAS, as these patients often have increased white blood cell and platelet counts as well as elevated serum levels of fibrinogen as a part of the sJIA inflammatory response (Schulert GS 2015). As for primary HLH, hemophagocytosis may not be present in a significant proportion of patients with MAS at presentation (Minoia F 2014). Moreover, hemophagocytosis, NK cell activity and sCD25 are not routinely assessed in the context of MAS.

An alternative approach has been proposed based on the application of preliminary diagnostic guidelines (PDG) for MAS complicating sJIA, which were created through the analysis of a cohort of patients with MAS compared with a group of patients with a flare of sJIA (Ravelli A(a) 2005).

The HLH-2004 diagnostic guidelines and the preliminary diagnostic guidelines for sJIA-associated MAS were compared for their capacity to discriminate sJIA/MAS from sJIA (in the absence of MAS) and systemic infection in a large patient population (Davì S 2014). Although with some limitations due to its retrospective nature, this study suggested that the preliminary MAS diagnostic guidelines may achieve a satisfactory balance between sensitivity and specificity, as well as concordance with the diagnosis made by the treating physician when differentiating patients with sJIA/MAS from sJIA, while their specificity in discriminating vs. systemic infections was < 30%. Moreover, it has been reported that the proportion of patients fulfilling each single criterion of the PDG is highly variable, and some clinical features (e.g. CNS dysfunction and hemorrhages) may manifest at a late stage of MAS, rendering their sensitivity low in incipient MAS (Lehmberg K 2013). The sensitivity of the adapted HLH-2004 set of 4 of 5 criteria was poor (35%), mainly explained by the low frequency of cytopenia and hypofibrinogenemia.

Very recently, an EULAR/ACR-approved set of classification criteria sets have been proposed through a multistep process combining expert consensus and retrospective analysis of patient data (Ravelli A(b) 2016). These classification criteria did not unequivocally prove to be useful for diagnosis in clinical practice (about 30% of patients diagnosed by the treating physician were

classified as not having MAS), and showed important limitations to identify patients who developed MAS while receiving IL-1 and IL-6 inhibitors (De Benedetti F(b) 2015, Grom AA(a) 2016).

The limitations of the thus far proposed criteria for MAS diagnosis render the clinical diagnosis by expert rheumatologists still key in the challenge to distinguish MAS from clinical conditions presenting with overlapping features such as flares of sJIA or sepsis-like syndromes.

There are currently no approved drugs for the treatment of MAS. Likewise, no prospective studies have been conducted to evaluate the safety and efficacy of the drugs currently used for the treatment of MAS, and data is only available as limited case reports or as retrospective surveys.

Usually, high-dose glucocorticoids are the first-line treatment for MAS. In patients failing to respond to glucocorticoids, Cyclosporine A (CsA) has been proposed as additional treatment (Stéphan JL 2001).
Being part of the HLH-94 treatment protocol developed for treating pHLH, the administration of etoposide is also considered in patients failing high dose glucocorticoids. However, the potential toxicity of the drug remains a major concern.
The utility of biologics inhibiting the IL-1, IL-6R or TNFα pathways in the treatment of MAS still remains unclear. Although biologics inhibiting these pathways have been reported to be effective in isolated cases, there have been a few reports of sJIA patients developing MAS while receiving these treatments (Ramanan AV 2003, Stern A 2001, De Benedetti F(a) 2012, Ruperto N 2012), as well as of patients who do not respond to these treatments, indicating that inhibition of IL-1, IL-6R or TNFα does not provide full protection against MAS development nor an efficacious treatment of the full blown syndrome.

A large retrospective, multicenter survey has investigated the clinical, laboratory, and histopathological characteristics as well as current practice treatment and outcome of MAS in a total of 362 patients (Minoia F 2014).
In approximately half of the patients, MAS occurred in the context of active sJIA in the absence of a specific trigger, 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. Nearly all patients were given glucocorticoids, given the well-established role of this treatment approach in MAS and HLH. Cyclosporine was the other most commonly prescribed drug (61% of patients), while intravenous immunoglobulins, biologic medications (in particular anakinra) and etoposide were given to 36%, 15% and 12% of the patients, respectively.

The identification of effective therapeutic regimens for MAS represents an area of unmet high medical need. Approximately 30% of patients with sJIA and MAS do not respond to systemic glucocorticoids alone, or may require prolonged treatment at high doses with associated significant morbidity. When patients fail to respond to glucocorticoids, no good evidence-based data is available on the effectiveness and safety of additional treatments such as CsA or etoposide. The course of MAS may become rapidly irreversible leading to a fatal outcome, with about one third of the patients requiring ICU admission. Furthermore, no clinical and/or laboratory features have thus far been identified to be predictive of poor response to the current standard of care, hence leaving the treating physicians with scarce possibility to identify those patients who would rapidly progress into an unfavorable clinical course.

1.3 STUDY RATIONALE

1.3.1 Rationale for developing emapalumab in MAS

MAS and HLH are characterized by sustained immune cell activation and an associated cytokine storm of proinflammatory cytokines with overproduction of IFNγ, TNFα, IL-1 and IL-6 (Henter JI(a) 1991, Imashuku S 1996, Put K 2015, Xu XJ 2012). During the last years, evidence has been accumulating in support of the pivotal role of IFNγ in the development of both HLH (Jordan MB(a) 2004, Pachlopnik Schmid J 2009, Zoller EE 2011) and MAS (Prencipe G(b) 2018, Behrens EM(a) 2011).

For primary HLH, perforin knock-out mice are considered a relevant model as these mice, once infected with LCMV, develop all the diagnostic and many of the clinical and laboratory characteristic features of the human disease. The HLH-like disease that they develop is dependent on CD8+ T cells and IFNγ produced in response to antigen stimulation (Jordan MB(a) 2004). It was demonstrated that when the high circulating levels of IFNγ are neutralized with the administration of an anti-IFNγ antibody, not only are the clinical and laboratory abnormalities reverted, but also survival rate is dramatically improved. On the contrary, the ablation of many other cytokines had no impact on survival (Jordan MB(a) 2004, Pachlopnik Schmid J 2009). Further strengthening the importance of IFNγ in HLH are the high concentrations of circulating IFNγ levels found in these patients (Henter JI(a) 1991, Xu XJ 2012). In a series of 71 patients monitored from HLH diagnosis to treatment and follow-up, IFNγ levels were above the upper limit of normal (17.3 pg/mL) in all patients, and in particular 53.5% had levels above 1000 pg/mL. It was also reported that IFNγ levels rise early and quickly, and can fall from > 5000 pg/mL to normal in 48 hours upon effective treatment of HLH.

Two animal models of secondary HLH have been investigated in the context of the emapalumab development program to elucidate the potential pathogenetic role of IFNγ:

- In a murine model that mimics an infection-driven HLH, repeated administrations of CpG via activation of TLR9 triggered a hypercytokinemia that led to clinical (e.g. body weight loss, splenomegaly) and laboratory (e.g. cytopenia, hyperferritinemia) features of HLH (Behrens EM(a) 2011). When IFNγ was neutralized by the administration of an anti-IFNγ antibody, clinical and laboratory features of the disease were reverted. The neutralization of IFNγ was shown to be complete also in relevant target tissues, such as the liver and the spleen. Interestingly, the administration of the anti-IFNγ antibody unveiled an amount of IFNγ 500- to 2,000-fold higher than that measured in blood, likely to better reflect the IFNγ production in tissues. The two IFNγ-inducible chemokines (CXCL9 and CXCL10) were upregulated after TLR9 stimulation both in blood and in liver, and a significantly correlation was observed between serum levels of IFNγ with CXCL9 and CXCL10 serum concentrations. The neutralization of IFNγ induced a significant decrease of serum CXCL9 and CXCL10, and of their mRNA levels in the liver (Buatois V 2017).
- An animal model of IL-6 transgenic mice expressing high levels of IL-6 has been studied, since it mimics the condition of patients with sJIA, the rheumatic disease most frequently associated with secondary forms of HLH. When triggered with Toll-Like Receptor (TLR) ligands, increased lethality, increased inflammatory cytokine production and hyperactivation of inflammatory signaling pathways was observed. Moreover, these mice showed a drop in platelet and neutrophil counts, increased sCD25, ferritin and LDH levels, resembling many of the features typically present in patients with MAS (Strippoli R 2012). In these mice, when IFNγ is neutralized with the administration of an anti-IFNγ antibody, survival is markedly improved and laboratory parameters reverted (Prencipe G(a) 2015).

1.3.2 Rationale for conducting a Clinical Study in MAS in sJIA/AOSD patients receiving emapalumab treatment

Evidence of high levels of IFNγ and of IFNγ-inducible chemokines has been gathered in an observational study conducted in patients with secondary forms of HLH, either consequent to infections, or of unknown origin (pHLH having been excluded by normal cytotoxic activity, absence of mutation in known genes causing pHLH and absence of family history) or with MAS occurring in the context of sJIA.

In 14 patients with secondary HLH (in 7 of whom an underlying infection was identifiable), serum samples were analyzed during active full blown disease and during disease remission. Levels of IFNγ, CXCL9 and CXCL10 were markedly higher in the active phase compared to disease remission (IFNγ: 34.7 *vs*. <3.5 pg/ml; CXCL9: 33598 *vs*. 745 pg/ml; CXCL10: 4420 *vs*. 132 pg/ml; median values). IFNγ levels significantly correlated with the levels of CXCL9 (p=0.0018) and, to a lesser extent, of CXCL10 (p=0.014). The levels of IFNγ and chemokines (in particular CXCL9) correlated significantly with parameters of disease severity, such as neutrophil and platelet counts, ferritin and ALT, further supporting the pathogenic role of IFNγ in secondary HLH and the potential use of chemokines as relevant biomarkers of the disease (Buatois V 2017).

Similar findings have been shown in patients with MAS occurring in patients with sJIA. Serum concentrations of IFNγ, IFNγ-inducible chemokines (CXCL9, CXCL10, CXCL11) and IL-6 were measured in 54 patients with sJIA, of whom 20 had MAS. The levels of IL-6 were comparable in patients with full-blown MAS and those with active sJIA but without MAS at the time of sampling. On the contrary, circulating IFNγ and chemokine levels were significantly higher in MAS, particularly for CXCL9, whose median levels were approximately 15-fold higher compared to patients with active sJIA without MAS (13392 vs. 837 pg/mL; p=0.005). Noteworthy, a significant correlation was demonstrated only in patients with MAS between CXCL9 levels and parameters typically abnormal such as ferritin (p=0.041), neutrophil (p=0.010) and platelet (p=0.022) counts, ALT (p=0.044) and LDH (p=0.013). Levels of IFNγ also correlated with laboratory parameters of disease severity, with the exception of LDH for which statistical significance was not achieved (Bracaglia C 2017). Increased levels of CXCL9 and CXCL10 have also been reported in patients with AOSD (Han JH 2017).

This pilot phase 2 study, as well as the twin study in Europe, is intended to assess the pharmacokinetics/pharmacodynamics profile, the safety and tolerability, and the efficacy of emapalumab as treatment of MAS in sJIA/AOSD patients.

Based on the evidence above described, there is a solid rationale for the neutralization of IFNγ as targeted therapy for MAS/sHLH occurring in sJIA/AOSD patient, and for investigating the benefit of emapalumab treatment in this patient population.

Additionally, preliminary clinical data previously gathered in a study conducted in patients with primary HLH receiving emapalumab treatment either as first and second line (NI-0501-04 study), indicated:

1. a favorable tolerability profile of emapalumab and absence of relevant safety concerns:
    - all infusions administered were well tolerated, confirming the observations made in healthy volunteers
    - emerging infections reported in the study generally resolved upon proper treatment and HLH control

- among the reported infections, only one (histoplasmosis) may have been favored by emapalumab mode of action, whereas all other infections have been related to patients' impaired immune status due to HLH and to previous or concomitant treatments. Of note, histoplasmosis resolved upon proper treatment
- no death has been attributed to emapalumab administration.

2. a favorable impact on disease parameters, with appreciable onset of effects within the first days of treatment:
    - typical clinical signs and symptoms of HLH started to improve rapidly after the first administration of emapalumab (fever within hours, spleno/hepatomegaly within days)
    - of the 30 patients that have received at least 4 weeks of treatment at the cut-off date of September 15th 2016, 18 patients have proceeded to HSCT and 4 are awaiting for transplant.
3. a predictable pharmacokinetic profile of emapalumab from the PK modeling and simulation approach, and evidence that neutralization of IFNγ is achieved and maintained

In conclusion, there is a strong rationale for neutralizing IFNγ in MAS secondary to rheumatic diseases based on pre-clinical and clinical evidence, and the preliminary data in pHLH patients indicates a favorable benefit/risk profile of emapalumab with a significant improvement to normalization of HLH features.

It is therefore anticipated that emapalumab can represent an innovative and effective therapeutic approach in the management of this severe, life-threatening complication of rheumatic diseases, potentially limiting side effects from long-term high dose glucocorticoid treatment.

Please refer to the most recent Investigator Brochure to review clinical data available to date.

The study population will be represented by patients with a diagnosis of sJIA or AOSD who develop MAS. No diagnostic criteria are available of sJIA. The classification criteria proposed by ILAR require the presence of arthritis persisting for at least 6 weeks. While they appear to be used to classify patients, they cannot be used at disease presentation. In order to allow inclusion of patients presenting with MAS as a feature of onset of sJIA, the operational criteria designed by CARRA (childhood arthritis and rheumatology research alliance) to identify patients with sJIA early in their disease course (DeWitt EM et al. Arthritis Care Res 2012, Appendix A) have been also considered to assess patient eligibility.

The number of patients meeting the ILAR classification criteria will be in any case included in the description of the NI-0501-06 study results.

Patients enrolled under these twin protocols will be analyzed jointly and data reported in a single CSR.

2 OBJECTIVES

The objectives of this pilot phase 2 study are as follows:

- To describe the PK profile of emapalumab.
- To confirm the proposed dosing regimen of emapalumab.
- To evaluate the safety and tolerability profile of intravenous (i.v.) administrations of emapalumab.
- To assess the efficacy of emapalumab.

- To assess the levels of relevant pharmacodynamic markers, such as IFNγ and main IFNγ-induced chemokines CXCL9, CXCL10.
- To assess other potential disease markers (e.g., sCD25, sCD163, IL-10, IL-6, IL-18, TNFα).
- To assess the immunogenicity of emapalumab.

3 STUDY DESIGN

3.1 OVERALL DESIGN

This is an open-label, single arm, international, multicenter pilot phase 2.

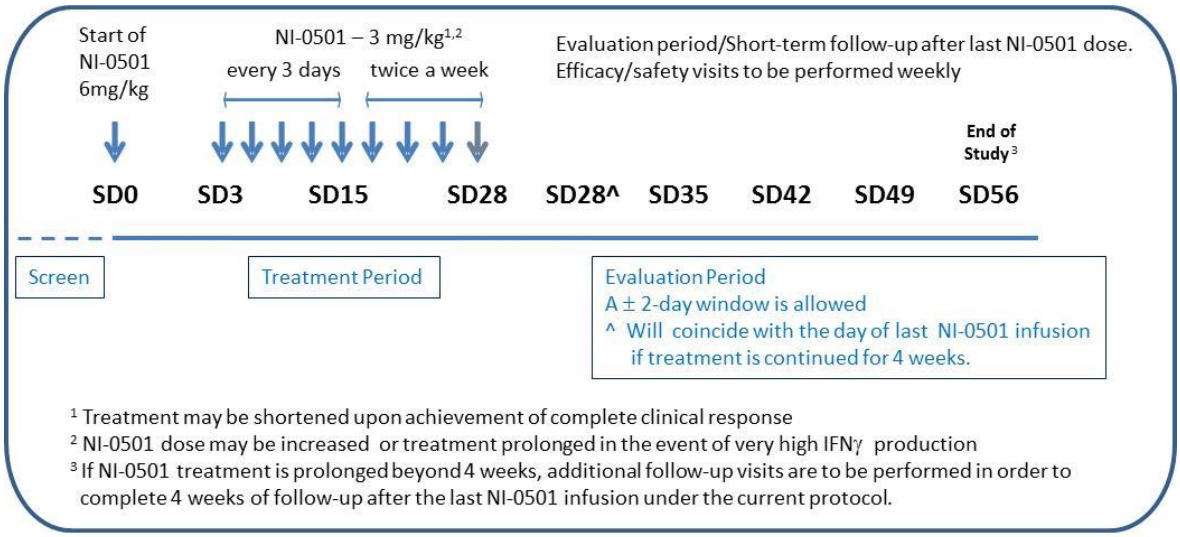
After signature of informed consent, patients will be screened and assessed for eligibility (Section 3.2).
The study will be conducted in hospitalized patients since, at minimum, the day before the first administration of the study drug (study day minus one, SD-1) until SD15 at the earliest.

Discharge from the hospital can occur from SD15 onwards, at the Investigator's discretion if the patient's condition allows, provided that no active infections requiring i.v. antimicrobial therapy are present.

For a detailed description of the study procedures, see Section 8.

The study flow-chart is summarized in Figure 1.

Figure 1: NI-0501-06 Study Flow-chart



3.2 SCREENING PERIOD

Screening will be carried out within up to 1 week prior to first administration of emapalumab (SD0) to enable confirmation of patient eligibility and following the signature of the Informed Consent Form.

In the event that a patient's medical condition warrants rapid treatment initiation, and to avoid unnecessary repetition of recent interventions, results of tests which have been performed as part of the normal patient's care at the site (or at the referring hospital) not more than 2 weeks prior to first

emapalumab infusion, can be considered for screening purposes (inclusion/exclusion criteria checks), with the agreement of both the Sponsor and the Investigator.

Detailed information regarding the inadequate response to high dose i.v. glucocorticoids (as required for patient eligibility) and to any other initial MAS treatments administered prior to emapalumab, will be collected and recorded in the CRF.

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

In the case of a patient having received BCG vaccination, a PPD test must be performed and combined with an IFNγ-release assay.

A negative serum pregnancy test has to be documented in female patients who are post-pubescent.

For a detailed description of the study procedures during the screening period see Section 8.

3.3 TREATMENT PERIOD

Emapalumab will be administered i.v. at the initial dose of 6 mg/kg, and continued at the dose of 3 mg/kg, every 3 days until SD15, and then twice-a-week for additional 2 weeks, i.e. until SD28.
Treatment may be shortened upon achievement of complete clinical response (i.e. MAS remission), however at least two infusions of emapalumab at the dose of 3 mg/kg have to be administered (i.e. after SD6). In such circumstances, efficacy/safety visits have to be in any case performed every 3 days until SD15 and then twice-a-week until SD28.

In the absence of a trend of improvement in key MAS parameters (including but not limited to ferritin, LDH, AST/ALT and PLT count) suggestive of lack of response, the emapalumab regimen may be adapted (the frequency between infusions shortened, the dose increased or the treatment prolonged beyond 4 weeks) upon confirmation of a favorable benefit/risk profile in that individual patient.

3.4 FOLLOW-UP PERIOD

All patients who have received at least one dose of emapalumab will be monitored after the last administration of emapalumab. A short-term follow-up of at least 4 weeks has to be performed under the current protocol, therefore should emapalumab treatment in a given patient need to be prolonged beyond 4 weeks, additional visits will be performed weekly until completion of the 4-week short-term follow-up.

The last visit for a given patient under the NI-0501-06 study will normally be on SD56 (except in case of prolongation of emapalumab treatment beyond 4 weeks, as above described).

Afterwards all patients will be asked to enter a long-term follow-up study, NI0501-05, to allow long-term outcome and safety surveillance, and to monitor emapalumab elimination profile.

In the event that additional monitoring of emapalumab concentrations is required (e.g., emapalumab serum levels still measurable at EoS) and cannot be performed in the context of the long-term follow-up study, unscheduled visits will have to be performed beyond SD56, until serum emapalumab levels are no longer detectable. These measurements should occur not less than every two weeks.

3.5 STUDY END

The end of the study is defined as the last visit of the last patient.

In case of an ongoing serious adverse event (SAE), the patient will continue to be monitored until resolution or until the outcome of the event is known and stable, beyond the defined study end, as necessary.

3.6 LONG-TERM FOLLOW-UP STUDY

All patients having received at least one dose of emapalumab in the study will be asked to participate in a long-term follow-up study, to monitor long-term outcome and safety after emapalumab treatment, and, when relevant, to complete the assessment of the emapalumab elimination profile.

4 TARGET POPULATION

The study population comprises patients of both genders, with confirmed sJIA/AOSD or high presumption of sJIA, presenting with MAS (as per Appendix A) and having shown inadequate response to high dose i.v. glucocorticoid treatment, see Section 4.1.1.

4.1 ELIGIBILITY CRITERIA

To be eligible for the study, patients must meet all inclusion criteria and not meet any of the exclusion criteria:

4.1.1 Inclusion Criteria

1. Patients of both genders,
2. For sJIA patients: Confirmed sJIA diagnosis. For patients presenting with MAS in the context of the onset of sJIA, high presumption of sJIA (as per Appendix A) will suffice for eligibility. For AOSD patients: confirmed AOSD diagnosis as per Yamaguchi criteria (Appendix E)
3. A diagnosis of active MAS confirmed by the treating rheumatologist, having ascertained the following:

   Febrile patient presenting with:
   - Ferritin > 684 ng/mL

   and any two of:
   - Platelet count ≤ 181 x10^9/L
   - AST levels > 48 U/L
   - Triglycerides > 156 mg/dL
   - Fibrinogen levels ≤ 360 mg/dL

   (see Appendix B).
4. An inadequate response to high dose i.v. glucocorticoid treatment administered for at least 3 days as per local standard of care (including but not limited to pulses of 30 mg/kg PDN on 3 consecutive days).
   High dose i.v. glucocorticoid should not be lower than 2 mg/kg/day of PDN equivalent in 2 divided doses (or at least 60 mg/day in patients of 30 kg or more). In case of rapid worsening of the patient's condition and/or lab parameters, inclusion may occur within less than 3 days from starting high dose i.v. glucocorticoids.
5. Tocilizumab, TNF inhibitors and canakinumab, if administered, have to be discontinued before emapalumab initiation.
6. Informed consent provided by the patient (as required by local law), or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as applicable.

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

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

   Highly effective contraceptive measures include:

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

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

4.1.2 Exclusion Criteria

1. Diagnosis of suspected or confirmed primary HLH or HLH consequent to a neoplastic disease.
2. Active mycobacteria (typical and atypical), *Histoplasma Capsulatum, Shigella, Salmonella, Campylobacter* and *Leishmania* infections.
3. Clinical suspicion of latent tuberculosis.
4. Positive serology for HIV antibodies.
5. Presence of malignancy.
6. Patients who have another concomitant disease or malformation severely affecting cardiovascular, pulmonary, CNS, liver or renal function, that in the opinion of the Investigator may significantly affect likelihood to respond to treatment and/or assessment of emapalumab safety.
7. History of hypersensitivity or allergy to any component of the study regimen.
8. Receipt of BCG vaccine within 12 weeks prior to screening.
9. Receipt of live or attenuated live vaccine within 6 weeks prior to screening.
10. Pregnant or lactating female patients.

5 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

5.1 DESCRIPTION OF IMP

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

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

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

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

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

5.2 DOSING REGIMEN

Emapalumab will be administered at the initial dose of 6 mg/kg by infusion over a period of one to two hours depending on the volume to infuse. Treatment will be continued at the dose of 3 mg/kg every 3 days until SD15, and twice-a-week thereafter for a total of 4 weeks (i.e. up to SD28).

Treatment may be shortened upon achievement of complete clinical response (i.e. MAS remission), however at least two infusions of emapalumab at the dose of 3 mg/kg have to be administered (i.e. after SD6).

In the absence of a trend of improvement in key MAS parameters (including, but not limited to ferritin, LDH, AST/ALT and PLT count) suggestive of lack of response, the emapalumab regimen may be adapted (the frequency between infusions shortened, the dose increased or the treatment prolonged beyond 4 weeks) upon assessment of a favorable benefit/risk profile in that individual patient.

5.3 RATIONALE FOR DOSE SELECTION

The rationale for the dosing strategy foreseen for this study is based on:

- Data from *in vitro* experiments investigating the binding kinetics of emapalumab to human IFNγ and the functional inhibition of human IFNγ by emapalumab;
- PK information from recombinant IFNγ in human;
- Data from the Phase 1 NI-0501-03 study in which emapalumab was administered to healthy volunteers;
- Data gathered from the NI-0501-04 study in pediatric primary HLH patients receiving emapalumab in first or second line;
- Data from an observational study in patients with MAS developing on a background of sJIA (Bracaglia C 2017);
- Data from an observational study in pediatric patients with secondary HLH (having excluded a rheumatic or neoplastic origin) (Buatois V 2017).

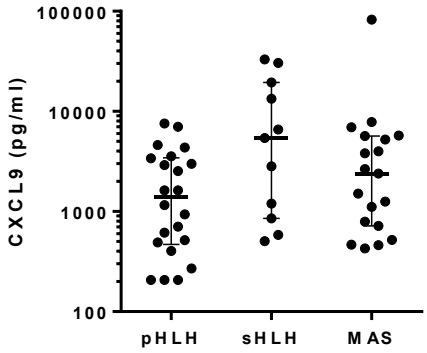
The analysis of data generated from the ongoing study in which primary HLH patients have been treated with emapalumab has allowed to estimate the production rate of IFNγ through the assessment of the "total IFNγ" (i.e. IFNγ bound to emapalumab and free IFNγ), and consequently the concentration of emapalumab required to neutralize the variably high IFNγ concentrations. It has also been possible to determine that when there is a high production of IFNγ, target mediated drug disposition occurs. Importantly, the relationship between IFNγ and the IFNγ-inducible chemokines

CXCL9 and CXCL10 has been investigated establishing the tight correlation between those chemokines measured prior to the administration of emapalumab and "Total IFNγ" at 48 hours after emapalumab administration, indicating that these chemokines can be used as exploratory markers of IFNγ production.

The key observations that have constituted the foundation of the dosing rationale for this protocol and led to the selection of the emapalumab doses to be administered to patients with MAS not responding to high dose glucocorticoid therapy are the followings:

- there is a tight correlation between IFNγ and the IFNγ-related chemokines CXCL9 and CXCL10, as well as between disease parameters and levels of IFNγ and IFNγ-related chemokines in patients suffering from HLH (Buatois V 2017, Bracaglia C 2017);
- the higher the circulating levels of the IFNγ-related chemokines, the higher is the concentration of emapalumab (and therefore the dose of emapalumab) required to neutralize the corresponding levels of IFNγ (data from the NI-0501-04 study on file at Sobi AG);
- the neutralization of IFNγ has been shown to have a therapeutic role in primary HLH patients (Jordan MB(b) 2015);
- a trend towards higher levels of circulating IFNγ-related chemokines has been observed in patients with secondary forms of HLH compared to primary HLH patients (Buatois V 2017, Bracaglia C 2017) during or soon after HLH conventional therapy (see Figure 2; data from the NI-0501-04 study on file at Sobi AG);
- the onset of MAS is usually acute and the disease worsens rapidly therefore requiring prompt and complete neutralization of IFNγ from the very beginning of treatment;
- in MAS patients, differently from patients with primary HLH, the risk of reactivation is extremely low once HLH remission is achieved, and HSCT is not required. Therefore in patients with MAS, shorter treatment duration is anticipated compared to primary HLH patients, not requiring a maintenance phase while awaiting for HSCT.

Figure 2: CXCL9 levels in patients with pHLH, sHLH and MAS



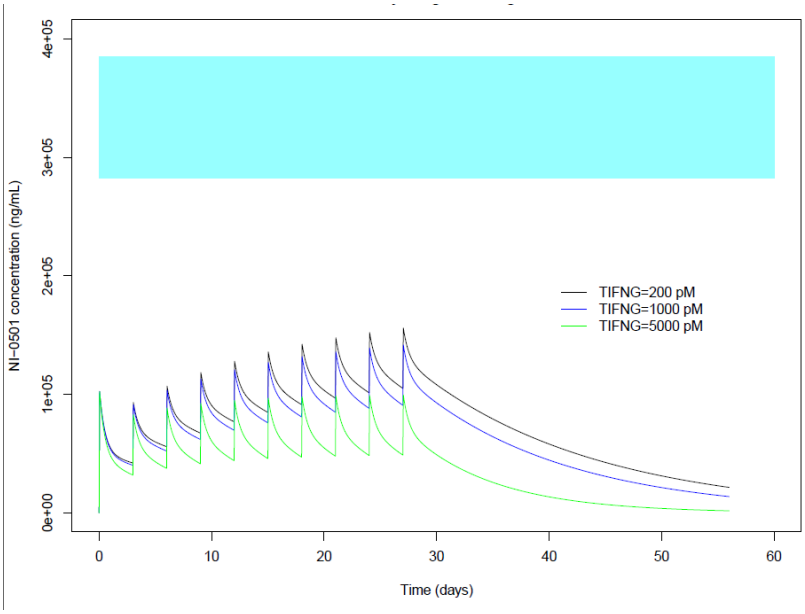
Note:
pHLH: CXCL9 levels from the patients with primary HLH treated with emapalumab in second line in the NI-0501-04 study prior to receiving emapalumab (measured by Affymetrix)
sHLH and MAS: CXCL9 levels in patients with active disease (values extrapolated from Millipore to Affymetrix)

Simulations performed considering different IFNγ production rates that are anticipated to potentially occur in MAS patients are presented in Figure 3. The simulations clearly show that the risk of emapalumab accumulation, as well as the risk of exceeding the highest emapalumab concentration

observed so far in pHLH patients is negligible. Therefore, the expected highest peak and trough concentrations will remain within the ones already achieved in primary HLH patients treated in the ongoing study.

The PK model used to produce these simulations is a two compartment model with linear elimination assuming allometric scaling based on body weight (BW) to which an additional non-linear (TMDD) elimination pathway characterized by a VMAX and a KM has been added. Parameters used in the simulations are from a population pharmacokinetic analysis of study NI-0501-03 and assuming allometric scaling. VMAX is the IFNγ concentration (0.1 nM) multiplied by the recombinant IFNγ clearance (1.2 L/h/kg) divided by the number of binding sites per antibody. KM is assumed to be equal to KD.

Figure 3: Predicted concentration-time profiles after administration of emapalumab at the initial dose of 6 mg/kg followed by 9 doses of 3 mg/kg every 3 days



Note:
Simulations are shown for sJIA MAS patients of an approximate body weight of 23 kg with different levels of total IFNγ. The blue area corresponds to the mean of the 3 highest peak and trough concentrations observed in HLH patients from study NI-0501-04/05 (data cut-off date of June 24, 2016).

The proposed dosing strategy is further supported by the following evidence:

- primary HLH patients treated with emapalumab in the context of the ongoing study who were characterized by levels of CXCL9 comparable to the ones expected in MAS all required a rapid and significant emapalumab dose increase;
- primary HLH patients having a high production of IFNγ, required a high dose of emapalumab, demonstrating the presence of target mediated drug disposition (TMDD), i.e. a pronounced increased clearance of emapalumab due to the high production of IFNγ. The presence of TMDD, while requiring to administer emapalumab at high doses and sometimes more frequently, prevents emapalumab accumulation to occur;
- to date emapalumab has shown a good safety profile when administered to primary HLH patients up to the dose of 10 mg/kg, achieving similar or even higher emapalumab exposures compared to the ones expected to occur in MAS patients. More than 850 infusions have been performed in all patients treated (including CU) and around 20% have been performed at a dose of ≥ 6mg/kg.

In conclusion, based on a production rate of IFNγ expected to be high in sJIA/AOSD patients with overt MAS (Bracaglia C 2017), an initial dose of 6 mg/kg followed by repeated administrations of 3 mg/kg is deemed appropriate to achieve rapidly and maintain the concentrations of emapalumab estimated to ensure a fast neutralization of IFNγ activity.

5.4 IMP HANDLING

5.4.1 Packaging and Labeling

Emapalumab will be supplied to study sites in single-use glass vials containing a 2 or a 10 ml solution at a concentration of 5 mg/ml. Labeling and packaging will be prepared to meet local regulatory requirements.

5.4.2 IMP Supply

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

5.4.3 IMP Receipt and Storage

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

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

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

Regular inspections of the emapalumab vials are required, as detailed in the IMP manual indications for the Preparation and Administration of Individual Doses of Study Drug emapalumab.

5.4.4 IMP Preparation, Administration, Accountability and Destruction

5.4.4.1 Preparation

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

The specific dose to be administered for an individual infusion is determined as detailed in Section 5.2.

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

5.4.4.2 Administration

The patient should receive the designated volume of the infusate through an infusion pump over a period of 1 to 2 hours depending on the volume to infuse. IMP must be administered using either a syringe that has been sterilized by gamma irradiation or using any appropriate sized non-PVC polyolefin infusion bag and a 0.2 µm filter, which must be added to all infusion lines. (See the IMP manual for details.)

It is recommended that a central venous access is maintained during the treatment period. This will improve patient's comfort and ensure a reliable drug administration. However, as per previous experience in HLH patients in whom central venous access was not possible or not maintained, emapalumab infusions have been performed safely via peripheral venous access. Since no data is available on the compatibility of emapalumab with other intravenous substances or additives, other medications/substances should not be added to the infusion material or infused simultaneously through the same intravenous line. If the same intravenous line is used for subsequent infusions of other drugs, the line should be flushed with saline before and after infusion of emapalumab.

The infusion of emapalumab will be administered under the direct supervision of the Investigator (or delegate). It should be preferably performed in the morning, and at the same time of the day during the study whenever possible.
Details of the infusion administered must be recorded, including:

- The date of administration
- The time (start and end) of infusion
- The volume administered
- Any adverse effects or general illness experienced by the patient.
- Any other event(s) judged relevant by the site personnel.

5.4.4.3 Accountability

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

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

Drug accountability records shall include:

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

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

Unused study drug must not be discarded or used for any purpose not authorized by Sobi AG.

5.4.4.4 Destruction, Return and Disposal

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

6 PATIENT BACKGROUND TREATMENT AND CARE

6.1 GLUCOCORTICOIDS

For a patient to be eligible for the study, an inadequate response to high dose i.v. glucocorticoids administered for at least 3 days as per local standard of care (including but not limited to pulses of 30 mg/kg PDN on 3 consecutive days) must be documented. Inclusion can however occur within less

than 3 days from starting high dose i.v. glucocorticoids, in case the patient's condition and/or lab parameters are rapidly worsening.

High dose i.v. glucocorticoids should not be lower than 2 mg/kg/day of PDN equivalent in 2 divided doses (or at least 60 mg/day in patients of 30 kg or more).

During the study, emapalumab will be initially administered on a background of at least 2 mg/kg/day of PDN equivalent (or at least 60 mg/day in patients of 30 kg or more).

Glucocorticoid tapering may be initiated as soon as the patient's conditions allow, according to the Investigator's assessment. The tapering scheme can be selected by the Investigator, with the objective of reaching the same (or lower) dose being administered before the occurrence of MAS (in patients already on treatment for sJIA/AOSD) or decreasing by 50% (or more) the glucocorticoid dose administered at initiation of emapalumab treatment (in patients presenting with MAS as first manifestation of sJIA/AOSD).

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

6.2 PROPHYLACTIC TREATMENT

Prophylaxis for *Herpes Zoster* (*HZ*) virus infection will be administered to mitigate the potential risk associated to emapalumab administration (see Benefit/Risk Management, Section 10.5).

Patients will therefore receive the prophylactic treatment starting preferably the day before (i.e. SD-1), and in any case prior to, initiation of emapalumab treatment on SD0, and continued until serum emapalumab levels are no longer detectable, as follows:

- For *HZ* virus prevention, according to Institution/Country Guidelines/Recommendations (e.g. Acyclovir 200 mg four times daily for children over two years, for children under two years 100 mg four times daily).

In the unlikely event that a patient, previously vaccinated for TB, shows a Purified Protein Derivative (PPD) test result ≥ 5mm and a negative IFNγ-release assay, the patients will receive TB prophylaxis according to Institution/Country Guidelines/Recommendations (e.g. Isoniazid).

In case emapalumab concentrations are still measurable after the end of the study, it is required that the above mentioned prophylaxis be maintained, until serum emapalumab levels are no longer detectable.

6.3 CONCOMITANT THERAPY

6.3.1 Cyclosporine A, methotrexate and anakinra

Cyclosporine A (CsA) may be continued, if already started at least 3 days prior to initiation of emapalumab treatment. CsA dose adjustments will be performed if required based on results of therapeutic drug monitoring, in order to maintain therapeutic levels. CsA can be withdrawn at any time during the study, upon judgment of the Investigator. CsA should not be introduced once emapalumab administration has started.

Methotrexate may be continued if ongoing as treatment for the underlying disease.

If ongoing and if started (at any dose) at least 3 days before initiation of emapalumab treatment, anakinra may be continued at a maximum daily dose of 4 mg/kg. In the case of an acute inflammatory flare of the underlying sJIA/AOSD during treatment with emapalumab, anakinra may be introduced at

a dose of 1 to 4 mg/kg (max. daily dose of 100 mg). Such episodes shall be adjudicated by at least two members of the SSC (excluding the treating physician, if applicable), in order to ascertain their nature (i.e. sJIA/AOSD versus MAS flare).

6.3.2 Intrathecal Therapy

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

6.3.3 Other possible concomitant therapies

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

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

6.3.4 Not allowed concomitant therapies

Tocilizumab, canakinumab or TNF inhibitors have to be discontinued before initiation of emapalumab treatment.

As long as emapalumab is being administered, no concomitant use of etoposide, T-cell depleting agents, or any other biologic drug is allowed with the exception of:

- ✓ G-CSF, in case of prolonged neutropenia
- ✓ Rituximab, in case of documented EBV infection
- ✓ Anakinra, if administered as described in section 6.3.1

Vaccination with a live or attenuated-live (including BCG) vaccine must be avoided during the whole study. In the event that emapalumab concentrations are still measurable after the end of the study, the period with no vaccinations should be extended until serum emapalumab levels are no longer detectable.

6.4 EMERGENCY TREATMENT

As none of the emapalumab infusions administered to healthy volunteers or patients has triggered any medically significant reaction, this is considered an unlikely event during the study. However, should severe allergic reactions (such as anaphylactic shock) occur, they would require prompt i.v. treatment with adrenaline and antihistamines. Oxygen shall be supplied through a face mask. Patients must have an appropriately sized i.v. line that allows rapid infusion of colloid volume substitution. Transfer to the intensive care unit of the hospital should be possible.

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

6.5 RESCUE THERAPY

Patients who are withdrawn from the study due to a safety issue or for lack of efficacy (i.e. worsening of MAS/no response to emapalumab) will be treated according to the standard of care at the site.

7 ENDPOINTS

The main objective of the study is to confirm that the proposed dosing regimen is adequate in relation to the IFNγ production in patients with MAS secondary to sJIA/AOSD.

For this purpose, a PK-PD analysis will be performed based on:

- levels of circulating emapalumab
- levels of total IFNγ
- levels of main IFNγ–induced chemokines (namely CXCL9 and CXCL10).

7.1 PHARMACOKINETICS ENDPOINTS

Free emapalumab concentrations will be measured in serum to determine the PK profile of emapalumab in this patient population, and to confirm the adequacy of the proposed dosing regimen.

All PK data will be summarised using appropriate graphical and tabular presentations. Descriptive non-compartmental pharmacokinetic analysis (NCA) will be applied: C_{max} (concentration corresponding to T_{max}), T_{max} (time of maximum observed concentration), C_{EOI} (concentration at the end of infusion), C_{trough} (concentration just before administration), AUCτ (area under curve of a dosing interval), AUC_{last} (area under curve from the time of dosing to the last measurable concentration), $t_{½}$ (plasma half-life), Individual and mean PK parameters will be tabulated. Exploratory compartmental PK analysis and population PK analysis will be undertaken to investigate linear and non-linear (TMDD) kinetics.
In addition, PK analysis will be done when a total of 5 patients have been recruited in Europe and North America inclusive, to assess the appropriateness of the dose selection.

7.2 PHARMACODYNAMICS ENDPOINTS

Assessment of PD parameters will include, but will not be limited to, the followings:

- Levels of circulating free IFNγ at pre-dose, and of total IFNγ (free IFNγ+bound to emapalumab) after initiation of emapalumab treatment.
- Levels of the main IFNγ-induced chemokines (CXCL9, CXCL10).
- Correlation between chemokine levels (CXCL9, CXCL10) and levels of free emapalumab, free IFNγ (pre-dose) and total IFNγ (*exploratory analysis*).
- Correlation between chemokine and total IFNγ levels, and laboratory parameters of MAS severity, e.g. ferritin, platelet counts, LFTs (*exploratory analysis*).
- Levels of other potential disease markers (e.g. sCD25, sCD163, IL-18, IL-10, IL-6, TNFα,).
- Levels (if any) of circulating antibodies against emapalumab to determine immunogenicity, i.e. the development of anti-drug antibodies (ADAs).

7.3 SAFETY ENDPOINTS

The tolerability and safety of emapalumab treatment will be assessed as follows:

- Incidence, severity, causality and outcomes of AEs (serious and non-serious), with particular attention being paid to infections.
- Evolution of laboratory parameters, in particular CBC, LFTs, inflammatory markers (ferritin and CRP) and coagulation parameters.
- Number of patients withdrawn due to safety reasons.

7.4 EFFICACY ENDPOINTS

The efficacy of emapalumab in this patient population will be evaluated based on the evolution of the MAS distinct features of cytopenias, liver function and coagulopathy.

In particular the following variables will be assessed:

- Number of patients achieving MAS remission by Week 8 after initiation of emapalumab treatment.
- Time to MAS remission.
- Number of patients for whom at any time during the study glucocorticoids can be tapered *i)* to the same (or lower) dose being administered before the occurrence of MAS (in those patients who are already treated for sJIA/AOSD) or *ii)* by 50% (or less) of the dose administered at emapalumab treatment start (in those patients who present with MAS at sJIA/AOSD onset).
- Time to achievement of glucocorticoids tapering (as defined above).
- Survival time.
- Number of patients withdrawn from the study due to lack of efficacy.

MAS remission is defined as

- ✓ Resolution of clinical signs and symptoms according to the Investigator
  and
- ✓ Normalization of laboratory parameters relevant to MAS, as follows:
  - WBC and platelet count above LLN
  - LDH below 1.5 ULN
  - ALT/AST below 1.5 ULN
  - fibrinogen higher than 100 mg/dL
  - ferritin levels decreased by at least 80% from values at screening or baseline (whichever is higher) or below 2000 ng/ml, whichever is lower.

8 OUTLINE OF STUDY PROCEDURES

8.1 STUDY VISITS

For a detailed description of the visit schedule and assessments, please refer to Table 1 (Schedule of Assessment – Screening and emapalumab Treatment Period) and Table 2 (Schedule of Assessment – Evaluation Period).

Patients will be recruited from specialized study centers in North America, in which an intensive care unit is available. If not already hospitalized, the patient will enter the hospital on SD-1.

During the emapalumab Treatment Period, Infusion Visits will occur every 3 days until SD15, and twice-a-week thereafter until SD28, and will also serve as Efficacy/Safety visits. In case emapalumab treatment is shortened after SD6, Efficacy/Safety visits have to be in any case performed with the same schedule until SD28, in order to assess the evolution of MAS clinical and laboratory features, and to closely monitor safety.

From SD28 and during the Evaluation Period, visits will occur on a weekly schedule (a ± 2-day window is allowed) for efficacy and safety evaluation, and follow-up after emapalumab last infusion.

Discharge from the hospital cannot occur before SD15. After SD15, in case the patient condition allows, the patient can be discharged, at the Investigator's discretion, provided that no active infections requiring i.v. antimicrobial therapy are present.

Some procedures are not mandatory or do not need to be done systematically but only when applicable according to the following specifications:

- ECG is mandatory at screening, after first infusion, and at the end of the study, however it should also be performed whenever required based on clinical judgment.
- Broad search for pathogens during the study (beside the ones required per protocol) should be done if there is any suspicion of infection.
- Chest X-ray during the study (beside the ones required per protocol) should be done more frequently in case of clinical suspicion of a pulmonary infection.
- Functional tests relevant to HLH diagnosis should be performed whenever possible; however availability of results is not required for patient inclusion in the study.

The following situations will not be considered as protocol deviations:

- Missing data if not occurring at 2 consecutive time-points.

8.2 INFORMED CONSENT AND SCREENING PROCEDURES

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

Patients will be screened for eligibility prior to enrolment into the study. The Investigator must keep a log of the patients screened for the study and reasons for non-eligibility, if applicable.

Screening evaluations should be completed within up to 1 week prior to the first administration of the study drug (SD0). Clinical and laboratory assessments should be performed as close as possible to initiation of emapalumab treatment, preferably on SD-1, as described in Table 1.

In the event that a patient's medical condition warrants rapid treatment initiation, and to avoid unnecessary repetition of recent interventions, results of tests which have been performed as part of the normal patient's care at the site (or at the referring hospital) not more than 2 weeks prior to first emapalumab infusion, may be considered for screening purposes (inclusion/exclusion criteria checks) with the agreement of both the Sponsor and Investigator.

The following patient information must be collected:

- Demographic and medical history
- Detailed information on inadequate response to high dose i.v. glucocorticoids and to other MAS treatments, including VAS of MAS activity and MAS laboratory parameters including, but not limited to: blood cell counts, ferritin, AST/ALT/LDH, fibrinogen, d-dimer, triglycerides,
- Concomitant medication at screening.
- Date of sJIA diagnosis/high presumption of sJIA or AOSD diagnosis.
- sJIA/AOSD treatment previously received and ongoing at the time of screening.
- Date and criteria of eligibility.
- Relevant clinical and laboratory data in order to characterize *a posteriori* the study population according to HLH-2004 criteria.

Samples for the molecular characterization with respect to the known HLH causative genes have to be collected and send to a centralized laboratory only if the patient has given consent for genetic testing.

A panel of genes already known to be involved in primary HLH (PRF1, UNC13D, STX11, STXBP2, LYST, RAB27A, SH2D1A, XIAP) will be tested.

Given the evolving knowledge and new findings within the scientific community with regard to potential modifying genes for HLH [e.g. AP3B1, HPS1, IRF5, ITK, KIR2DL1, MyD88, SLC7A7, TNFRSF7/ CD27, IL2RG, ARHGAP21, CADPS2, CCDC141 (CAMD1), EXPH5 (SLAC2B), FAM160A2, FKBPL, GDI1, LRGUK, MICAL2, TNFRSF10B, XIRP2], the panel may be extended, if relevant.

Functional tests relevant to the diagnosis of HLH should be performed whenever possible; however availability of these results is not required for inclusion of the patient in the study.

Prophylactic treatments for *HZ* virus and for TB (when applicable, as described in Section 6.2), have to be started.

Table 1 – Schedule of assessment: Screening and emapalumab treatment period (from SD-1 to SD28)

Assessments		Protocol Section	Screening (up to one week prior to 1st infusion)	SD0 Infusion #1[1]		SD1	SD2	SD3 Infusion #2[2]		SD5	SD6 to SD28[3] Infusion/Efficacy/ Safety visits
			SD-1	pre	post			pre	post		
Hospitalization[4]		8.1	From SD-1								
Patient information and Informed Consent		8.2	X								
Medical history including MAS laboratory parameters and MAS treatments		8.2	X								
Concomitant medication (including recording on glucocorticoid tapering when relevant)		8.2	X	X		X	X	X		X	X
MAS diagnosis and Eligibility Criteria[5]		8.2	X								
Prophylactic treatments		8.2	From SD-1								
Clinical assessments	- Vital signs	8.3.1	X	X	X[6]	X	X	X	X[6]	X	X[7]
	- Physical examination[8]	8.3.2	X	X		X	X	X		X	X
	- MAS clinical signs and symptoms[15]	8.3.3	x								X
Laboratory assessments	- CBC	8.4	X	X		X	X	X		X	X
	- Lymphocyte subset	8.4	X								
	- Coagulation (aPTT, PT, D-Dimers, Fibrinogen)	8.4	X	X		X	X	X		X	X
	- Biochemistry	8.4	X	X		X	X	X		X	X
	- Serum pregnancy test (if applicable)	8.4	X								
	- Urinalysis	8.4	X	X[9]							
Search for infections	-*Mycobacterium Tuberculosis*	8.5	X								X[10]
	-*Atypical mycobacteria, Shigella, Salmonella, Campylobacter, Leishmania, Histoplasma Capsulatum*	8.5	X								
	-*EBV, CMV, Adenoviruses*	8.5	X								X[10]
	-*HSV, HZV, HIV, HBV, HCV*	8.5	X								
Procedure	- ECG	8.7.1	X[11]		X						
Imaging	- Abdominal Ultrasound	8.6.1	X								X[10]

Assessments		Protocol Section	Screening (up to one week prior to 1st infusion)	SD0 Infusion #1[1]		SD1	SD2	SD3 Infusion #2[2]		SD5	SD6 to SD28[3] Infusion/Efficacy/ Safety visits
			SD-1	pre	post			pre	post		
	- Chest X-ray	8.6.2	X								X[10]
	- Brain MRI[12]	8.6.3	X								
Histopathology	- CSF analysis (if coagulation allows) [12]	8.7.2	X								
PK	- emapalumab serum concentration	8.8.1		X	X	X	X	X	X	X	X[13]
PD 1	- IFNγ, CXCL9, CXCL10, sCD25	8.8.2		X	X[14]	X	X	X		X	X
PD 2	- Other markers	8.8.2		X							X
Immunogenicity (ADA)		8.8.3		X							

[1] Start of emapalumab treatment: loading dose of 6 mg/kg.

[2] Continuation of emapalumab treatment: 3 mg/kg every 3 days from SD3 onwards until SD15, and twice-a-week thereafter.

[3] After a minimum of two infusions at the dose of 3 mg/kg (i.e. after SD6), emapalumab treatment may be shortened as per Investigator's decision upon achievement of a complete clinical response (i.e. MAS remission). In this circumstance, efficacy/safety visits have to be in any case performed according to the same schedule until (and including) SD28.

[4] Hospitalization: please note that the patients can be discharged from SD15 if their conditions allow, provided that there is no active infections requiring i.v. antimicrobial therapy.

[5] Include molecular and functional tests relevant to the diagnosis of primary HLH. Include detailed documentation of inadequate response to high dose i.v. glucocorticoids and MAS treatments

[6] Continuous monitoring of HR and SpO2 as well as body temperature and BP recording at regular time points (see Section 8.3.1)

[7] If emapalumab infusions are performed, HR, BP, SpO2, body temperature are to be measured pre-, during, and post-dose (see Section 8.3.1).

[8] Body weight to be recorded prior to infusion and every 2 weeks during the evaluation period for patients weighing less than 10 kg, and every 2 weeks throughout the study for patients weighing more than 10 kg.

[9] If not performed at screening.

[10] Abdominal US and Search for infection to be performed on SD15 and SD28; chest X-ray on SD28 only.

[11] At screening, three consecutive recordings are required in order to obtain a stable baseline.

[12] Brain MRI & CSF analysis: to be performed in case of neurological involvement prior to emapalumab initiation (or at the latest by SD6 for brain MRI), whenever possible.

[13] When emapalumab is administered, PK samples have to be taken before and after the infusion.

[14] Total IFNγ only.

[15] MAS activity on VAS at all indicated visits. Assessment of clinical parameters as per section 8.3.3 at the following visits: SD-1, SD14, SD21, SD28. In addition for cases where emapalumab treatment may be shortened (after SD6 and prior to SD28) due to a complete clinical response, the assessment is also to be made at this corresponding time-point.

Table 2 – Schedule of assessment: Evaluation period - from SD28 to SD56 (End of Study)

Assessments			SD35 1st Week Follow-up	SD42 2nd Week Follow-up	SD49 3rd Week Follow-up	SD56[1] 4th Week Follow-up – EoS[2]	Unscheduled Visit (UV)[3]
Hospitalization[4]		8.1					
Concomitant medication (including information on glucocorticoid tapering)		8.2	X	X	X	X	
Clinical assessments	- Vital signs	8.3.1	X	X	X	X	X
	- Physical examination	8.3.2	X	X	X	X	X
	- MAS clinical signs and symptoms[6]	8.3.3	X	X	X	X	
Laboratory assessments	- CBC	8.4	X	X	X	X	
	- Lymphocyte subset	8.4				X	
	- Coagulation (aPTT, PT, D-Dimers, Fibrinogen)	8.4	X	X	X	X	
	- Biochemistry	8.4	X	X	X	X	
	- Serum pregnancy test	8.4				X	
	- Urinalysis	8.4				X	
Search for infections	- *Mycobacterium Tuberculosis*	8.5		X		X	
	- *EBV, CMV, Adenoviruses*	8.5		X		X	
Procedure	- ECG	8.7.1				X	
Imaging	- Abdominal US	8.6.1		X		X	
	- Chest X-ray	8.6.2				X	
	- Brain MRI[5]	8.6.3				X	
Histopathology	- CSF analysis (if coagulation allows)[5]	8.7.2				X	
PK	- emapalumab serum concentration	8.8.1	X	X	X	X	
PD 1	- IFNγ, CXCL9, CXCL10, sCD25	8.8.2	X	X	X	X	
PD 2	- Other markers	8.8.2		X		X	
Immunogenicity (ADA)		8.8.3				X	

[1] If Emapalumab treatment needs to be prolonged beyond 4 weeks, additional weekly visits must be scheduled as appropriate in order to complete the required short-term 4-week follow-up.
[2] The same procedures described for End of Study Visit should be followed for any patient who is withdrawn prematurely from the study (see protocol Section 8.9)
[3] Unscheduled Visit: depending on the reason for UV, additional assessments may be added according to the Investigator's clinical judgment (see protocol Section 8.10).
[4] Hospitalization: please note that the patients can be discharged from SD15 if their conditions allow, provided that there is no active infections requiring i.v. antimicrobial therapy.
[5] Brain MRI & CSF analysis: to be performed in case of neurological symptoms occurrence, whenever possible. If brain MRI and CSF analysis were done at screening, an End of Study exam should be performed, whenever possible.
[6] MAS activity on VAS at all indicated visits. In addition an assessment of clinical parameters as per section 8.3.3 at the following visits: SD42 and SD56. For cases where emapalumab treatment may be prolonged beyond SD28, the assessment of the specified clinical parameters is to be made at the time of last infusion and at the follow-up visits corresponding to 2 weeks and 4 weeks after the last emapalumab infusion.

8.3 CLINICAL ASSESSMENTS

8.3.1 Vital signs

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

Body temperature will be recorded in the morning of visit days as indicated in the SoA.

On the day of emapalumab infusion, heart rate and oxygen saturation will be recorded before and continuously monitored after the infusion for 4 hours.

Body temperature and blood pressure will be recorded before and at regular intervals after emapalumab infusion as follows:

- at the first infusion, every hour ± 10-min during the first 4 hours post-dose, at all other infusions, every hour ± 10-min during the first 4 hours post-dose (if no safety concerns have emerged after the first infusion).

Blood pressure, heart rate and oxygen saturation will be measured every 15 minutes (± 5-min) during emapalumab infusion.

8.3.2 Physical examination

A complete physical examination will be performed at screening and at each study visit (before the infusion when emapalumab is administered).
Physical examination prior to each infusion may be performed in the late afternoon of the previous day instead of the morning of the infusion (the data will be captured on the infusion day of the CRF).

At screening height (in cm), weight (in kg) and Body Surface Area (BSA) as calculated by the site will be recorded.

Subsequent physical examinations will include *i*) recording of body weight prior to infusion and every 2 weeks during the evaluation period for patients weighing less than 10 kg [for patients weighing more than 10 kg, weight will be measured every 2 weeks throughout the study]; *ii*) abdominal palpation for assessment of liver and spleen size (in cm from costal grill); *iii*) follow-up of any abnormalities previously recorded as well as occurrence of new signs and symptoms.

8.3.3 MAS clinical signs and symptoms

The Investigator will be asked to provide his assessment of improvement/resolution of MAS signs and symptoms at the study timepoints indicated in the SoA. In addition, the Investigator will assess and document the clinical parameters as listed below at the visits on SD-1, SD14, SD21, SD28, SD42 and SD56 (and additional time-points as indicated in the SoA in case emapalumab treatment is shortened after SD6 due to a complete response or if study treatment is prolonged beyond SD28):

- Fever (greater than 38.0 C°)
- Skin Rash
- Hemorragic manifestations
    - Skin bleeding (petecchiae, 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 O2 required to maintain O2 saturation)
  - Mechanical ventilation (choose among "present" or "absent")
- Cardiac
  - Pericarditis (if echocardiography is performed, results should be reported)
  - Inotropic support
- Kidney
  - Ultrafiltration/dialysis

8.4 LABORATORY ASSESSMENTS

Blood and urine laboratory analyses are part of the routine monitoring of MAS patients, thus samples will be analyzed locally. Analyses done on blood samples will favor as much as possible the use of micro-sampling techniques.

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

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

- Hematology: complete blood cell count (CBC) with differential count, a dedicated lymphocyte subsets count (at screening and EoS visit), and platelets.
- Biochemistry: Ferritin, Triglycerides, C-Reactive Protein (CRP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), gamma Glutamyl Transferase (γGT), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH), total bilirubin, glucose, electrolytes, albumin, creatinine, Blood Urea Nitrogen (BUN).
- Coagulation tests: activated partial thromboplastin (aPTT), prothrombin time (PT), D-dimers and fibrinogen.
- Urinalysis: glucose, blood, protein, leucocytes, ketones, pH and specific gravity. On SD0, urinalysis will be performed before emapalumab infusion (only if not already performed at screening). Urinalysis will be repeated at EoS.
- Serum pregnancy test (if applicable) at screening 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.

8.5 SEARCH FOR INFECTIONS

Search for infections that represent exclusion criteria include the following pathogens:

- *Mycobacterium Tuberculosis*

  At screening, it will be performed via IFNγ-release assay or PPD test. In addition, a baseline via polymerase chain reaction [PCR] in a relevant specimen (e.g., urine or blood, if sputum is not easily obtained) has to be obtained, as this test will be used during the course of the study to perform regular TB monitoring.

  After initiation of emapalumab treatment, search for TB via PCR has to be performed every 2 weeks as long as emapalumab is detectable in serum.

In the case of a patient having received BCG vaccination, a PPD test must be performed and combined with an IFNγ-release assay.

- *Atypical mycobacteria*, *Shigella*, *Salmonella*, *Campylobacter, Histoplasma Capsulatum* and *Leishmania*

  Search for all these pathogens have to be performed at screening. During the study, search for these pathogens has to be performed if there is any suspicion of infection.

  A first screening for *Histoplasma Capsulatum* may be performed using galactomannan assay, however if the test is positive, confirmation should be obtained by using a *Histoplasma Capsulatum* specific test. The presence of *Leishmania* can be ascertained by direct bone marrow observation.

In addition, search for the following infections is required:

- *Herpes Simplex Virus* (*HSV*), *Herpes Zoster Virus* (*HZV*), *Hepatitis B Virus* (*HBV*), *Hepatitis C Virus* (*HCV*), *Human Immune Deficiency Virus* (*HIV*) by PCR monitoring or serology, at screening and whenever there is a suspicion of infection.
- *EBV, CMV, Adenoviruses* by quantitative PCR, at screening and every 2 weeks as long as emapalumab is detectable in serum.

A patient with a clinical assessment (including chest X-ray) not indicative of the presence of an active infection, provided that a usable specimen has been taken and the microbiological analysis is ongoing, can be enrolled prior to the availability of the results, if the patient's clinical conditions require a rapid initiation of emapalumab treatment.

8.6 IMAGING

8.6.1 Abdominal ultrasound

Abdominal ultrasounds, including spleen (longitudinal) measurements and assessment of hepatomegaly presence, will be performed at screening and every 2 weeks during the study.

8.6.2 Chest X-ray

Chest X-ray will be performed as a measure for detection of pulmonary infections at screening and every 4 weeks during the study. Chest X-ray should be done more frequently in case of clinical suspicion of a pulmonary infection.

8.6.3 Brain MRI

Brain MRI should be performed in case of neurological symptoms occurrence, prior to emapalumab initiation (or at latest by SD6), and repeated at the end of the study, whenever possible.

8.7 OTHER PROCEDURES

8.7.1 ECG

12-lead ECG will be performed and interpreted locally by the Investigator or delegate for immediate clinical assessment.

At screening, triplicate ECG (three consecutive recordings) is required in order to obtain a stable baseline.

ECG is mandatory at screening, after the first emapalumab infusion, and at the end of the study, however it should also be performed whenever required based on clinical judgment.

8.7.2 Cerebrospinal fluid assessment

Lumbar puncture for CSF analysis should be done in case of neurological symptoms occurrence, whenever possible and if coagulation parameters allow, prior to emapalumab initiation, during the course of the study and at the end of the study, as clinically indicated.

8.8 PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.8.1 Pharmacokinetics

Serum samples for PK analysis will be collected at the visits indicated in the SoA (Table 1 and Table 2). In case of need for prioritization of blood analysis (considering weight and health status of the patient), laboratory safety parameters (which would be done as normal disease monitoring) may need to be prioritized over samples for PK assessments, that in turn will be prioritized over biomarkers exploratory parameters.

On the days of infusion, PK samples should be collected before and after (between 15 and 30 minutes after) the infusion.

After the first emapalumab infusion, PK samples will be also collected on SD1 (around 24 hrs. post-infusion) and SD2 (around 48 hrs. post-infusion). Additionally, PK samples will be collected on SD5 (around 48 hrs. after the second emapalumab infusion).

After completion of emapalumab infusions, samples for PK assessment will be collected until serum emapalumab concentration are no longer detectable (or until consent is withdrawn), as indicated in the SoA until the EoS visitIn case of CNS involvement, if lumbar puncture is performed for diagnostic and/or therapeutic purposes, PK analysis in CSF samples may be performed.

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

8.8.2 Pharmacodynamics

Serum samples for PD analysis will be collected at the visits indicated in the SoA (Table 1 and Table 2). In case of need for prioritization of blood analysis (considering weight and health status of the patient), laboratory safety parameters and PK assessments will be prioritized over biomarkers exploratory parameters.

Pharmacodynamics assessments include the measurement of:

- Free IFNγ levels prior to emapalumab treatment start, and total IFNγ (free IFNγ+bound to emapalumab) during emapalumab treatment. Samples for total IFNγ measurements will be taken pre-dose on infusion visits, except for the first infusion when free IFNγ will be measured pre-dose and total IFNγ post-dose.
- Chemokines known to be induced by IFNγ (CXCL9, CXCL10) and sCD25. On infusion visits, serum samples will be collected pre-dose only.
- Other potential disease markers (e.g., sCD163, IL-18, IL-10, IL-6, TNFα). Serum samples will be collected on SD0 and every 2 weeks during the course of the study.

In case of CNS involvement, if lumbar puncture is performed for diagnostic and/or therapeutic purposes, biomarker analysis in CSF samples may be performed.

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

8.8.3 Immunogenicity

Serum samples for the assessment of ADAs will be collected on SD0 (prior to emapalumab infusion) and at the End of Study visit, and in case of PK Clearance of emapalumab is faster than expected during the study. Details on sample preparation and handling will be described in a separate laboratory manual.

8.9 WITHDRAWAL VISIT

The same procedures described for the EoS Visit should be followed by the Investigator for any patient who is withdrawn prematurely from the study, as soon as possible after the decision to withdraw is made.

For patients who withdraw from the study as a result of their own decision or the decision of their parent/guardian, the Investigator should contact the patient (or parent/guardian) and ask them to attend a withdrawal visit as soon as possible and in any case within 30 days from termination.

Patients who are withdrawn due to a serious adverse event (SAE) should be followed-up until the resolution of the event or until the outcome of the event is known and stable.

8.10 UNPLANNED (UNSCHEDULED) VISITS

Unplanned visits may occur, should the patient need to be assessed or treated for any clinical condition that arises during the study. This may include the evaluation and follow-up of AEs, SAEs or laboratory tests. The assessments (as detailed in the SoA) should always be performed *at minimum*, but additional evaluations may be added according to the clinical judgment of the Investigator.

8.10.1 Unplanned Assessments

Additional samples to assess laboratory parameters and PK/PD may be required for safety reasons and/or for a better characterization of the PK/PD profile.

The number of additional samples taken will depend on the body weight and health status of the patient. Sampling schedule will be proposed by the Sponsor and discussed with the Investigator.

9 STUDY SCIENTIFIC OVERSIGHT

A Scientific Steering Committee (SSC) composed of international experts in pediatric rheumatology as well as in HLH has been involved in the preparation of study design and protocol writing.
The SSC is also to be consulted for the composition of the independent Data Monitoring Committee (iDMC).

The SSC will continue to play an advisory role throughout the course of the study, including the support to the iDMC oversight, and will perform evaluations of the data to support the Sponsor in the interpretation of the results of the study.

Please refer to Appendix C for full details of membership of the SSC.

10 SAFETY MONITORING

10.1 INDEPENDENT DATA MONITORING COMMITTEE

The iDMC, composed of relevant experts (pediatric rheumatologist, pediatric onco-hematologist with experience in HLH, pediatric immunodeficiency/infectious disease specialist, bio-statistician and a specialist in ethics), will oversee the study, with particular regard to the evaluation of safety parameters and benefit/risk profile of emapalumab, reviewing all data generated on an ongoing basis with the aim to ensure that patients are not exposed to unnecessary risks. Some of the iDMC members have been already

involved in the oversight of the ongoing emapalumab studies. Please refer to Section 10.5.1 for further details on the iDMC.

10.2 DESCRIPTION OF SAFETY PARAMETERS

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

- Adverse events (AEs), with special attention being paid to potential infusion related reactions (IRRs), (i.e events occurring during or within 24 hours post infusion) and to the occurrence of infections, particularly with pathogens associated with lack of IFNγ biological activity (due to emapalumab mode of action).
- Laboratory parameters, as described in Section 8.4
- Vital signs, as described in Section 8.3.1
- Physical examination with particular attention paid to evolution of signs and symptoms present at baseline, and to any emergent new signs or symptoms (see Section 8.3.2 for more details).

10.3 RECORDING AND REPORTING SAFETY PARAMETERS

10.3.1 Adverse events

Adverse events (AEs) are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the IMP. All AEs reported by the patients or his/her relatives or observed by the Investigator or his staff during the clinical study from the signature of the ICF up to and including the EoS visit will be reported on the AE data collection form.

Medical conditions present at screening (before ICF signature) should be recorded in the medical history section of the CRF.

All AEs will be reported in the appropriate section of the CRF.

An AE which occurs between start of screening visit (after ICF signature) and start of first IMP administration will be considered as a pre-treatment AE.

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

However, if a pre-existing medical condition recorded in the medical history worsens (clinically significant change in intensity or frequency), it must be recorded as an AE in the CRF and, depending on the time of its occurrence, will be considered as a pre-treatment AE or a TEAE. If a medical condition, recorded as a pre-treatment AE, worsens it will be recorded in the CRF as a separate TEAE.

For each AE, the following will be assessed and recorded: intensity, relationship to the IMP, action taken regarding the IMP, any treatment received for the event and outcome of AE to date.

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

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

For a given AE, the assessment of its intensity should reflect the highest grade (on the 3 points scale mentioned above) reported during its course (except when the intensity of a pre-treatment AE increases after treatment initiation, as indicated above).

The relationship of the AE to the IMP will be assessed by the Investigator using a "Yes/No" classification. A "Yes" relationship infers that there is a reasonable possibility of causal relationship between the AE and IMP. The expression "reasonable possibility" is meant to convey that there are facts, evidence or arguments to suggest a causal relationship. Conversely, a "No" relationship infers that there is no reasonable possibility of causal relationship between the AE and IMP. Usually it implies that other possible causes have been identified.

In this study emapalumab is the only IMP.

Abnormal laboratory findings should be reported as AEs if requiring specific treatment. Exception to this is the onset of any new or worsened abnormal laboratory findings [e.g. cytopenias (all three lines), abnormalities denoting liver dysfunction, coagulopathy, abnormal ferritin, fibrinogen and triglyceride levels] indicative of an HLH/MAS reactivation or worsening: in this specific instance, the reactivation or worsening of HLH/MAS must be reported as the AE and not the abnormal laboratory findings, even if requiring intervention.

If an abnormal laboratory finding leads to a new diagnosis, this diagnosis should be reported as AE (e.g. hyperglycaemia leading to diagnosis of diabetes mellitus).

10.3.2 Serious Adverse Events

An adverse event is considered serious if it:

- results in death (note: death is an outcome, not an event);
- is life-threatening; (note: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe);
- requires in-patient hospitalization or prolongs an existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is an important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of this study, the following will not be considered as serious adverse events:

- Elective hospitalizations or surgical procedures that are a result of a patient's pre-existing condition(s) which has (have) not worsened since receiving IMP. Such events should still be recorded as adverse events in the CRF;
- Hospitalization as requested per protocol for emapalumab infusion and study visits.

Any serious adverse event (SAE) that occurs during the course of the study, irrespective of the treatment received by the subject and regardless of causality to the study drug, must be communicated by the Investigator to Sobi AG, by fax or electronic transmission, within 24 hours of awareness.

For the initial SAE report, the Investigator should report all available case details concerning the patient and the event, using the Sobi AG SAE reporting standard form provided to the Investigators.

Sobi AG contact information for SAE reporting:

-

E-mail: [redacted]

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

All SAEs must be recorded as an AE in the CRF. They should be reviewed, evaluated and followed through to resolution (or stabilization) by the Investigator.

For any new SAE, the following minimum information is required in the initial report:

- Clear identification of the Investigator, with full contact information or site number
- Subject's identification details (study number, site number, subject's unique study identification number and date of birth),
- IMP administration details (dose and dates)
- Diagnosis of the event (or a brief description of signs/symptoms/clinical course, if the diagnosis is not available) and the date of onset,
- Seriousness criteria.

In addition causal relationship (Investigator's opinion) of the event with the IMP or with the study procedure (e.g. the causality according to the Investigator during screening) should be provided whenever possible in this initial report, otherwise it must be included in a follow-up report.

The Sponsor will also conduct its own assessment on seriousness and causality of all recorded AEs during the study. If the Sponsor becomes aware of an AE, which has not been reported by the Investigator as serious, but is assessed by the Sponsor as serious (e.g. medically important), the Investigator will be asked to report such AEs to the Sponsor as an SAE, according to the timelines and rules described above.

10.3.3 SUSAR reporting

Suspected unexpected serious adverse reactions (SUSARs) are adverse events that are both serious and unexpected (i.e. as per the Investigator's Brochure), and are considered, by the Investigator or the Sponsor, to have a reasonable possibility of causal relationship between the administered IMP and the adverse event.

Some of the SAEs reported by the Investigator may qualify as SUSARs, and such need to be reported in an expedited manner by the Sponsor to Health Authorities and Central Ethics Committees/Independent Ethics Committees/ Research Ethics Boards.

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

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

For Canada, the sponsor is required to inform Health Canada of any serious, unexpected adverse drug reaction that has occurred inside or outside Canada. An adverse drug report must be filed in the cases where the adverse drug reaction is neither fatal nor life-threatening, within 15 days after becoming aware of the information, within 7 days where it is fatal or life-threatening, immediately where possible and, in any event, after becoming aware of the information.

10.4 FOLLOW-UP OF SAFETY PARAMETERS

10.4.1 Treatment and Follow-up of Adverse Events

Adverse events, especially those for which the relationship to the study drug has been assessed as 'Yes', should be followed-up until the event has returned to baseline status or has stabilised. If a clear explanation is established, it should be recorded on the CRF.

All SAEs must be followed-up until the event has either resolved or reached a stable clinical outcome.

10.4.2 Pregnancy

In the event that a pregnancy occurs during the trial course, it must be reported to Sobi AG within 24 hours of awareness. This includes pregnancies occurring in partners of male enrolled patients. All information pertaining to the pregnancy should be reported using the Sobi AG Pregnancy form provided to the investigators. Pregnancies should be followed until conclusion to obtain outcome information.

Occurrence of a pregnancy in a study participant will preclude any further IMP administration.

If the patient is withdrawn from the study, the assessments presented in the Schedule of Assessments for EoS are to be performed (see Section 8.9).

10.5 BENEFIT/RISK MANAGEMENT

10.5.1 Safety Surveillance Management - iDMC

The main responsibility of the iDMC is to review all safety and efficacy data as they are generated to ensure that no patient is exposed to unnecessary risk and to continuously assess the benefit/risk profile of emapalumab.

The iDMC can recommend treatment discontinuation for individual patients as well as to halt the entire study temporarily or permanently. Predefined stopping rules will guide the iDMC review process. For more details, see stopping rules in Section 11.

10.5.2 General Benefit/Risk Considerations

10.5.2.1 Potential benefits

Patients presenting MAS secondary to sJIA may not respond to systemic glucocorticoids and have limited alternative therapeutic options. These options are represented by prolonged treatment with high doses glucocorticoids, and administration of CsA or chemotherapy such as etoposide, all options carrying an increased risk of morbidity and mortality. For those non-responders patients, an alternate therapy should aim to obtain remission of MAS with none or limited safety issues.

Three elements strongly suggest that the use of emapalumab would enable MAS remission:

- In animal model mimicking MAS, administration of an anti-IFNγ enables the recovery/remission of the signs and symptoms associated with hypercytokinemia
- Observational studies have shown a strong correlation between biomarkers (IFNγ as well as IFNγ-induced chemokines) and disease parameters at MAS onset and during disease evolution.

According to the data collected to date in pHLH patients (ongoing NI-0501-04 study), emapalumab administration has shown the potential to improve or resolve relevant clinical and laboratory abnormalities of HLH, including CNS signs and symptoms when present, allowing patients to proceed to HSCT.

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

Based on these considerations, sJIA patients with MAS having inadequately responded to systemic high dose glucocorticoids are expected to benefit from a targeted therapy with emapalumab aiming at neutralizing IFNγ and achieving MAS remission.

10.5.2.2 Risks analysis

- Risks related to emapalumab

emapalumab is a fully human IgG1monoclonal antibody (mAb).

Upon the administration of mAbs, which are proteins, acute infusion reactions can occur. These may happen during the infusion or in the subsequent hours (usually within the first 24 hours) (Kang SP 2007, Maggi E 2011).

These reactions are either IgE-mediated type I hypersensitivity reactions (anaphylactic reactions), or anaphylactoid reactions not mediated by IgE. True anaphylactic reactions usually do not occur upon initial infusion and require a certain sensitization. In contrast, the pathophysiology of anaphylactoid reactions appears to be secondary to the release of cytokines consequent to a mAb binding to circulating antigen-expressing cells. However, the clinical manifestations of anaphylactic and anaphylactoid reactions overlap, and both may lead to life-threatening conditions, involving cardiovascular, respiratory, central nervous, gastro-intestinal, and cutaneous systems. The management of anaphylactic and anaphylactoid reactions involves immediate administration of oxygen, epinephrine, vasopressors, bronchodilators, corticosteroids, and/or antihistamines.

More than 850 infusions have been administered to HLH patients (either in the context of the NI-0501-04 and NI-0501-05 studies or in patients who have received emapalumab in compassionate use) up to and including the dose of 10 mg/kg, without any serious or severe infusion related reaction reported. In less than 2% of infusions, mild or moderate transient erythematous rashes localized to the extremities (feet and/or hands) have been reported in a few patients. They occurred in most of the cases during the first infusions of emapalumab and resolved spontaneously. When administration of emapalumab has been performed occasionally through a peripheral venous access, infusions were all uneventful.

In the population intended to be enrolled in the study, the risk of developing infusion related reactions compared to previously exposed HLH patients is not expected to be higher. All patients enrolled in this study will continue to receive glucocorticoids concomitantly, and will be monitored during and after the infusion.

When administered to humans, most mAb therapeutics elicit some level of antibody response (anti-drug antibodies or ADAs) against the therapeutic product, as early as after the first exposure. No sign of immunogenicity has been reported in the emapalumab study in healthy volunteers. The presence of ADAs will be measured during this study as per regulatory recommendations, and the analysis is planned to be performed at the end of the NI-0501-06 study, unless PK or safety concerns possibly related to

immunogenicity would justify an interim analysis. Data accumulated so far (in particular PK profiles and a negative ADA search performed in the first pHLH patient treated with emapalumab) have not led to suspect the presence of ADA.

- Risks related to the target

The impact on the immune defense caused by the neutralization of IFNγ is known from patients with inborn errors of the IL-12/23-IFN-γ circuit, particularly patients with complete or partial IFNγ receptor (R) deficiency, and subjects developing neutralizing auto anti-IFNγ antibodies.

Patients with IFNγ R deficiency are prone to developing mycobacterial infections and, although to a lesser extent, *Salmonella* infections (Dorman SE 2000, Jouanguy E 1997). The mean age of the first environmental mycobacterial infection is 3.1 and 13.4 years in patients with complete and partial deficiency, respectively (Remus N 2001). No systematic prophylaxis has been recommended in these patients.
If an infection occurs, appropriate antibiotherapy based on sensitivity of isolated species is prescribed. Individuals with anti-IFNγ auto-antibodies are also susceptible to develop mycobacterial infections (for the vast majority atypical mycobacterial infections), but also opportunistic infections (e.g. by *Histoplasma Capsulatum, Salmonella*, *Herpes Zoster* virus infections) (Browne SK 2012).

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

A reactivation of *Herpes Zoster* virus after the single emapalumab infusion at 3 mg/kg, was observed in one healthy volunteer in the NI-0510-03 study with a non-uneventful course and full recovery.

Preliminary data on infections collected in patients treated with emapalumab to date allow the following conclusions to be drawn:

- Active infections, in particular bacterial and viral infections (among them EBV or CMV infections, which are often the trigger of the HLH), were present at the first administration of emapalumabin some of them. During emapalumab administration these infections resolved with appropriate antimicrobial treatment and while achieving control of HLH.
- Some HLH patients treated in second line after immune-chemotherapy developed infections during the course of emapalumab treatment. A long and profound generalized immune suppression caused by HLH treatments administered prior to the initiation of emapalumab constitutes a higher risk for infection development. However in the presence of a satisfactory control of HLH, and upon appropriate anti-microbial treatment, infections have usually resolved.
- Patients treated in first line or after a limited exposure to glucocorticoids or chemotherapy seem to develop less infections during the course of emapalumab.
- Systematic search for tuberculosis was negative and no atypical mycobacteria were detected in any of the patients. Stool/blood cultures were negative for *Salmonella*, *Shigella* or *Campylobacter* in all patients. No *Herpes Zoster* infection has been reported.
- Only one infection reported (disseminated histoplasmosis in a patient with a severely compromised immune status and suspected to carry the pathogen prior to the administration of emapalumab) was reported as a serious adverse reaction as it is one of the few pathogens known to be favored by IFNγ neutralization. However the patient recovered from it rapidly after the administration of an effective antifungal treatment.

- The severity and duration of neutropenia, a hallmark of HLH as well as a potential consequence of previous HLH treatments, seemed to contribute significantly to the development of infections.

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

- Risk related to the study population

Most of the patients are expected to have already received at least glucocorticoid treatments as well as having possibly been previously treated by sJIA specific therapies, some of them for a relatively long time depending on the duration of their underlying rheumatic disease; therefore they may carry variable degree of toxicities caused by those treatments. The data collected to date in pHLH patients who have been heavily pretreated by immune-chemotherapy show that administration of emapalumab does not aggravate toxicities of previous therapies while showing, in general, a favorable impact on HLH activity.

All information collected on disease severity and previous treatments will be taken into account for the analysis of adverse events.

Toxicities of concomitant treatments, authorized or recommended during the administration of emapalumab, may also potentially expose the patients to adverse events; however their benefits may outweigh their risks. No safety concern related to the concomitant administration of emapalumab with other treatments (e.g., antimicrobial agents, anti-hypertensive drugs) has been reported so far. Corticosteroids have already been administered with anti-IFNγ therapy in Crohn's Disease without any particular safety concerns (Reinisch W 2010). Of interest, tapering of glucocorticoids had no impact on safety and tolerability of emapalumab infusions and has shown benefit for patients with steroids-related hypertension and generalized immunosuppression.

Although the risk that the emapalumab treatment will not be able to control the disease may exist, the close monitoring and the stopping rules of the study ensure that, in this event, emapalumab treatment will be discontinued and the patients will rapidly receive rescue treatments according to the standard clinical practice at the participating sites. The risks of administering alternate therapy after having received emapalumab seems to be low, since no particular safety concerns were observed during treatment with emapalumab.

10.5.2.3 Risk minimization measures

In view of the expected benefits and previous experience gathered with patients exposed to emapalumab the above listed risks are considered to be manageable in this patient population, if adequate minimization measures are put in place. An overview of specific measures to minimize the subject's risk is provided below:

- Study designed with rheumatologists experienced in the treatment of sJIA and MAS, forming the SSC.
- Patients are hospitalized in specialized centers for the treatment of MAS, and therefore with all necessary emergency assistance equipment.
- Inclusion/exclusion criteria: patients with malformations or severely altered functions (either due to the disease stage or to a concomitant disease), as well as patients with evidence of patent or latent TB infections or active mycobacteria*, Shigella, Salmonella, Campylobacter, Histoplasma Capsulatum* or *Leishmania* infections, will not be included in the study (for details see Section 4.1).
- Although unlikely to be observed based on preliminary results gathered from patients treated with emapalumab up to 10mg/kg, Infusion Related Reactions (IRRs) will be detected and managed in due time through patients' monitoring during and after drug infusions. Each of the specialized centers will have physicians adequately trained in IRR management.

- Recommendations on prophylaxis for Herpes Zoster virus for all patients and Tuberculosis for a defined subpopulation (see Section 6.2) in the protocol to avoid occurrence of these infections.
- The monitoring for specific infections, known to be favored by IFNγ neutralization, will continue after emapalumab discontinuation as long as serum emapalumab levels are detectable.
- Close monitoring of potential infections through careful physical examination, laboratory parameters, active search for EBV, CMV, Adenoviruses, detection of tuberculosis
- Study safety surveillance by an independent Data Monitoring Committee

The Development Risk Management Plan addresses risks, identify signals for early detection of safety concerns and propose mitigating actions. It will be part of the study documentation shared with Investigators and any relevant third party involved in the study.Stopping rules have been also developed to ensure individual patient safety and determine whether the study should be put on hold or terminated prematurely.

11 STOPPING RULES

11.1 AT PATIENT LEVEL

11.1.1 Investigator's or Patient's Decision to Discontinue

An Investigator can decide at any time during the study to discontinue the treatment for an individual patient based on his/her own medical judgment, taking into account the individual benefit risk ratio for his/her patient. In addition, the patient (or their legal representative) can decide at any time to withdraw from the study.

In any case the decision to withdraw or be withdrawn will have no impact on the patient's care and further treatments administered to him/her after withdrawal.

Patients who are withdrawn from the study will receive alternative treatments according to the standard of care at the site.

11.1.2 Decision to Discontinue Treatment due to Safety Reason or Lack of Efficacy

11.1.2.1 Treatment Discontinuation for a Safety Reason

A patient must be discontinued from study treatment if a SAE occurring after emapalumab administration is:

1. considered by the Investigator to be related to emapalumab (with guidance from the iDMC if needed)

   AND

2. is a life-threatening event.

11.1.2.2 ***All other related SAEs will be judged by the iDMC on a case-by-case basis taking into account the disease evolution (such as signs of improvement in HLH) and the possibility of managing the SAE and ensuring that no patient is exposed to unnecessary risks.*** *Treatment Discontinuation for Lack of Efficacy*

A patient should be discontinued from study treatment for lack of efficacy in the event of any of the followings:

- Rapid worsening of MAS representing immediate risk for the patient and requiring the use of a salvage therapy.
- No Response to emapalumab, provided that there is evidence of IFNg neutralization.

However, upon request by the Investigator to continue emapalumab treatment in the absence of therapeutic alternatives, the iDMC can authorize it after a thorough review of the patient's data and confirmation of lack of risks for the patient.

11.1.3 Systemic and local reaction to emapalumab infusion

In case of clinical relevant changes in vital signs compared to pre-infusion values, the rate of emapalumab infusion may be decreased or the infusion temporarily interrupted, if deemed necessary by the Investigator.

A decision to definitely stop the infusion should only be taken in case of very severe systemic reactions and be based on the evolution of patient status after appropriate symptomatic measures, e.g. oxygenation, and upon physician's own medical judgment.

All changes in the infusion rate should be recorded on the Infusion Worksheet: each time with the rate modification.

Unless related to a hypersensitivity reaction, the occurrence of local issues related to the infusion (such as catheter displacement, obstruction or product extravasation) should be managed through the identification of a new venous access as soon as possible to complete the infusion. All relevant information needs to be recorded in the Infusion Worksheet, including the volume of IMP potentially lost (in order to calculate the quantity of drug infused), and the time at which the infusion was stopped and restarted.

11.2 AT STUDY LEVEL

11.2.1 Suspension of Recruitment

Recruitment may be suspended in the following situations:

- Any occurrence of death or life-threatening SAE related to the drug
- At the iDMC's own request as an outcome of their regular study review.

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

The suspension will allow the iDMC to analyse the data already generated and consider a recommendation.

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

- To resume recruitment without any change
- To implement minimisation measures that may require protocol amendment
- To implement conditions for study termination, e.g. next occurrence of a particular serious drug reaction or at the next patient worsening or reactivation

11.2.2 Study Termination

11.2.2.1 Study Termination for Safety Reason

Occurrence of two deaths suggesting a reasonably possible relationship with continuous exposure to emapalumab and occurring in similar conditions will trigger the decision to terminate the study.

This process will involve both the iDMC and the Investigator. The management of patients already enrolled in the study will also be part of the iDMC recommendations.

11.2.2.2 Study Termination for Absence of a Demonstrated Benefit

The decision to terminate the study due to absence of a demonstrated benefit will be one of the responsibilities of the iDMC, based on the ongoing review of the individual patient data and benefit/risk analysis.

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

12 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

Full details of all planned analyses will be specified in separate documents describing PK/PD and Statistical Analyses, which will be finalized prior to the locking of the study database. This section contains an overview of the planned methods of analysis with regard to safety and efficacy variables.

12.1 SAMPLE SIZE

Approximately 12 patients (a minimum of 10 sJIA patients) will be enrolled across North America and Europe. The sample size is based on pragmatic considerations, and on the experience acquired from primary HLH patients treated with emapalumab.

12.2 ANALYSIS SETS

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

12.2.1 Safety Analysis Set

The safety analysis set will include all patients who receive any part of an infusion of study drug.

12.2.2 Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will coincide with the Safety Analysis Set.

12.2.3 Per-Protocol Analysis Set

The per-protocol analysis set will consist of all ITT patients who complete the study without major violations of the study protocol. Detailed listing of major protocol deviations will be defined in the SAP prior to locking of the final database.

12.3 STATISTICAL AND ANALYTICAL METHODS

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

All study variables are considered to be exploratory in this study, and no hierarchy of endpoints has been specified, as the objective of this pilot study is to confirm that the proposed dose regimen is adequate in this patient population.

Analysis will focus on descriptive statistics and confidence intervals. As this is a pilot study, statistical methods will focus on summarizing the data collected using descriptive statistics and on appropriate graphical presentations.

12.3.1 Efficacy Data

Graphical and tabular summaries will be prepared for each of the MAS distinct features, e.g. *fever; splenomegaly; WBC; platelet counts; liver function test (in particular ALT/AST); fibrinogen; ferritin; LDH.*

For binary endpoints (MAS remission by Week 8, number of patients who taper glucocorticoids, number of patients who discontinue due to lack of efficacy), 95% confidence intervals will be calculated for proportions.

For time to event endpoints (time to MAS remission, time to achievement of glucocorticoids tapering and time to death), Kaplan-Meier curves will be calculated and summary statistics, such as medians, proportions event-free at various time points will be calculated and presented, and 95% confidence intervals calculated where possible.

12.3.2 Safety Data

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

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

For each clinical laboratory test, individual patient values will be listed and summarized and change from pre-treatment baseline values calculated and summarized. Summaries of marked abnormalities and shift tables will be tabulated for each laboratory test.

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

12.3.3 Pharmacodynamic Data

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

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

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

12.3.4 Immunogenicity Data

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

12.3.5 Missing Data

No imputations of missing data will be performed. However, the following rules will be applied to ensure that all patients can be included in the final analysis:

- patients who are withdrawn from the study prior to Week 8 because of safety concerns or poor efficacy will be classified as non-responders from the time of their withdrawal in all

analyses of response status, and their data will be censored at time of withdrawal in all time-to-event analyses. For continuous endpoints in such patients, all analyses for time points beyond the point of withdrawal will exclude missing data for these patients.

12.4 INTERIM ANALYSIS

No interim analysis is planned.

12.5 WITHDRAWAL AND REPLACEMENT

12.5.1 Patients

Additional patients will be recruited into the study if patients are withdrawn from the study for reasons other than safety or lack of efficacy to ensure a sample size of approximately12 patients across North America and Europe.

12.5.2 For Centers

Centers may be closed down for the following administrative reasons: excessively slow recruitment, poor protocol adherence.

PART II

13 ETHICAL AND LEGAL ASPECTS

13.1 GOOD CLINICAL PRACTICE

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

13.2 INVESTIGATOR'S RESPONSIBILITIES

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

The Investigator is responsible for keeping a record of all patients (or their legally authorised representative) who sign an informed consent document and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in their source documents and the study-screening log.

The Investigator, or a designated member of the Investigators' staff, must be available during monitoring visits, audits and inspections to review data, resolve queries and allow direct access to patients' records (e.g. medical/hospital records, office charts, hospital charts, and study related charts) for source data and other type of verification. The Investigator must ensure timely and accurate completion of CRFs and queries. The Investigator must make himself/herself personally available during at least one monitoring visit per month, in order to address questions and to generally demonstrate his/her direct oversight of the conduct of the study.

The Investigator must allow regular visits at the site when patients are enrolled, to be not less than one 2 day visit every 14 days. In addition, the Investigator must ensure that all source data, including but not limited to medical records and hospital charts are available for review by the monitor for at least 30 days after a study day.

13.3 CONSENT

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

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

If applicable, since minors are involved in the trial, assent must be obtained from the minor and informed consent from at least one of the parents or as mandated by local rules (individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedures involved in the research). The language used in the Assent Form is adapted to the maturity level of the minor involved in the trial. Since minors of different age groups are likely to be entered into the trial different versions of the Assent Form will be provided. The modalities for obtaining informed consent from the parents and Assent from the minor will be defined at the site initiation visit and documented at the clinical trial center.

The Investigator, or designee, will obtain consent for participation in the study in writing. The written informed consent will be obtained prior to conducting any study-related procedures or tests, although procedures or tests that are done as a part of routine medical care and conducted before consent can be used for the purposes of screening. The patient's consent (or the consent of the patient's legally authorized representative) must be confirmed at the time of consent by the personally dated signature of the person conducting the informed consent discussions. A copy of the signed consent document must be given to the patient or their legally authorized representative. The Investigator will retain the original signed consent document.

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

13.4 CONFIDENTIALITY AND DATA PRIVACY

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

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

13.5 PROTOCOL AMENDMENTS

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

13.6 APPROVAL OF THE CLINICAL STUDY PROTOCOL AND AMENDMENTS

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

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

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

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

All documents handed over to patients or their legal representative will be reviewed by Sobi AG prior to submission to the competent Regulatory Authorities and to IRB/IEC. This includes but is not limited to the informed consent form, patient information sheet, assent form, advertisements, training materials, etc.

13.7 ONGOING INFORMATION FOR IRB/IEC

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

- Information on SAEs or SUSARs as per local applicable rules and timelines;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to patients.

13.8 CLOSURE OF THE STUDY

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

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

- Lack of screening or recruiting activities
- Significant non-compliance with contractual enrolment timelines and targets
- Persistent GCP non-compliance
- Inaccurate, incomplete or delayed data collection
- Persistent failure to adhere to the study protocol
- Persistent failure to provide requested follow-up information for data queries

13.9 RECORD RETENTION

The investigator will ensure that essential records are kept in a secure archiving facility for the retention period stipulated in the study contract. Essential documents include, but are not limited to, the following:

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

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

13.10 LIABILITY AND INSURANCE

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

13.11 FINANCIAL DISCLOSURE

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

13.12 DISCLOSURE OF PROTOCOL AND STUDY RESULTS AND PUBLICATION POLICY

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

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

Sobi AG will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Sobi AG will support publication of multicenter trials only in their entirety

and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the trial.

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

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

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

14 MONITORING AND AUDITING

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

14.1 STUDY MONITORING AND SOURCE DATA VERIFICATION

As part of the responsibilities commensurate with participating in the study, the investigator agrees to maintain and have available for monitoring, adequate case records (accurate source documents and CRFs) for the patients treated under this protocol. In addition, the investigator agrees to maintain all administrative documents (e.g. IEC correspondence, investigational product and supplies shipment manifests, monitoring logs, or correspondence with Sobi AG and with any of its representative for this study).

14.2 ON-SITE AUDITS

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

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

14.3 SERIOUS GCP BREACHES

Sobi AG is required to report a serious GCP Breach within 7 days to applicable health authorities. Therefore, should an Investigator become aware of a possible serious GCP breach, e.g. a protocol violation, or non-reporting of critical safety information that has the potential of jeopardizing patients' safety, Sobi AG must be notified within 24 hours.

15 DOCUMENTATION AND USE OF STUDY FINDINGS

15.1 DOCUMENTATION OF STUDY RESULTS

A CRF (including electronic data capture) is used in this study and a specific CRF will correspond to each patient.

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

The CRF must be reviewed by the Investigator named in the study protocol or by a designated sub-investigator, and final signature will be required.

15.2 USE OF COMPUTERIZED SYSTEMS AT THE CLINICAL TRIAL CENTER

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e. in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

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

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17 APPENDICES

Appendix A – Literature reference for sJIA diagnosis: "Operational case definition of new onset sJIA used in development of treatment plans"

Appendix B – Literature reference for MAS diagnosis: "2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis"

Appendix C – Membership of the Scientific Steering Committee (SSC)

Appendix D – Estimated blood volumes to be drawn during the study

Appendix E – Literature reference for Yamaguchi AOSD Criteria: "Preliminary Criteria for Classification of Adult Still's Disease"

APPENDIX A: OPERATIONAL CASE DEFINITION OF NEW ONSET SJIA USED IN DEVELOPMENT OF TREATMENT PLANS (DESIGNED BY CHILDHOOD ARTHRITIS AND RHEUMATOLOGY RESEARCH ALLIANCE)

(DeWitt EM 2012)

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 erythematous 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

[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 has to 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 B: 2016 CLASSIFICATION CRITERIA FOR MACROPHAGE ACTIVATION SYNDROME COMPLICATING SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS: A EUROPEAN LEAGUE AGAINST RHEUMATISM/AMERICAN COLLEGE OF RHEUMATOLOGY/PAEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION COLLABORATIVE INITIATIVE

(Ravelli A(b) 2016)

Classification of macrophage activation syndrome in systemic juvenile idiopathic arthritis

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 C: MEMBERSHIP OF THE SCIENTIFIC STEERING COMMITTEE (SSC)

- [redacted]
- [redacted]
- [redacted]
- [redacted]

APPENDIX D: ESTIMATED BLOOD VOLUMES TO BE DRAWN DURING THE STUDY

Assessments		Screening	Emapalumab Treatment period						Evaluation period	EoS
		SD-1	SD0	SD1	SD2	SD3	SD5	Infusion Visits[1] SD6 to SD28	SD35 – SD42 – SD49	SD 56 Week 8
Laboratory assessments	- CBC (including Lymphocyte subset)	1	1	1	1	1	1	1	1	1
	- Coagulation, Fibrinogen	1	1	1	1	1	1	1	1	1
	- Biochemistry	2	2	2	2	2	2	2	2	2
	- Serum pregnancy test (if applicable)	0.5								0.5
	-*Search for EBV, CMV, Adenoviruses, Mycobacteria*	0.5						0.5[2]	0.5[3]	0.5
	-*Search for HSV, HZV, HIV, HBV, HCV*	0.5								
	-*Search for other pathogens (if needed)*	1								
Subtotal per visit		6.5	4	4	4	4	4	4/4.5[2]	4/4.5[3]	5
Subtotal per month								59.5		17.5
PK	- Emapalumab serum concentration		1	0.5	0.5	1	0.5	1	0.5	0.5
PD 1	- IFNγ, CXCL9, CXCL10, sCD25		1	1	1	1	1	1	1	1
PD 2	- Other biomarkers		1					1[2]	1[3]	1
Immunogenicity (ADA)			0.5							0.5
Molecular diagnosis (if consent for genetic testing is given)		(3)								
Subtotal per visit		(3)	3.5	1.5	1.5	2	1.5	2/3[2]	1.5/2.5[3]	3.0
Total per month (maximum)								**90.5**		**26.0**
TOTAL OVERALL STUDY (maximum)										**116.5**

[1] Assumes worst case scenario in terms of blood volumes, i.e. emapalumab treatment is continued until SD28 (total of 10 infusions). If treatment is shortened, the amount of blood to be drawn would be less.

[2] At SD15 and SD28.

[3] At SD42.

APPENDIX E: PRELIMINARY CRITERIA FOR CLASSIFICATION OF ADULT STILL'S DISEASE

(Yamaguchi M 1992)

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)

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.

RF: rheumatoid factor, ANA: antinuclear antibody.

novimmune

Clinical Study Protocol

A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of NI-0501, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) developing Macrophage Activation Syndrome/secondary HLH (MAS/sHLH)

Protocol number:	NI-0501-06
Version:	1.0 US – Final
Date:	October 19, 2017
P-IND Number:	111015
Sponsor:	Novimmune SA 14 Chemin des Aulx 1228 Plan-les-Ouates Switzerland
Study Principal Investigator	[redacted]
Clinical Science Leader NI-0501	[redacted]
Chief Medical Officer	[redacted]

INVESTIGATOR AGREEMENT

Protocol Number: NI-0501-06

Protocol date and version: October 19, 2017 – VERSION 1.0 US

Study drug: NI-0501

Study title: A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of NI-0501, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) developing Macrophage Activation Syndrome/secondary HLH (MAS/sHLH).

Investigator endorsement:

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

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

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

_____ _____

Site Investigator's Signature Date

_____

Site Investigator's Name

CONTACT LIST

Study Location:	Multicenter in North America
Study Principal Investigator:	[redacted]
Sponsor:	Novimmune SA 14 Chemin des Aulx 1228 Plan les Ouates Switzerland [redacted]
Chief Medical Officer:	[redacted]
Safety Officer:	[redacted]
Clinical Science Leader NI-0501:	[redacted]
Head Clinical Operations:	[redacted]
Clinical Pharmacologist:	[redacted]

NI-0501-06 SYNOPSIS

Title:	A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of NI-0501, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) developing Macrophage Activation Syndrome/ secondary HLH (MAS/sHLH)
Sponsor:	Novimmune SA, Switzerland
Study Type, Phase and Design:	• Interventional Phase 2 study • Open-label, single arm, international, multicenter study. ***Please note***: any reference made to MAS in this protocol should be intended as referring to the secondary form of HLH occurring in patients with sJIA.
Study Objectives:	The main objectives of the study are: • To describe the pharmacokinetics (PK) profile of NI-0501 in sJIA patients with MAS. • To confirm the proposed dosing regimen of NI-0501 in sJIA patients with MAS. • To evaluate the safety and tolerability profile of intravenous (i.v.) administrations of NI-0501 in sJIA patients with MAS. • To preliminary assess the efficacy of NI-0501 in sJIA patients with MAS. • To assess the levels of relevant biomarkers, such as IFNγ and main IFNγ-induced chemokines (CXCL9, CXCL10). • To assess other potential disease biomarkers (e.g. sCD25, sCD163, IL-10, IL-6, IL-18, TNFα, CXCL11). • To assess the immunogenicity of NI-0501 in sJIA patients with MAS.
Study Population:	• sJIA patients with MAS having shown inadequate response to high dose glucocorticoid treatment.
Inclusion Criteria:	• Patients of both genders, aged <18 years • Confirmed sJIA diagnosis. For patients presenting with MAS in the context of the onset of sJIA , high presumption of sJIA (as per Appendix A) will suffice for eligibility. • Diagnosis of active MAS confirmed by the treating rheumatologist, having ascertained the followings: *Febrile patient presenting with:* - Ferritin > 684 ng/mL *and any two of:* - Platelet count ≤ 181 x10^9/L - AST levels > 48 U/L - Triglycerides > 156 mg/dL - Fibrinogen levels ≤ 360 mg/dL.

	(see Appendix B) • Patient presenting an inadequate response to high dose i.v. glucocorticoid treatment administered for at least 3 days as per local standard of care (including but not limited to pulses of 30 mg/kg methylprednisolone (mPDN) on 3 consecutive days). High i.v. glucocorticoid dose should not be lower than 2 mg/kg/day of mPDN equivalent in 2 divided doses (to a maximum of 60 mg/day in patients of 30 kg or more). In case of rapid worsening of the patient's condition and/or lab parameters, inclusion may occur within less than 3 days from starting high dose i.v. glucocorticoids. • Informed consent provided by the patient (as required by local law), or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as applicable. • Having received guidance on contraception for both male and female patients sexually active and having reached puberty: Females of child-bearing potential require use of highly effective contraceptive measures (failure rate of less than 1% per year) from screening until 6 months after receiving last dose of the study drug. Highly effective contraceptive measures include: o Sexual abstinence o Hormonal contraceptives: combination or progesterone only o Intrauterine methods: intrauterine devices or systems o Bilateral tubal occlusion o Vasectomised partner Males with partners(s) of child-bearing potential must agree to take appropriate precautions (such as sexual abstinence, barrier contraception, vasectomy) to avoid fathering a child from screening until 6 months after receiving last dose of the study drug.
Exclusion Criteria:	• Diagnosis of suspected or confirmed primary HLH or HLH consequent to a neoplastic disease. • Patients treated with Tocilizumab, Canakinumab or TNF inhibitors within 5 times of their defined half-life. • Active mycobacteria (typical and atypical), *Histoplasma Capsulatum*, *Shigella*, *Salmonella*, *Campylobacter* and *Leishmania* infections. • Clinical suspicion of latent tuberculosis. • Positive serology for HIV antibodies. • Presence of malignancy. • Patients who have another concomitant disease or malformation severely affecting the cardiovascular, pulmonary, CNS, liver or renal function that in the opinion of the Investigator may significantly affect likelihood to respond to treatment and/or assessment of NI-0501 safety. • History of hypersensitivity or allergy to any component of the study drug.

	• Receipt of a BCG vaccine within 12 weeks prior to screening. • Receipt of live or attenuated live vaccines (other than BCG) within 6 weeks prior to screening. • Pregnant or lactating female patients.
Study Drug:	• NI-0501 is a fully human IgG1 monoclonal antibody (mAb) directed against human IFNγ.
Dosing Regimen, Frequency of Administration & Treatment Duration:	• NI-0501 will be administered at the initial dose of 6 mg/kg by infusion. • NI-0501 treatment will be continued at the dose of 3 mg/kg, every 3 days until SD15, and then twice-a-week for additional 2 weeks, i.e. until SD28. • Treatment may be shortened upon achievement of complete clinical response (i.e. MAS remission), however at least two infusions of NI-0501 at the dose of 3 mg/kg have to be administered (i.e. after SD6). • In the event that the PK profile of NI-0501 in a given patient indicates a Target Mediated Drug Disposition (TMDD) suggestive for very high IFNγ production, the dose of NI-0501 may be increased upon assessment of a favorable benefit/risk profile in that individual patient. • NI-0501 treatment may be prolonged beyond 4 weeks guided by clinical and PK/PD evidence in an individual patient, upon assessment of a favorable benefit/risk profile.
Background Therapy & Concomitant Medication:	• NI-0501 will be administered on a background of at least 2 mg/kg/day of mPDN equivalent (to a maximum of 60 mg/day in patients of 30 kg or more), which can be tapered during the treatment depending on patient conditions. • Patients must receive prophylactic treatment for *Herpes Zoster* infections starting preferably the day before (and in any case prior to initiation of NI-0501 treatment), and treatment must continue until serum NI-0501 levels are no longer detectable. • Anakinra must be discontinued at latest before the first NI-0501 infusion; no wash-out period is required given its short half-life. • A wash-out period of 5 times of respective half-lives is required in patients who have received Tocilizumab, Canakinumab or TNF inhibitors as sJIA treatment. • It is recommended background treatment of sJIA not to be re-introduced during the 8 weeks of the study, unless the patient's clinical condition requires it. • Cyclosporine A (CsA) may be continued if started at least 3 days prior to initiation of NI-0501 treatment. CsA dose adjustments are allowed in order to maintain therapeutic levels. CsA can be withdrawn at any time during the study, upon judgment of the Investigator. CsA cannot be introduced once NI-0501 treatment has started. • If the patient is receiving intrathecal therapy (e.g. methotrexate and glucocorticoids) at the time of NI-0501 treatment initiation, this treatment will be continued until clinically indicated.

	• Vaccination with a live or attenuated-live (including BCG) vaccine must be avoided during the whole study until serum NI-0501 levels are no longer detectable. • Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, i.v. parenteral nutrition, inotropic support, antibiotics, anti-fungal and anti-viral treatments, ultrafiltration or hemodialysis, as well as general supportive care are permitted.
Sample Size:	• A minimum of 5 evaluable patients will be enrolled in North America. • The sample size of 5 patients is based on pragmatic considerations, and on the experience acquired from primary HLH patients treated with NI-0501.
Number of Sites and Recruitment Duration:	• International, multi-center. • The recruitment period, in this rare population, is estimated to be approximately 2 years in North America. A twin protocol NI-0501-06 EUDRACT 2016-004223-23is running in Europe. • Patients enrolled under these two protocols (for a total of 10 patients) will be analyzed jointly and data reported in a single CSR.
Study Duration and Study End Definition:	• The duration of the study will be 8 weeks for each patient (*plus* up to 1 week screening period). The study duration of 8 weeks allows performing a short-term follow-up of 4 weeks after the last NI-0501 infusion on SD28. [***Note***: If NI-0501 treatment is prolonged beyond 4 weeks in a given patient, additional visits will be performed weekly until completion of a 4-week follow-up after the last NI-0501 infusion, follow-up that should occur under the present protocol]. • End of the study is defined as last patient last visit. • All patients who have received at least one dose of NI-0501 will be asked to enter a long-term follow-up study.
Study Scientific Oversight/ Study Safety Monitoring :	• A Scientific Steering Committee (SSC) composed of international experts in pediatric rheumatology as well as in HLH, has been involved in the preparation of study design and will continue to play an advisory role throughout the course of the study, to support the iDMC in the study oversight, and the Sponsor in the interpretation of the study results. • An independent Data Monitoring Committee (iDMC) composed of relevant experts (pediatric rheumatologist, hemato-oncologist with experience in HLH, pediatric immune deficiency/infectious disease specialist, bio-statistician and a specialist in ethics) will oversee the safety management of the study, reviewing all data generated on an ongoing basis with the aim to ensure that patients are not exposed to unnecessary risks.
Study Endpoints:	**Pharmacokinetics and Pharmacodynamics** • PK profile of NI-0501. • Levels of circulating free IFNγ at predose, and total IFNγ (free

IFNγ+bound to NI-0501) after initiation of NI-0501.

- Levels of the main IFNγ-induced chemokines (CXCL9, CXCL10).
- Correlation between chemokine levels (CXCL9, CXCL10) and levels of free NI-0501, free IFNγ (pre-dose) and total IFNγ (*exploratory analysis*).
- Correlation of chemokine and total IFNγ levels, and laboratory parameters of MAS severity, e.g. ferritin, platelet count, LFTs (*exploratory analysis*).
- Levels of other potential disease biomarkers (e.g. sCD25, sCD163, IL-10, IL-6, IL-18, TNFα, CXCL11).
- Levels (if any) of circulating antibodies against NI-0501 to determine immunogenicity (ADA).

In particular, based on:

- levels of circulating NI-0501
- levels of total IFNγ
- levels of main IFNγ–induced chemokines (namely CXCL9 and CXCL10)

a PK/PD modelling will be used to confirm that the proposed dose regimen is adequate in relation to the IFNγ production in this patient population.

Safety

The tolerability and safety of NI-0501 treatment will be assessed as follows:

- Incidence, severity, causality and outcomes of AEs (serious and non-serious), with particular attention being paid to infections.
- Evolution of laboratory parameters, in particular CBC, LFTs, inflammatory markers (ferritin and CRP) and coagulation parameters.
- Number of patients withdrawn from the study due to safety reasons.

Efficacy

A preliminary assessment of NI-0501 efficacy in this patient population will be based on the following variables:

- Number of patients achieving MAS remission by Week 8 after initiation of NI-0501 treatment.
- Time to MAS remission.
- Number of patients for whom at any time during the study glucocorticoids can be tapered *i)* to the same (or lower) dose being administered before the occurrence of MAS ((in those patients who are already treated for sJIA) or *ii)* by 50% (or less) of the dose administered at NI-0501 treatment start (in those patients who present with MAS at sJIA onset).
- Time to glucocorticoids tapering (as above described).
- Survival time.
- Number of patients withdrawn from the study due to lack of efficacy.

Statistical Analysis:	• All study variables are considered to be exploratory in this study, and no hierarchy of endpoints has been specified, as the objective of this pilot study is to collect and analyze data to confirm that the proposed dose regimen is adequate in this patient population. Statistical methods will therefore focus on summarizing the data collected using descriptive statistics and on appropriate graphical presentations. • For binary endpoints (MAS remission by Week 8, number of patients who taper glucocorticoids, number of patients who discontinue due to lack of efficacy), 95% confidence intervals will be calculated for proportions. • For time to event endpoints (time to MAS remission, time to achievement of glucocorticoids tapering and time to death), Kaplan-Meier curves will be calculated and summary statistics, such as medians, proportions event-free at various time points will be calculated and presented, and 95% confidence intervals calculated where possible. • Data relating to safety will be listed and summarised using descriptive statistics.

LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-drug-antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BCG	Bacillus Calmette-Guérin
BSA	Body Surface Area
CBC	Complete blood cell count
CDC	Complement Dependent Cytotoxicity
CL	Systemic drug clearance
C_{max}	Peak drug plasma concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CpG	Cytosine-phosphate-guanine
CRF	Case report form
CRP	C-reactive protein
CsA	Cyclosporin A
CSF	Cerebrospinal fluid
C_{trough}	Plasma drug concentration immediately prior next dosing
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
EBV	Epstein-Barr virus
EoT	End of treatment
EoS	End of study
γGT	Gamma Glutamyl Transferase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
HSCT	Hematopoietic stem cell transplantation

HSV	Herpes simplex virus
HZ	Herpes Zoster
HZV	Herpes Zoster virus
ICMJE	International Committee of Medical Journal Editors
iDMC	Independent Data Monitoring Committee
IFNγ	Interferon gamma
IFNγ-R1	Interferon gamma receptor chain 1
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IgG1	Immunoglobulin G1
IL	Interleukin
ILAR	International League of Associations for Rheumathology
IMP	Investigational medicinal product
ITT	Intention-to-treat
i.v.	Intravenous
KD	Dissociation constant
KM	Michaelis-Menten constant
KO	Knock Out
LCMV	Lymphocytic choriomeningitis virus
LDH	Lactate dehydrogenase
LFTs	Liver function tests
LLN	Lower limit of normal
mAb	Monoclonal antibody
MAS	Macrophage activation syndrome
mPDN	Methylprednisolone
MRI	Magnetic resonance imaging
NK	Natural killer
NaCl	Sodium chloride
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PDG	Preliminary diagnostic guidelines (Ravelli *et al.*, 2005)
pHLH	Primary HLH
PK	Pharmacokinetic
PPD	Purified protein derivative
PT	Prothrombin Time
SAE	Serious adverse event
SAP	Statistical analysis plan
SAD	Single ascending dose
sCD25	soluble CD25 (i.e. soluble IL-2 receptor)

SD(n)	Study Day number (e.g. Study day 1 = SD1)
sJIA	Systemic Juvenile Idiopathic Arthritis
SoA	Schedule of assessments
SSC	Scientific steering committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
$t_{1/2}$	Elimination half-life
Tmax	Time when plasma concentration is at peak
TMDD	Target mediated drug disposition
TMF	Trial Master File
TNFα	Tumor necrosis factor alpha
ULN	Upper limit of normal
US	Ultrasonography
Vss	Volume of distribution at steady state

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PART I

1 BACKGROUND INFORMATION

1.1 NI-0501

1.1.1 Description and mode of action

NI-0501 is a fully human IgG1 anti-interferon gamma (IFNγ) monoclonal antibody (mAb) which binds and neutralizes IFNγ. NI-0501 binds to soluble and receptor (IFNγR1)-bound forms of IFNγ.

Since NI-0501 is a human IgG1, it retains the characteristics of this immunoglobulin isotype.

After binding to its receptor, IFNγ acts to produce a variety of physiological and cellular responses. Numerous studies over the last 20 years have associated IFNγ with the pathogenesis and the maintenance of inflammatory diseases[1–3], and most recently, in the pathogenesis of HLH.

1.1.2 Preclinical Data

1.1.2.1 Non-clinical Pharmacology

NI-0501 has shown similar binding affinity and blocking activity for IFNγ from non-human species, including *Rhesus* and *Cynomolgus* monkeys, but not from dogs, cats, pigs, rabbits, rats or mice.

Due to NI-0501 capacity to bind free and IFNγR1-bound IFNγ, studies were performed to investigate the potential of NI-0501 to mediate antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) activities, in the presence of target. A lack of ADCC activity was demonstrated and no induction of CDC activity was observed.

1.1.2.2 Toxicology

Binding and functional data demonstrated *Rhesus* or *Cynomolgus* monkeys to be relevant species to evaluate the safety of NI-0501. No off-target toxicity was attributed to the drug when administered to *Cynomolgus* monkeys in 13 weekly doses of up to 200 mg/kg. An enhanced susceptibility to infections due to the pharmacological effect of the drug was observed at all dose levels (10 to 200 mg/kg/week) in animals originally harboring gastrointestinal pathogens (*Shigella, Salmonella, Campylobacter*) prior to NI-0501 administration. In a study where *Cynomolgus* monkeys were not initially found to be harboring gastrointestinal pathogens, weekly administrations of NI-0501 for 8 consecutive weeks at doses up to 30 mg/kg were well tolerated, without the need for antibiotic prophylaxis.

Results from a human tissue cross-reactivity study, involving a panel of 35 different human tissues, demonstrated that NI-0501 did not cross-react with any of the human samples tested.

1.1.2.3 Safety pharmacology

There were no abnormal findings in ECGs taken periodically during treatment and recovery periods in the 8 week and 13 week repeated dose toxicology studies in *Cynomolgus* monkeys, where animals were exposed to doses up to 200 mg/kg of NI-0501 weekly. No abnormal findings were observed in the histopathological investigations of the hearts and lungs in these animals compared to untreated animals. Histopathological analysis of kidneys from these animals revealed no abnormal findings and the periodic urinalysis readings were also normal, indicating no abnormal effects on renal function. There were no histopathological findings in brains in both studies. Furthermore, no abnormal behavior of the animals was observed throughout the study periods, suggesting no effects on CNS.

1.1.3 Clinical Data

A Phase 1 randomized double-blinded placebo-controlled single ascending dose study in 20 healthy adult volunteers investigating the safety, tolerability and pharmacokinetic profiles of single intravenous (i.v.) administrations of NI-0501 was conducted between September 2011 and April 2012. During this study a total of 14 subjects received increasing doses of 0.01, 0.1, 1, and 3 mg/kg NI-0501 (3, 3, 4, and 4 subjects, respectively), while 6 subjects received placebo.

The pharmacokinetics (PK) analysis of NI-0501 revealed the expected profile for an IgG1 with a half-life of approx. 22 days, a slow clearance (≤ 0.007 L/h) and a low volume of distribution (< 6 L on average).

All NI-0501 infusions were uneventful.

A similar incidence of commonly reported infections (e.g., upper respiratory tract infections) was observed after administration of NI-0501 and in subjects who had received placebo.
A Herpes Zoster (HZ) infection was reported in one subject ([redacted]), 14 days after his infusion of 3 mg/kg of NI-0501. This event was assessed as related to the NI-0501 infusion and considered as serious (medically significant) in the context of a Phase 1 study in healthy volunteers (HVs). Its intensity was moderate and its course normal under antiviral therapy. The subject recovered with no sequelae.
An increased susceptibility to HZ infections in patients having developed auto-antibodies against IFNγ[4] or having received ustekinumab (a mAb which decreases IFNγ production by inhibiting the p40 subunit of IL-12) has been described in the literature[5].

In conclusion, the infusion of NI-0501 was well tolerated and the effects observed during the 8 week monitoring after drug infusion did not reveal any serious or unexpected off-target safety or immunogenicity concerns.

A study is presently ongoing to evaluate the efficacy and safety of NI-0501 treatment in patients with primary HLH (protocol NI-0501-04). The protocol allows for inclusion of patients either treatment-naïve (first line patients) or reactivating after initial response to conventional therapy or not achieving a satisfactory response or showing intolerance to conventional therapy (second line patients). Based on preliminary efficacy and safety evidence, and on the positive benefit/risk profile observed so far, the study, which originated as Phase 2 trial, has been recently amended to continue as Phase 2/3 study with the inclusion of the same study population (i.e., first and second line pHLH patients). Thirty-one patients have been enrolled as of September 15th 2016, of whom 18 received transplantation. Five patients received NI-0501 as 1st line therapy. More than 500 NI-0501 infusions have been performed in the study patients who have received a median of 7 weeks of therapy (range 4 days-31 weeks; continuation of NI-0501 treatment beyond 8 weeks can occur under the long-term follow-up protocol NI-0501-05). Infusions have been well tolerated with no premedication needed, and no safety concerns after NI-0501 administration have emerged to date. Based on data gathered so far, NI-0501 treatment has shown the potential to improve relevant clinical and laboratory features of HLH such as fever, splenomegaly, cytopenia, hyperferritinemia, hypofibrinogenemia, and also CNS signs and symptoms. Early tapering of glucocorticoids has been possible in the majority of patients.

1.2 HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

HLH is a rare, serious and life threatening disease of pathologic immune activation, characterized by clinical signs and symptoms of extreme inflammation (fever, splenomegaly, cytopenias, coagulopathy), leading to the development of abnormal immune-mediated pathologies which, through tissue damage, ultimately may cause multi-organ failure and death[6].
HLH comprises primary (genetic/familial) HLH and secondary HLH.

Primary HLH is a heterogeneous autosomal recessive disorder, mostly seen in infancy and early childhood with an estimated prevalence in Europe of 1/50,000 live births[7]. The disease is invariably fatal with a median survival of less than 2 months after onset of symptoms, if untreated[8].

The genetic defects in primary HLH affect genes involved in cytotoxic pathway of NK-cells and/or cytotoxic lymphocytes required to eliminate activated macrophages, encoding proteins for perforin synthesis, cytolytic granule maturation, granule exocytosis and release[9]. In addition, some immunodeficiency syndromes, e.g. Griscelli syndrome type 2 (GS-2) and Chediak-Higashi syndrome (CHS), present frequently with HLH[10].

Secondary forms of HLH can occur during the course of an infection, an autoimmune/rheumatic disease or in association to a malignancy. Secondary forms present with the same signs and symptoms of primary HLH and can be equally severe.

The presence of signs and symptoms of HLH in patients suffering from a rheumatic disease, such as systemic Juvenile Idiopathic Arthritis (sJIA) and Systemic Lupus Erythematosus (SLE), is often referred to by rheumatologists as Macrophage Activation Syndrome (MAS), as more specifically described in the following section.

In the present protocol, any reference made to MAS should be intended as referring to the secondary form of HLH occurring in patients with sJIA.

1.2.1 Macrophage Activation Syndrome (MAS)

MAS is a severe, potentially life-threatening complication of rheumatic diseases which is caused by excessive activation and expansion of T lymphocytes and macrophages. The uncontrolled expansion of these immune cells results in a marked hypercytokinemia and a hyperinflammatory state associated with fever, cytopenias, hepatosplenomegaly, liver dysfunction, coagulation abnormalities and hyperferritinemia, and may progress to multiple organ failure and death[11].

Because of its strong clinical and pathological similarity to HLH, MAS is classified among the secondary or acquired forms of HLH. In fact, it has been recently demonstrated that the majority of patients with MAS have impaired NK and perforin functional tests and that a significant number of MAS patients show polymorphisms or heterozygous mutations in PRF1 and UNC13D[12].

MAS occurs most frequently in patients with sJIA and, less often with systemic lupus erythematosus (SLE), but is also described, though more rarely, in patients with vasculitis, particularly with Kawasaki disease. Approximately 7–17% of patients with sJIA develop overt MAS[13,14], some evidence suggests that subclinical MAS may be seen in as many as one third of patients with active systemic disease[15].

Because MAS is potentially fatal, a timely diagnosis and immediate therapeutic intervention are essential for appropriate management of the disease. The reported mortality rates in MAS reach 20-30%, and it remains the major source of mortality in pediatric rheumatology[16].

Different sets of criteria have been proposed for the diagnosis of MAS in patients with sJIA. The HLH-2004 diagnostic guidelines[17], primarily developed for primary (genetic) forms of HLH, have sometimes been recommended. However, they present several limitations when applied to patients with sJIA. For example, criteria such as cytopenias and hypofibrinogenemia below the thresholds required by HLH-2004 become evident only in the later stages of MAS, as these patients often have increased white blood cell and platelet counts as well as elevated serum levels of fibrinogen as a part of the sJIA inflammatory response[11]. As for primary HLH, hemophagocytosis may not be present in a significant proportion of patients with MAS at presentation[18]. Moreover, hemophagocytosis, NK cell activity and sCD25 are not routinely assessed in the context of MAS.

An alternative approach has been proposed based on the application of preliminary diagnostic guidelines (PDG) for MAS complicating sJIA, which were created through the analysis of a cohort of patients with MAS compared with a group of patients with a flare of sJIA[19].

The HLH-2004 diagnostic guidelines and the preliminary diagnostic guidelines for sJIA-associated MAS were compared for their capacity to discriminate sJIA/MAS from sJIA (in the absence of MAS) and systemic infection in a large patient population[20]. Although with some limitations due to its retrospective nature, this study suggested that the preliminary MAS diagnostic guidelines may achieve a satisfactory balance between sensitivity and specificity, as well as concordance with the diagnosis made by the treating physician when differentiating patients with sJIA/MAS from sJIA, while their specificity in discriminating vs. systemic infections was < 30%. Moreover, it has been reported that the proportion of patients fulfilling each single criterion of the PDG is highly variable, and some clinical features (e.g. CNS dysfunction and hemorrhages) may manifest at a late stage of MAS, rendering their sensitivity low in incipient MAS[21]. The sensitivity of the adapted HLH-2004 set of 4 of 5 criteria was poor (35%), mainly explained by the low frequency of cytopenia and hypofibrinogenemia.

Very recently, an EULAR/ACR-approved set of classification criteria sets have been proposed through a multistep process combining expert consensus and retrospective analysis of patient data[22]. These classification criteria did not unequivocally prove to be useful for diagnosis in clinical practice (about 30% of patients diagnosed by the treating physician were classified as not having MAS), and showed important limitations to identify patients who developed MAS while receiving IL-1 and IL-6 inhibitors[23,24].

The limitations of the thus far proposed criteria for MAS diagnosis render the clinical diagnosis by expert rheumatologists still key in the challenge to distinguish MAS from clinical conditions presenting with overlapping features such as flares of sJIA or sepsis-like syndromes.

There are currently no approved drugs for the treatment of MAS. Likewise, no prospective studies have been conducted to evaluate the safety and efficacy of the drugs currently used for the treatment of MAS, and data is only available as limited case reports or as retrospective surveys.

Usually, high-dose glucocorticoids are the first-line treatment for MAS. In patients failing to respond to glucocorticoids, Cyclosporine A (CsA) has been proposed as additional treatment[25].
Being part of the HLH-94 treatment protocol developed for treating pHLH, the administration of etoposide is also considered in patients failing high dose glucocorticoids. However, the potential toxicity of the drug remains a major concern.
The utility of biologics inhibiting the IL-1, IL-6R or TNFα pathways in the treatment of MAS still remains unclear. Although biologics inhibiting these pathways have been reported to be effective in isolated cases, there have been a few reports of sJIA patients developing MAS while receiving these treatments[26–29], as well as of patients who do not respond to these treatments, indicating that inhibition of IL-1, IL-6R or TNFα does not provide full protection against MAS development nor an efficacious treatment of the full blown syndrome.

A large retrospective, multicenter survey has investigated the clinical, laboratory, and histopathological characteristics as well as current practice treatment and outcome of MAS in a total of 362 patients[18].
In approximately half of the patients, MAS occurred in the context of active sJIA in the absence of a specific trigger, 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. Nearly all patients were given glucocorticoids, given the well-established role of this treatment approach in MAS and HLH. Cyclosporine was the other most commonly prescribed drug

(61% of patients), while intravenous immunoglobulins, biologic medications (in particular anakinra) and etoposide were given to 36%, 15% and 12% of the patients, respectively.

The identification of effective therapeutic regimens for MAS represents an area of unmet high medical need. More than 50% of patients with sJIA and MAS do not respond to systemic glucocorticoids alone, or may require prolonged treatment at high doses with associated significant morbidity. When patients fail to respond to glucocorticoids, no good evidence-based data is available on the effectiveness and safety of additional treatments such as CsA or etoposide. The course of MAS may become rapidly irreversible leading to a fatal outcome, with about one third of the patients requiring ICU admission. Furthermore, no clinical and/or laboratory features have thus far been identified to be predictive of poor response to the current standard of care, hence leaving the treating physicians with scarce possibility to identify those patients who would rapidly progress into an unfavorable clinical course.

1.3 STUDY RATIONALE

1.3.1 Rationale for developing NI-0501 in MAS

MAS and HLH are characterized by sustained immune cell activation and an associated cytokine storm of proinflammatory cytokines with overproduction of IFNγ, TNFα, IL-1 and IL-6[6,30–32]. During the last years, evidence has been accumulating in support of the pivotal role of IFNγ in the development of both HLH[33–35] and MAS[36,37].

For primary HLH, perforin knock-out mice are considered a relevant model as these mice, once infected with LCMV, develop all the diagnostic and many of the clinical and laboratory characteristic features of the human disease. The HLH-like disease that they develop is dependent on CD8+ T cells and IFNγ produced in response to antigen stimulation[33]. It was demonstrated that when the high circulating levels of IFNγ are neutralized with the administration of an anti-IFNγ antibody, not only are the clinical and laboratory abnormalities reverted, but also survival rate is dramatically improved. On the contrary, the ablation of many other cytokines had no impact on survival[33,34]. Further strengthening the importance of IFNγ in HLH are the high concentrations of circulating IFNγ levels found in these patients[6,32]. In a series of 71 patients monitored from HLH diagnosis to treatment and follow-up, IFNγ levels were above the upper limit of normal (17.3 pg/mL) in all patients, and in particular 53.5% had levels above 1000 pg/mL. It was also reported that IFNγ levels rise early and quickly, and can fall from > 5000 pg/mL to normal in 48 hours upon effective treatment of HLH.

Two animal models of secondary HLH have been investigated in the context of the NI-0501 development program to elucidate the potential pathogenetic role of IFNγ:

- In a murine model that mimics an infection-driven HLH, repeated administrations of CpG via activation of TLR9 triggered a hypercytokinemia that led to clinical (e.g. body weight loss, splenomegaly) and laboratory (e.g. cytopenia, hyperferritinemia) features of HLH[37]. When IFNγ was neutralized by the administration of an anti-IFNγ antibody, clinical and laboratory features of the disease were reverted. The neutralization of IFNγ was shown to be complete also in relevant target tissues, such as the liver and the spleen. Interestingly, the administration of the anti-IFNγ antibody unveiled an amount of IFNγ 500- to 2,000-fold higher than that measured in blood, likely to better reflect the IFNγ production in tissues. The two IFNγ-inducible chemokines (CXCL9 and CXCL10) were upregulated after TLR9 stimulation both in blood and in liver, and a significantly correlation was observed between serum levels of IFNγ with CXCL9 and CXCL10 serum concentrations. The neutralization of IFNγ induced a significant decrease of serum CXCL9 and CXCL10, and of their mRNA levels in the liver[38].

- An animal model of IL-6 transgenic mice expressing high levels of IL-6 has been studied, since it mimics the condition of patients with sJIA, the rheumatic disease most frequently associated with secondary forms of HLH. When triggered with Toll-Like Receptor (TLR) ligands, increased lethality, increased inflammatory cytokine production and hyperactivation of inflammatory signaling pathways was observed. Moreover, these mice showed a drop in platelet and neutrophil counts, increased sCD25, ferritin and LDH levels, resembling many of the features typically present in patients with MAS[39]. In these mice, when IFNγ is neutralized with the administration of an anti-IFNγ antibody, survival is markedly improved and laboratory parameters reverted[40].

1.3.2 Rationale for conducting a Clinical Study in MAS/sJIA patients receiving NI-0501 treatment

Evidence has been recently gathered in an observational study conducted in patients with secondary forms of HLH, either consequent to infections, or of unknown origin (pHLH having been excluded by normal cytotoxic activity, absence of mutation in known genes causing pHLH and absence of family history) or with MAS occurring in the context of sJIA.

In 14 patients with secondary HLH (in 7 of whom an underlying infection was identifiable), serum samples were analyzed during active full blown disease and during disease remission. Levels of IFNγ, CXCL9 and CXCL10 were markedly higher in the active phase compared to disease remission (IFNγ: 34.7 *vs*. <3.5 pg/ml; CXCL9: 33598 *vs*. 745 pg/ml; CXCL10: 4420 *vs*. 132 pg/ml; median values). IFNγ levels significantly correlated with the levels of CXCL9 (p=0.0018) and, to a lesser extent, of CXCL10 (p=0.014). The levels of IFNγ and chemokines (in particular CXCL9) correlated significantly with parameters of disease severity, such as neutrophil and platelet counts, ferritin and ALT, further supporting the pathogenic role of IFNγ in secondary HLH and the potential use of chemokines as relevant biomarkers of the disease[38].

Similar findings have been shown in patients with MAS occurring in patients with sJIA. Serum concentrations of IFNγ, IFNγ-inducible chemokines (CXCL9, CXCL10, CXCL11) and IL-6 were measured in 54 patients with sJIA, of whom 20 had MAS. The levels of IL-6 were comparable in patients with full-blown MAS and those with active sJIA but without MAS at the time of sampling. On the contrary, circulating IFNγ and chemokine levels were significantly higher in MAS, particularly for CXCL9, whose median levels were approximately 15-fold higher compared to patients with active sJIA without MAS (13392 vs. 837 pg/mL; p=0.005). Noteworthy, a significant correlation was demonstrated only in patients with MAS between CXCL9 levels and parameters typically abnormal such as ferritin (p=0.041), neutrophil (p=0.010) and platelet (p=0.022) counts, ALT (p=0.044) and LDH (p=0.013). Levels of IFNγ also correlated with laboratory parameters of disease severity, with the exception of LDH for which statistical significance was not achieved[41].

This pilot phase 2 study, as well as the twin study in Europe, is intended to assess the pharmacokinetics/pharmacodynamics profile, the safety and tolerability, and the preliminary efficacy of NI-0501 as treatment of MAS in sJIA patients.

Based on the evidence above described, there is a solid rationale for the neutralization of IFNγ as targeted therapy for MAS/sHLH occurring in sJIA patient, and for investigating the benefit of NI-0501 treatment in this patient population.

Additionally, clinical data gathered in an ongoing study conducted in patients with primary HLH receiving NI-0501 treatment either as first and second line (NI-0501-04 study), to date indicate:

1. a favorable tolerability profile of NI-0501 and absence of relevant safety concerns:

- all infusions administered were well tolerated, confirming the observations made in healthy volunteers
- emerging infections reported in the study generally resolved upon proper treatment and HLH control
- among the reported infections, only one (histoplasmosis) may have been favored by NI-0501 mode of action, whereas all other infections have been related to patients' impaired immune status due to HLH and to previous or concomitant treatments. Of note, histoplasmosis resolved upon proper treatment
- no death has been attributed to NI-0501 administration.

2. a favorable impact on disease parameters, with appreciable onset of effects within the first days of treatment:
   - typical clinical signs and symptoms of HLH started to improve rapidly after the first administration of NI-0501 (fever within hours, spleno/hepatomegaly within days)
   - of the 30 patients that have received at least 4 weeks of treatment at the cut-off date of September 15th 2016, 18 patients have proceeded to HSCT and 4 are awaiting for transplant.
3. a predictable pharmacokinetic profile of NI-0501 from the PK modeling and simulation approach, and evidence that neutralization of IFNγ is achieved and maintained

In conclusion, there is a strong rationale for neutralizing IFNγ in MAS secondary to rheumatic diseases based on pre-clinical and clinical evidence, and the preliminary data in pHLH patients indicates a favorable benefit/risk profile of NI-0501 with a significant improvement to normalization of HLH features.

It is therefore anticipated that NI-0501 can represent an innovative and effective therapeutic approach in the management of this severe, life-threatening complication of rheumatic diseases, potentially limiting side effects from long-term high dose glucocorticoid treatment.

The study population will be represented by children with a diagnosis of sJIA who develop MAS. No diagnostic criteria are available of sJIA. The classification criteria proposed by ILAR require the presence of arthritis persisting for at least 6 weeks. While they appear to be used to classify patients, they cannot be used at disease presentation. In order to allow inclusion of patients presenting with MAS as a feature of onset of sJIA a, the operational criteria designed by CARRA (childhood arthritis and rheumatology research alliance) to identify patients with sJIA early in their disease course (DeWitt EM et al. *Arthritis Care Res 2012* , Appendix A) have been also considered to assess patient eligibility.

The number of patients meeting the ILAR classification criteria will be in any case included in the description of the NI-0501-06 study results.

Patients enrolled under these twin protocols (for a total of 10 patients, 5 in Europe and 5 in North America) will be analyzed jointly and data reported in a single CSR.

2 OBJECTIVES

The objectives of this pilot phase 2 study are as follows:

- To describe the PK profile of NI-0501 in sJIA patients with MAS.

- To confirm the proposed dosing regimen of NI-0501 in sJIA patients with MAS.
- To evaluate the safety and tolerability profile of intravenous (i.v.) administrations of NI-0501 in sJIA patients with MAS.
- To preliminary assess the efficacy of NI-0501 in sJIA patients with MAS.
- To assess the levels of relevant biomarkers, such as IFNγ and main IFNγ-induced chemokines (CXCL9, CXCL10).
- To assess other potential disease biomarkers (e.g., sCD25, sCD163, IL-10, IL-6, IL-18, TNFα, CXCL11).
- To assess the immunogenicity of NI-0501 in sJIA patients with MAS.

3 STUDY DESIGN

3.1 OVERALL DESIGN

This is an open-label, single arm, international, multicenter pilot phase 2.

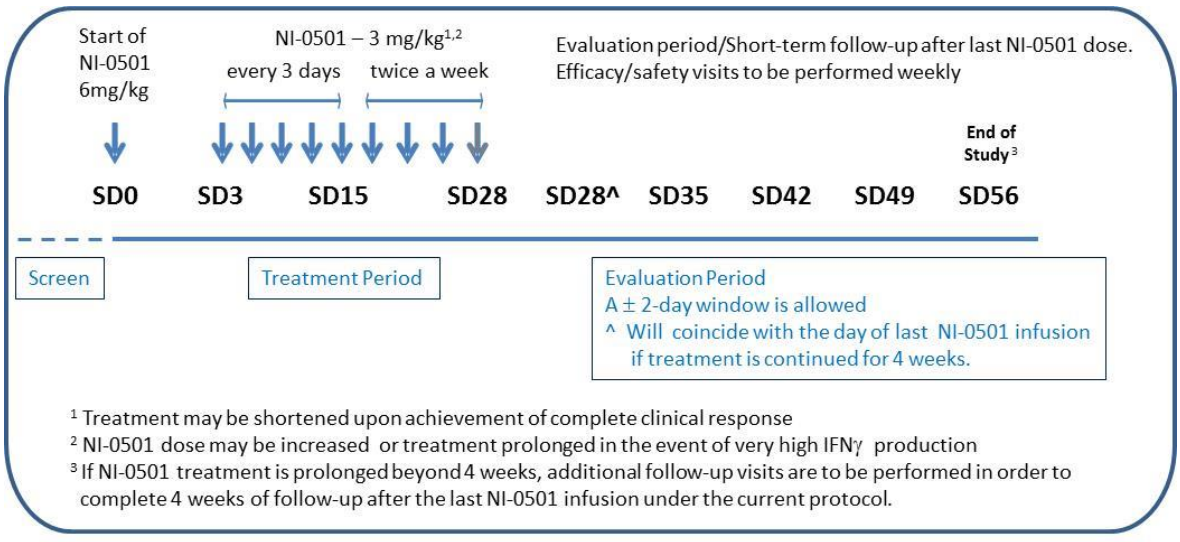
After signature of informed consent, patients will be screened and assessed for eligibility (Section 3.2). The study will be conducted in hospitalized patients since, at minimum, the day before the first administration of the study drug (study day minus one, SD-1) until SD15 at the earliest.

Discharge from the hospital can occur from SD15 onwards, at the Investigator's discretion if the patient's condition allows, provided that no active infections requiring i.v. antimicrobial therapy are present.

For a detailed description of the study procedures, see Section 8.

The study flow-chart is summarized in Figure 1.

Figure 1: NI-0501-06 Study Flow-chart



3.2 SCREENING PERIOD

Screening will be carried out within up to 1 week prior to first administration of NI-0501 (SD0) to enable confirmation of patient eligibility and following the signature of the Informed Consent Form.

In the event that a patient's medical condition warrants rapid treatment initiation, and to avoid unnecessary repetition of recent interventions, results of tests which have been performed as part of the normal patient's care at the site (or at the referring hospital) not more than 2 weeks prior to first NI-0501 infusion, can be considered for screening purposes (inclusion/exclusion criteria checks), with the agreement of both the Sponsor and the Investigator.

Information regarding the inadequate response to high dose i.v. glucocorticoids (as required for patient eligibility), will be collected and recorded in the CRF.

Samples for infection screening need to be collected for analysis according to the protocol requirements; however availability of the results is not required prior to NI-0501 initiation if the patient's medical condition warrants rapid treatment, provided that there are no clinical findings suggestive for the presence of any of the infections which represent exclusion criteria.

In the case of a patient having received BCG vaccination, a PPD test must be performed and combined with an IFNγ-release assay.

A negative serum pregnancy test has to be documented in female patients who are post-pubescent.

For a detailed description of the study procedures during the screening period see Section 8.

3.3 TREATMENT PERIOD

NI-0501 will be administered i.v. at the initial dose of 6 mg/kg, and continued at the dose of 3 mg/kg, every 3 days until SD15, and then twice-a-week for additional 2 weeks, i.e. until SD28.
Treatment may be shortened upon achievement of complete clinical response (i.e. MAS remission), however at least two infusions of NI-0501 at the dose of 3 mg/kg have to be administered (i.e. after SD6). In such circumstances, efficacy/safety visits have to be in any case performed every 3 days until SD15 and then twice-a-week until SD28.

In the event that the PK profile of NI-0501 in a given patient indicates a Target Mediated Drug Disposition (TMDD) suggestive for very high IFNγ production, the planned NI-0501 regimen may be adapted (e.g. the dose of NI-0501 may be increased or the NI-0501 treatment may be prolonged beyond 4 weeks) guided by clinical and PK evidence, upon confirmation of a favorable benefit/risk profile in that individual patient.

3.4 FOLLOW-UP PERIOD

All patients who have received at least one dose of NI-0501 will be monitored after the last administration of NI-0501. A short-term follow-up of 4 weeks has to be performed under the current protocol, therefore should NI-0501 treatment in a given patient need to be prolonged beyond 4 weeks, additional visits will be performed weekly until completion of the 4-week short-term follow-up.

The last visit for a given patient under the NI-0501-06 study will normally be on SD56 (except in case of prolongation of NI-0501 treatment beyond 4 weeks, as above described).

Afterwards all patients will be asked to enter a long-term follow-up study, NI0501-05, to allow long-term outcome and safety surveillance, and to monitor NI-0501 elimination profile.

In the event that additional monitoring of NI-0501 concentrations is required (e.g., NI-0501 serum levels still measurable at EoS) and cannot be performed in the context of the long-term follow-up study,

unscheduled visits will have to be performed beyond SD56, until serum NI-0501 levels are no longer detectable. These measurements should occur not less than every two weeks.

3.5 STUDY END

The end of the study is defined as the last visit of the last patient.

In case of an ongoing serious adverse event (SAE), the patient will continue to be monitored until resolution or until the outcome of the event is known and stable, beyond the defined study end, as necessary.

3.6 LONG-TERM FOLLOW-UP STUDY

All patients having received at least one dose of NI-0501 in the study will be asked to participate in a long-term follow-up study, to monitor long-term outcome and safety after NI-0501 treatment, and, when relevant, to complete the assessment of the NI-0501 elimination profile.

4 TARGET POPULATION

The study population comprises patients of both genders, , aged < 18 years, with confirmed sJIA or high presumption of sJIA, presenting with MAS (as per appendix A) and having shown inadequate response to high dose i.v. glucocorticoid treatment, see Section 4.1.1.

4.1 ELIGIBILITY CRITERIA

To be eligible for the study, patients must meet all inclusion criteria and not meet any of the exclusion criteria:

4.1.1 Inclusion Criteria

1. Patients of both genders, aged < 18 years
2. Confirmed sJIA diagnosis. For patients presenting with MAS in the context of the onset of sJIA, high presumption of sJIA (as per Appendix A) will suffice for eligibility.
3. A diagnosis of active MAS confirmed by the treating rheumatologist, having ascertained the following:

   Febrile patient presenting with:
   - Ferritin > 684 ng/mL

   and any two of:
   - Platelet count ≤ 181 x10^9/L
   - AST levels > 48 U/L
   - Triglycerides > 156 mg/dL
   - Fibrinogen levels ≤ 360 mg/dL

   (see Appendix B[22]).
4. An inadequate response to high dose i.v. glucocorticoid treatment 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).
   High dose i.v. glucocorticoid should not be lower than 2 mg/kg/day of mPDN equivalent in 2 divided doses (to a maximum of 60 mg/day in patients of 30 kg or more). In case of rapid worsening of the patient's condition and/or lab parameters, inclusion may occur within less than 3 days from starting high dose i.v. glucocorticoids.

5. Informed consent provided by the patient (as required by local law), or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as applicable.
6. Having received guidance on contraception for both male and female patients sexually active and having reached puberty:

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

   Highly effective contraceptive measures include:

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

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

4.1.2 Exclusion Criteria

1. Diagnosis of suspected or confirmed primary HLH or HLH consequent to a neoplastic disease.
2. Patients treated with Tocilizumab, Canakinumab or TNF inhibitors within 5 times of their defined half-life.
3. Active mycobacteria (typical and atypical), *Histoplasma Capsulatum, Shigella, Salmonella, Campylobacter* and *Leishmania* infections.
4. Clinical suspicion of latent tuberculosis.
5. Positive serology for HIV antibodies.
6. Presence of malignancy.
7. Patients who have another concomitant disease or malformation severely affecting cardiovascular, pulmonary, CNS, liver or renal function, that in the opinion of the Investigator may significantly affect likelihood to respond to treatment and/or assessment of NI-0501 safety.
8. History of hypersensitivity or allergy to any component of the study regimen.
9. Receipt of BCG vaccine within 12 weeks prior to screening.
10. Receipt of live or attenuated live vaccine within 6 weeks prior to screening.
11. Pregnant or lactating female patients.

5 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

5.1 DESCRIPTION OF IMP

NI-0501 is a fully human anti-IFNγ monoclonal antibody which binds and neutralizes IFNγ.

NI-0501 is manufactured by a third party manufacturing facility duly qualified by Novimmune. It will be supplied to study sites in single-use 2 and/or 10 mL filled single-use glass vials at a concentration of 5 mg/mL, for dilution prior to administration.

The nominal composition of the NI-0501 sterile concentrate for infusion (per mL) is as follows:

Ingredient	Quantity (per mL)
NI-0501	5 mg
L-Histidine	1.55 mg
L-Histidine monohydrochloride, monohydrate	3.14 mg
Sodium chloride (NaCl)	7.31 mg
Polysorbate 80	0.05 mg
pH	6.0 ± 0.2

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

5.2 DOSING REGIMEN

NI-0501 will be administered at the initial dose of 6 mg/kg by infusion over a period of one to two hours depending on the volume to infuse. Treatment will be continued at the dose of 3 mg/kg every 3 days until SD15, and twice-a-week thereafter for a total of 4 weeks (i.e. up to SD28).

Treatment may be shortened upon achievement of complete clinical response (i.e. MAS remission), however at least two infusions of NI-0501 at the dose of 3 mg/kg have to be administered (i.e. after SD6).

In the event that the PK profile of NI-0501 in a given patient indicates a Target Mediated Drug Disposition (TMDD) suggestive for very high IFNγ production, the planned NI-0501 regimen may be adapted by increasing the dose of NI-0501 upon assessment of a favorable benefit/risk profile in that individual patient. NI-0501 treatment may be prolonged beyond 4 weeks guided by clinical and PK/PD evidence, upon confirmation of a favorable benefit/risk profile in that individual patient.

5.3 RATIONALE FOR DOSE SELECTION

The rationale for the dosing strategy foreseen for this study is based on:

- Data from *in vitro* experiments investigating the binding kinetics of NI-0501 to human IFNγ and the functional inhibition of human IFNγ by NI-0501;
- PK information from recombinant IFNγ in human;
- Data from the Phase 1 NI-0501-03 study in which NI-0501 was administered to healthy volunteers;
- Data gathered so far from the ongoing NI-0501-04 study in pediatric primary HLH patients receiving NI-0501 in first or second line;
- Data from an observational study in patients with MAS developing on a background of sJIA[41];
- Data from an observational study in pediatric patients with secondary HLH (having excluded a rheumatic or neoplastic origin)[38].

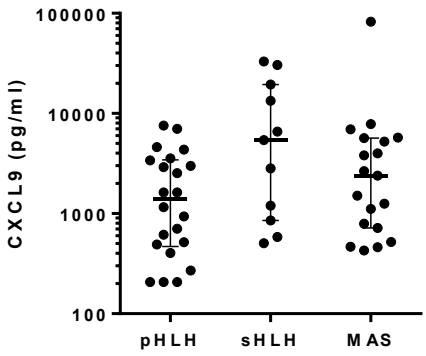
The analysis of data generated from the ongoing study in which primary HLH patients have been treated with NI-0501 has allowed to estimate the production rate of IFNγ through the assessment of the "total IFNγ" (i.e. IFNγ bound to NI-0501 and free IFNγ), and consequently the concentration of NI-0501 required to neutralize the variably high IFNγ concentrations. It has also been possible to determine that when there is a high production of IFNγ, target mediated drug disposition occurs. Importantly, the relationship between IFNγ and the IFNγ-inducible chemokines CXCL9 and CXCL10 has been investigated establishing the tight correlation between those chemokines measured prior to the

administration of NI-0501 and "Total IFNγ" at 48 hours after NI-0501 administration, indicating that these chemokines can be used as exploratory markers of IFNγ production.

The key observations that have constituted the foundation of the dosing rationale for this protocol and led to the selection of the NI-0501 doses to be administered to patients with MAS not responding to high dose glucocorticoid therapy are the followings:

- there is a tight correlation between IFNγ and the IFNγ-related chemokines CXCL9 and CXCL10, as well as between disease parameters and levels of IFNγ and IFNγ-related chemokines in patients suffering from HLH[38,41];
- the higher the circulating levels of the IFNγ-related chemokines, the higher is the concentration of NI-0501 (and therefore the dose of NI-0501) required to neutralize the corresponding levels of IFNγ (data from the NI-0501-04 study on file at Novimmune);
- the neutralization of IFNγ has been shown to have a therapeutic role in primary HLH patients[42];
- a trend towards higher levels of circulating IFNγ-related chemokines has been observed in patients with secondary forms of HLH compared to primary HLH patients[38,41] during or soon after HLH conventional therapy (see Figure 2; data from the NI-0501-04 study on file at Novimmune);
- the onset of MAS is usually acute and the disease worsens rapidly therefore requiring prompt and complete neutralization of IFNγ from the very beginning of treatment;
- in MAS patients, differently from patients with primary HLH, the risk of reactivation is extremely low once HLH remission is achieved, and HSCT is not required. Therefore in patients with MAS, shorter treatment duration is anticipated compared to primary HLH patients, not requiring a maintenance phase while awaiting for HSCT.

Figure 2: CXCL9 levels in patients with pHLH, sHLH and MAS

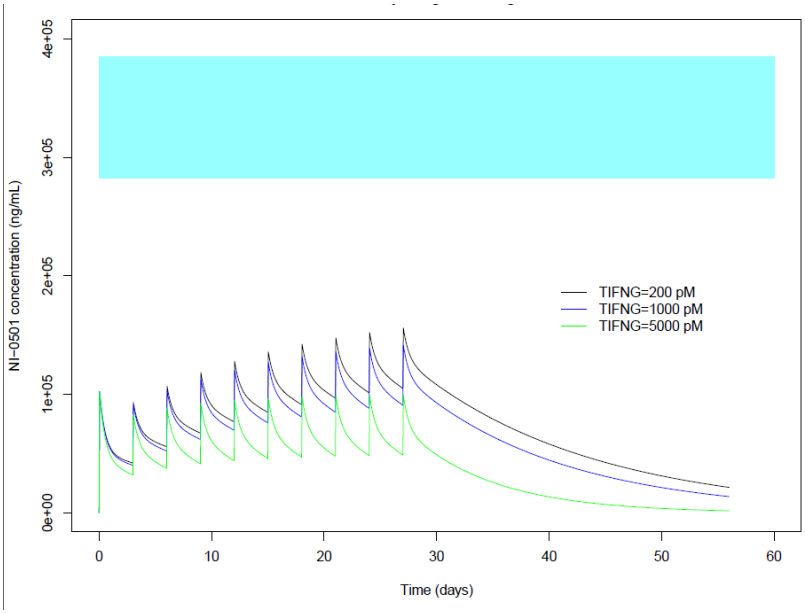


Note:
pHLH: CXCL9 levels from the patients with primary HLH treated with NI-0501 in second line in the NI-0501-04 study prior to receiving NI-0501 (measured by Affymetrix)
sHLH and MAS: CXCL9 levels in patients with active disease (values extrapolated from Millipore to Affymetrix)

Simulations performed considering different IFNγ production rates that are anticipated to potentially occur in MAS patients are presented in Figure 3. The simulations clearly show that the risk of NI-0501 accumulation, as well as the risk of exceeding the highest NI-0501 concentration observed so far in pHLH patients is negligible. Therefore, the expected highest peak and trough concentrations will remain within the ones already achieved in primary HLH patients treated in the ongoing study.

The PK model used to produce these simulations is a two compartment model with linear elimination assuming allometric scaling based on body weight (BW) to which an additional non-linear (TMDD) elimination pathway characterized by a VMAX and a KM has been added. Parameters used in the simulations are from a population pharmacokinetic analysis of study NI-0501-03 and assuming allometric scaling. VMAX is the IFNγ concentration (0.1 nM) multiplied by the recombinant IFNγ clearance (1.2 L/h/kg) divided by the number of binding sites per antibody. KM is assumed to be equal to KD.

Figure 3: Predicted concentration-time profiles after administration of NI-0501 at the initial dose of 6 mg/kg followed by 9 doses of 3 mg/kg every 3 days



Note:
Simulations are shown for sJIA MAS patients of an approximate body weight of 23 kg with different levels of total IFNγ. The blue area corresponds to the mean of the 3 highest peak and trough concentrations observed in HLH patients from study NI-0501-04/05 (data cut-off date of June 24, 2016).

The proposed dosing strategy is further supported by the following evidence:

- primary HLH patients treated with NI-0501 in the context of the ongoing study who were characterized by levels of CXCL9 comparable to the ones expected in MAS all required a rapid and significant NI-0501 dose increase;
- primary HLH patients having a high production of IFNγ, required a high dose of NI-0501, demonstrating the presence of target mediated drug disposition (TMDD), i.e. a pronounced increased clearance of NI-0501 due to the high production of IFNγ. The presence of TMDD, while requiring to administer NI-0501 at high doses and sometimes more frequently, prevents NI-0501 accumulation to occur;
- to date NI-0501 has shown a good safety profile when administered to primary HLH patients up to the dose of 10 mg/kg, achieving similar or even higher NI-0501 exposures compared to the ones expected to occur in MAS patients. More than 850 infusions have been performed in all patients treated (including CU) and around 20% have been performed at a dose of ≥ 6mg/kg.

In conclusion, based on a production rate of IFNγ expected to be high in sJIA patients with overt MAS[41], an initial dose of 6 mg/kg followed by repeated administrations of 3 mg/kg is deemed appropriate to achieve rapidly and maintain the concentrations of NI-0501 estimated to ensure a fast neutralization of IFNγ activity.

5.4 IMP HANDLING

5.4.1 Packaging and Labeling

NI-0501 will be supplied to study sites in single-use glass vials containing a 2 or a 10 ml solution at a concentration of 5 mg/ml. Labeling and packaging will be prepared to meet local regulatory requirements.

5.4.2 IMP Supply

NI-0501 will be supplied to the study sites as open-label supplies.

5.4.3 IMP Receipt and Storage

The NI-0501 vials will be transported with temperature monitoring device, in order to ensure consistent temperatures during transit. When the study drug is received at the site, the Investigator or Pharmacist will check for accurate delivery and absence of temperature deviation alarms.

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

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

Regular inspections of the NI-0501 vials are required, as detailed in the IMP manual indications for the Preparation and Administration of Individual Doses of Study Drug NI-0501.

5.4.4 IMP Preparation, Administration, Accountability and Destruction

5.4.4.1 Preparation

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

The specific dose to be administered for an individual infusion is determined as detailed in Section 5.2.

Full instructions for the preparation, including dilution steps, and method for administration of NI-0501 are available in the IMP Manual that will be provided to all the investigational sites.

5.4.4.2 Administration

The patient should receive the designated volume of the infusate through an infusion pump over a period of 1 to 2 hours depending on the volume to infuse. IMP must be administered using either a syringe that has been sterilized by gamma irradiation or using any appropriate sized non-PVC polyolefin infusion bag and a 0.2 µm filter, which must be added to all infusion lines. (See the IMP manual for details.)

A central venous access is to be maintained during the treatment period. However, as per previous experience in HLH patients in whom central venous access was not possible or not maintained, NI-0501 infusions have been performed safely via peripheral venous access. Since no data is available on the compatibility of NI-0501 with other intravenous substances or additives, other medications/substances should not be added to the infusion material or infused simultaneously through the same intravenous line.

If the same intravenous line is used for subsequent infusions of other drugs, the line should be flushed with saline before and after infusion of NI-0501.

The infusion of NI-0501 will be administered under the direct supervision of the Investigator (or delegate). It should be preferably performed in the morning, and at the same time of the day during the study whenever possible.
Details of the infusion administered must be recorded, including:

- The date of administration
- The time (start and end) of infusion
- The volume administered
- Any adverse effects or general illness experienced by the patient.
- Any other event(s) judged relevant by the site personnel.

5.4.4.3 Accountability

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

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

Drug accountability records shall include:

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

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

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

5.4.4.4 Destruction, Return and Disposal

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

6 PATIENT BACKGROUND TREATMENT AND CARE

6.1 GLUCOCORTICOIDS

For a patient to be eligible for the study, an inadequate response to high dose i.v. glucocorticoids 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 can however occur within less than 3 days from starting high dose i.v. glucocorticoids, in case the patient's condition and/or lab parameters are rapidly worsening.

High dose i.v. glucocorticoids should not be lower than 2 mg/kg/day of mPDN equivalent in 2 divided doses (to a maximum of 60 mg/day in patients of 30 kg or more).

During the study, NI-0501 will be initially administered on a background of at least 2 mg/kg/day of mPDN equivalent (to a maximum of 60 mg/day in patients of 30 kg or more).

Glucocorticoid tapering may be initiated as soon as the patient's conditions allow, according to the Investigator's assessment. The tapering scheme can be selected by the Investigator, with the objective of reaching the same (or lower) dose being administered before the occurrence of MAS (in patients already on treatment for sJIA) or decreasing by 50% (or more) the glucocorticoid dose administered at initiation of NI-0501 treatment (in patients presenting with MAS as first manifestation of sJIA).

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

6.2 PROPHYLACTIC TREATMENT

Prophylaxis for *Herpes Zoster* (*HZ*) virus infection will be administered to mitigate the potential risk associated to NI-0501 administration (see Benefit/Risk Management, Section 10.5).

Patients will therefore receive the prophylactic treatment starting preferably the day before (i.e. SD-1), and in any case prior to, initiation of NI-0501 treatment on SD0, and continued until serum NI-0501 levels are no longer detectable, as follows:

- For *HZ* virus prevention, according to Institution/Country Guidelines/Recommendations (e.g. Acyclovir 200 mg four times daily for children over two years, for children under two years 100 mg four times daily).

In the unlikely event that a patient, previously vaccinated for TB, shows a Purified Protein Derivative (PPD) test result ≥ 5mm and a negative IFNγ-release assay, the patients will receive TB prophylaxis according to Institution/Country Guidelines/Recommendations (e.g. Isoniazid).

In case NI-0501 concentrations are still measurable after the end of the study, it is required that the above mentioned prophylaxis be maintained, until serum NI-0501 levels are no longer detectable.

6.3 CONCOMITANT THERAPY

6.3.1 Cyclosporine A

CsA may be continued, if already started at least 3 days prior to initiation of NI-0501 treatment. CsA dose adjustments will be performed if required based on results of therapeutic drug monitoring, in order to maintain therapeutic levels. CsA can be withdrawn at any time during the study, upon judgment of the Investigator. CsA cannot be introduced once NI-0501 administration has started.

6.3.2 Intrathecal Therapy

For patients receiving intrathecal therapy (e.g. methotrexate and glucocorticoids) at the time of NI-0501 treatment initiation, this treatment will be continued until clinically indicated.

6.3.3 Other possible concomitant therapies

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

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

6.3.4 Not allowed concomitant therapies

Any background treatment of sJIA has to be discontinued before initiation of NI-0501 treatment as follows:

- Anakinra must be discontinued at latest before the first NI-0501 infusion; however no wash-out period is required due to the short half-life of the drug.
- A wash-out period of 5 times of respective half-lives is required in patients who have been treated with Tocilizumab, Canakinumab or TNF inhibitors.

It is recommended background treatment of sJIA not to be re-introduced during the 8 weeks of the study, unless the patient's clinical conditions require it.

As long as NI-0501 is being administered, no concomitant use of etoposide, T-cell depleting agents, or any other biologic drug is allowed, with the exception of:

- ✓ G-CSF, in case of prolonged neutropenia
- ✓ Rituximab, in case of documented EBV infection.

Vaccination with a live or attenuated-live (including BCG) vaccine must be avoided during the whole study. In the event that NI-0501 concentrations are still measurable after the end of the study, the period with no vaccinations should be extended until serum NI-0501 levels are no longer detectable.

6.4 EMERGENCY TREATMENT

As none of the NI-0501 infusions administered to healthy volunteers or patients has triggered any medically significant reaction, this is considered an unlikely event during the study. However, should severe allergic reactions (such as anaphylactic shock) occur, they would require prompt i.v. treatment with adrenaline and antihistamines. Oxygen shall be supplied through a face mask. Patients must have an appropriately sized i.v. line that allows rapid infusion of colloid volume substitution. Transfer to the intensive care unit of the hospital should be possible.

Following the first administration of NI-0501 and before leaving the study site, each patient (and/or patient's legal representative) will be given a card to carry at all times in case of any emergency. The card gives details of the name of the drug, name of the responsible physician, and the address and telephone number of the study site.

6.5 RESCUE THERAPY

Patients who are withdrawn from the study due to a safety issue or for lack of efficacy (i.e. worsening of MAS/no response to NI-0501) will be treated according to the standard of care at the site.

7 ENDPOINTS

The main objective of the study is to confirm that the proposed dosing regimen is adequate in relation to the IFNγ production in patients with MAS secondary to sJIA.

For this purpose, a PK-PD analysis will be performed based on:

- levels of circulating NI-0501
- levels of total IFNγ
- levels of main IFNγ–induced chemokines (namely CXCL9 and CXCL10).

7.1 PHARMACOKINETICS ENDPOINTS

Free NI-0501 concentrations will be measured in serum to determine the PK profile of NI-0501 in this patient population, and to confirm the adequacy of the proposed dosing regimen.

All PK data will be summarised using appropriate graphical and tabular presentations. Descriptive non-compartmental pharmacokinetic analysis (NCA) will be applied: C_{max} (concentration corresponding to T_{max}), T_{max} (time of maximum observed concentration), C_{EOI} (concentration at the end of infusion), C_{trough} (concentration just before administration), AUCτ (area under curve of a dosing interval), AUC_{last} (area under curve from the time of dosing to the last measurable concentration), λz (first order rate constant associated with the terminal (log-linear) portion of the curve, estimated via linear regression of time versus log concentration), $t_{½}$ (plasma half-life), CL (systemic drug clearance), Vss (volume of distribution at steady state). Individual and mean PK parameters will be tabulated. Exploratory compartmental PK analysis and population PK analysis will be undertaken to investigate linear and non-linear (TMDD) kinetics.
In addition, PK analysis will be done when a total of 5 patients have been recruited in Europe and North America inclusive, to assess the appropriateness of the dose selection.

7.2 PHARMACODYNAMICS ENDPOINTS

Assessment of PD parameters will include, but will not be limited to, the followings:

- Levels of circulating free IFNγ at pre-dose, and of total IFNγ (free IFNγ+bound to NI-0501) after initiation of NI-0501 treatment.
- Levels of the main IFNγ-induced chemokines (CXCL9, CXCL10).
- Correlation between chemokine levels (CXCL9, CXCL10) and levels of free NI-0501, free IFNγ (pre-dose) and total IFNγ (*exploratory analysis*).
- Correlation between chemokine and total IFNγ levels, and laboratory parameters of MAS severity, e.g. ferritin, platelet counts, LFTs (*exploratory analysis*).
- Levels of other potential disease biomarkers (e.g. sCD25, sCD163, IL-18, IL-10, IL-6, TNFα, CXCL11).
- Levels (if any) of circulating antibodies against NI-0501 to determine immunogenicity, i.e. the development of anti-drug antibodies (ADAs).

7.3 SAFETY ENDPOINTS

The tolerability and safety of NI-0501 treatment will be assessed as follows:

- Incidence, severity, causality and outcomes of AEs (serious and non-serious), with particular attention being paid to infections.
- Evolution of laboratory parameters, in particular CBC, LFTs, inflammatory markers (ferritin and CRP) and coagulation parameters.
- Number of patients withdrawn due to safety reasons.

7.4 EFFICACY ENDPOINTS

The efficacy of NI-0501 in this patient population will be evaluated based on the evolution of the MAS distinct features of cytopenias, liver function and coagulopathy.

In particular the following variables will be preliminarily assessed:

- Number of patients achieving MAS remission by Week 8 after initiation of NI-0501 treatment.
- Time to MAS remission.
- Number of patients for whom at any time during the study glucocorticoids can be tapered *i)* to the same (or lower) dose being administered before the occurrence of MAS (in those patients who are already treated for sJIA) or *ii)* by 50% (or less) of the dose administered at NI-0501 treatment start (in those patients who present with MAS at sJIA onset).
- Time to achievement of glucocorticoids tapering (as defined above).
- Survival time.
- Number of patients withdrawn from the study due to lack of efficacy.

MAS remission is defined as

- ✓ Resolution of clinical signs and symptoms according to the Investigator
  and
- ✓ Normalization of laboratory parameters relevant to MAS, as follows:
  - WBC and platelet count above LLN
  - LDH below 1.5 ULN
  - ALT/AST below 1.5 ULN
  - fibrinogen higher than 100 mg/dL
  - ferritin levels decreased by at least 80% from values at screening or baseline (whichever is higher) or below 2000 ng/ml, whichever is lower.

8 OUTLINE OF STUDY PROCEDURES

8.1 STUDY VISITS

For a detailed description of the visit schedule and assessments, please refer to Table 1 (Schedule of Assessment – Screening and NI-0501 Treatment Period) and Table 2 (Schedule of Assessment – Evaluation Period).

Patients will be recruited from specialized study centers in North America, in which an intensive care unit is available. If not already hospitalized, the patient will enter the hospital on SD-1.

During the NI-0501 Treatment Period, Infusion Visits will occur every 3 days until SD15, and twice-a-week thereafter until SD28, and will also serve as Efficacy/Safety visits. In case NI-0501 treatment is shortened after SD6, Efficacy/Safety visits have to be in any case performed with the same schedule until SD28, in order to assess the evolution of MAS clinical and laboratory features, and to closely monitor safety.

From SD28 and during the Evaluation Period, visits will occur on a weekly schedule (a ± 2-day window is allowed) for efficacy and safety evaluation, and follow-up after NI-0501 last infusion.

Discharge from the hospital cannot occur before SD15. After SD15, in case the patient condition allows, the patient can be discharged, at the Investigator's discretion, provided that no active infections requiring i.v. antimicrobial therapy are present.

Some procedures are not mandatory or do not need to be done systematically but only when applicable according to the following specifications:

- ECG is mandatory at screening, after first infusion, and at the end of the study, however it should also be performed whenever required based on clinical judgment.

- Broad search for pathogens during the study (beside the ones required per protocol) should be done if there is any suspicion of infection.
- Chest X-ray during the study (beside the ones required per protocol) should be done more frequently in case of clinical suspicion of a pulmonary infection.
- Functional tests relevant to HLH diagnosis should be performed whenever possible; however availability of results is not required for patient inclusion in the study.

The following situations will not be considered as protocol deviations:

- Missing data if not occurring at 2 consecutive time-points.
- A ± 5-min difference in the timing of vital sign measurements during NI-0501 infusion.
- A ± 10-min difference in the timing of vital sign measurements after NI-0501 infusion.

8.2 INFORMED CONSENT AND SCREENING PROCEDURES

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

Patients will be screened for eligibility prior to enrolment into the study. The Investigator must keep a log of the patients screened for the study and reasons for non-eligibility, if applicable.

Screening evaluations should be completed within up to 1 week prior to the first administration of the study drug (SD0). Clinical and laboratory assessments should be performed as close as possible to initiation of NI-0501 treatment, preferably on SD-1, as described in Table 1.

In the event that a patient's medical condition warrants rapid treatment initiation, and to avoid unnecessary repetition of recent interventions, results of tests which have been performed as part of the normal patient's care at the site (or at the referring hospital) not more than 2 weeks prior to first NI-0501 infusion, may be considered for screening purposes (inclusion/exclusion criteria checks) with the agreement of both the Sponsor and Investigator.

The following patient information must be collected:

- Demographic and medical history
- Detailed information on inadequate response to high dose i.v. glucocorticoids.
- Concomitant medication at screening.
- Date of sJIA diagnosis.
- sJIA treatment previously received and ongoing at the time of screening.
- Date and criteria of eligibility.
- Relevant clinical and laboratory data in order to characterize *a posteriori* the study population according to HLH-2004 criteria.

Samples for the molecular characterization with respect to the known HLH causative genes have to be collected and send to a centralized laboratory only if the patient has given consent for genetic testing.

A panel of genes already known to be involved in primary HLH (PRF1, UNC13D, STX11, STXBP2, LYST, RAB27A, SH2D1A, XIAP) will be tested.

Given the evolving knowledge and new findings within the scientific community with regard to potential modifying genes for HLH [e.g. AP3B1, HPS1, IRF5, ITK, KIR2DL1, MyD88, SLC7A7, TNFRSF7/

CD27, IL2RG, ARHGAP21, CADPS2, CCDC141 (CAMD1), EXPH5 (SLAC2B), FAM160A2, FKBPL, GDI1, LRGUK, MICAL2, TNFRSF10B, XIRP2], the panel may be extended, if relevant.

Functional tests relevant to the diagnosis of HLH should be performed whenever possible; however availability of these results is not required for inclusion of the patient in the study.

Prophylactic treatments for *HZ* virus and for TB (when applicable, as described in Section 6.2), have to be started.

Table 1 – Schedule of assessment: Screening and NI-0501 treatment period (from SD-1 to SD28)

Assessments		Protocol Section	Screening (up to one week prior to 1st infusion)	SD0 Infusion #1[1]		SD1	SD2	SD3 Infusion #2[2]		SD5	SD6 to SD28[3] Infusion/Efficacy/ Safety visits
			SD-1	pre	post			pre	post		
Hospitalization[4]		8.1	From SD-1								
Patient information and Informed Consent		8.2	X								
Medical history		8.2	X								
Concomitant medication (including recording on glucocorticoid tapering when relevant)		8.2	X	X		X	X	X		X	X
MAS diagnosis and Eligibility Criteria[5]		8.2	X								
Prophylactic treatments		8.2	From SD-1								
Clinical assessments	- Vital signs	8.3.1	X	X	X[6]	X	X	X	X[6]	X	X[7]
	- Physical examination[8]	8.3.2	X	X		X	X	X		X	X
	- MAS clinical signs and symptoms	8.3.3									X
Laboratory assessments	- CBC	8.4	X	X		X	X	X		X	X
	- Lymphocyte subset	8.4	X								
	- Coagulation (aPTT, PT, D-Dimers, Fibrinogen)	8.4	X	X		X	X	X		X	X
	- Biochemistry	8.4	X	X		X	X	X		X	X
	- Serum pregnancy test (if applicable)	8.4	X								
	- Urinalysis	8.4	X	X[9]							
Search for infections	-*Mycobacterium Tuberculosis*	8.5	X								X[10]
	-*Atypical mycobacteria, Shigella, Salmonella, Campylobacter, Leishmania, Histoplasma Capsulatum*	8.5	X								
	-*EBV, CMV, Adenoviruses*	8.5	X								X[10]
	-*HSV, HZV, HIV, HBV, HCV*	8.5	X								
Procedure	- ECG	8.7.1	X[11]		X						

Assessments		Protocol Section	Screening (up to one week prior to 1st infusion)	SD0 Infusion #1[1]		SD1	SD2	SD3 Infusion #2[2]		SD5	SD6 to SD28[3] Infusion/Efficacy/ Safety visits
			SD-1	pre	post			pre	post		
Imaging	- Abdominal Ultrasound	8.6.1	X								X[10]
	- Chest X-ray	8.6.2	X								X[10]
	- Brain MRI[12]	8.6.3	X								
Histopathology	- CSF analysis (if coagulation allows) [12]	8.7.2	X								
PK	- NI-0501 serum concentration	8.8.1		X	X	X	X	X	X	X	X[13]
PD 1	- IFNγ, CXCL9, CXCL10, sCD25	8.8.2		X	X[14]	X	X	X		X	X
PD 2	- Other biomarkers	8.8.2		X							X
Immunogenicity (ADA)		8.8.3		X							

[1] Start of NI-0501 treatment: loading dose of 6 mg/kg.

[2] Continuation of NI-0501 treatment: 3 mg/kg every 3 days from SD3 onwards until SD15, and twice-a-week thereafter.

[3] After a minimum of two infusions at the dose of 3 mg/kg (i.e. after SD6), NI-0501 treatment may be shortened as per Investigator's decision upon achievement of a complete clinical response (i.e. MAS remission). In this circumstance, efficacy/safety visits have to be in any case performed according to the same schedule until (and including) SD28.

[4] Hospitalization: please note that the patients can be discharged from SD15 if their conditions allow, provided that there is no active infections requiring i.v. antimicrobial therapy.

[5] Include molecular and functional tests relevant to the diagnosis of primary HLH.

[6] Continuous monitoring of HR and SpO2 as well as body temperature and BP recording at regular time points (see Section 8.3.1)

[7] If NI-0501 infusions are performed, HR, BP, SpO2, body temperature are to be measured pre-, during, and post-dose (see Section 8.3.1).

[8] Body weight to be recorded prior to infusion and every 2 weeks during the evaluation period for patients weighing less than 10 kg, and every 2 weeks throughout the study for patients weighing more than 10 kg.

[9] If not performed at screening.

[10] Abdominal US and Search for infection to be performed on SD15 and SD28; chest X-ray on SD28 only.

[11] At screening, three consecutive recordings are required in order to obtain a stable baseline.

[12] Brain MRI & CSF analysis: to be performed in case of neurological involvement prior to NI-0501 initiation (or at the latest by SD6 for brain MRI), whenever possible.

[13] When NI-0501 is administered, PK samples have to be taken before and after the infusion.

[14] Total IFNγ only.

Table 2 – Schedule of assessment: Evaluation period - from SD28 to SD56 (End of Study)

Assessments			SD35 1st Week Follow-up	SD42 2nd Week Follow-up	SD49 3rd Week Follow-up	SD56[1] 4th Week Follow-up – EoS[2]	Unscheduled Visit (UV)[3]
Hospitalization[4]		8.1					
Concomitant medication (including information on glucocorticoid tapering)		8.2	X	X	X	X	
Clinical assessments	- Vital signs	8.3.1	X	X	X	X	X
	- Physical examination	8.3.2	X	X	X	X	X
	- MAS clinical signs and symptoms	8.3.3	X	X	X	X	
Laboratory assessments	- CBC	8.4	X	X	X	X	
	- Lymphocyte subset	8.4				X	
	- Coagulation (aPTT, PT, D-Dimers, Fibrinogen)	8.4	X	X	X	X	
	- Biochemistry	8.4	X	X	X	X	
	- Serum pregnancy test	8.4				X	
	- Urinalysis	8.4				X	
Search for infections	- *Mycobacterium Tuberculosis*	8.5		X		X	
	- *EBV, CMV, Adenoviruses*	8.5		X		X	
Procedure	- ECG	8.7.1				X	
Imaging	- Abdominal US	8.6.1		X		X	
	- Chest X-ray	8.6.2				X	
	- Brain MRI[5]	8.6.3				X	
Histopathology	- CSF analysis (if coagulation allows)[5]	8.7.2				X	
PK	- NI-0501 serum concentration	8.8.1	X	X	X	X	
PD 1	- IFNγ, CXCL9, CXCL10, sCD25	8.8.2	X	X	X	X	
PD 2	- Other biomarkers	8.8.2		X		X	
Immunogenicity (ADA)		8.8.3				X	

[1] If NI-0501 treatment needs to be prolonged beyond 4 weeks, additional weekly visits must be scheduled as appropriate in order to complete the required short-term 4-week follow-up.
[2] The same procedures described for End of Study Visit should be followed for any patient who is withdrawn prematurely from the study (see protocol Section 8.9)
[3] Unscheduled Visit: depending on the reason for UV, additional assessments may be added according to the Investigator's clinical judgment (see protocol Section 8.10).
[4] Hospitalization: please note that the patients can be discharged from SD15 if their conditions allow, provided that there is no active infections requiring i.v. antimicrobial therapy.
[5] Brain MRI & CSF analysis: to be performed in case of neurological symptoms occurrence, whenever possible. If brain MRI and CSF analysis were done at screening, an End of Study exam should be performed, whenever possible.

8.3 CLINICAL ASSESSMENTS

8.3.1 Vital signs

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

Body temperature will be recorded in the morning of visit days as indicated in the SoA.

On the day of NI-0501 infusion, heart rate and oxygen saturation will be recorded before and continuously monitored after the infusion (for 24 hours if the patient is hospitalized, and for 4 hours if patient is an outpatient).

Body temperature and blood pressure will be recorded before and at regular intervals after NI-0501 infusion as follows:

- at the first infusion, every hour during the first 4 hours post-dose, and every 4 hours thereafter to cover a 24-hour monitoring period
- at all other infusions, every hour during the first 4 hours post-dose (if no safety concerns have emerged after the first infusion).

Blood pressure, heart rate and oxygen saturation will be measured every 15 minutes during NI-0501 infusion.

8.3.2 Physical examination

A complete physical examination will be performed at screening and at each study visit (before the infusion when NI-0501 is administered).
Physical examination prior to each infusion may be performed in the late afternoon of the previous day instead of the morning of the infusion (the data will be captured on the infusion day of the CRF).

At screening height (in cm), weight (in kg) and Body Surface Area (BSA) as calculated by the site will be recorded.

Subsequent physical examinations will include *i*) recording of body weight prior to infusion and every 2 weeks during the evaluation period for patients weighing less than 10 kg [for patients weighing more than 10 kg, weight will be measured every 2 weeks throughout the study]; *ii*) abdominal palpation for assessment of liver and spleen size (in cm from costal grill); *iii*) follow-up of any abnormalities previously recorded as well as occurrence of new signs and symptoms.

8.3.3 MAS clinical signs and symptoms

The Investigator will be asked to provide his assessment of improvement/resolution of MAS signs and symptoms at the study timepoints indicated in the SoA.

8.4 LABORATORY ASSESSMENTS

Blood and urine laboratory analyses are part of the routine monitoring of MAS patients, thus samples will be analyzed locally. Analyses done on blood samples will favor as much as possible the use of micro-sampling techniques.

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

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

- Hematology: complete blood cell count (CBC) with differential count, a dedicated lymphocyte subsets count (at screening and EoS visit), and platelets.

- Biochemistry: Ferritin, Triglycerides, C-Reactive Protein (CRP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), gamma Glutamyl Transferase (γGT), Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH), total bilirubin, glucose, electrolytes, albumin, creatinine, Blood Urea Nitrogen (BUN).
- Coagulation tests: activated partial thromboplastin (aPTT), prothrombin time (PT), D-dimers and fibrinogen.
- Urinalysis: glucose, blood, protein, leucocytes, ketones, pH and specific gravity. On SD0, urinalysis will be performed before NI-0501 infusion (only if not already performed at screening). Urinalysis will be repeated at EoS.
- Serum pregnancy test (if applicable) at screening and EoS. Additional pregnancy tests will be performed upon suspicion of pregnancy or as mandated by local regulations, as long as NI-0501 serum concentrations are detectable.

8.5 SEARCH FOR INFECTIONS

Search for infections that represent exclusion criteria include the following pathogens:

- *Mycobacterium Tuberculosis*
  At screening, it will be performed via IFNγ-release assay or PPD test. In addition, a baseline via polymerase chain reaction [PCR] in a relevant specimen (e.g., urine or blood, if sputum is not easily obtained) has to be obtained, as this test will be used during the course of the study to perform regular TB monitoring.
  After initiation of NI-0501 treatment, search for TB via PCR has to be performed every 2 weeks as long as NI-0501 is detectable in serum.

  In the case of a patient having received BCG vaccination, a PPD test must be performed and combined with an IFNγ-release assay.
- *Atypical mycobacteria*, *Shigella*, *Salmonella*, *Campylobacter, Histoplasma Capsulatum* and *Leishmania*
  Search for all these pathogens have to be performed at screening. During the study, search for these pathogens has to be performed if there is any suspicion of infection.
  A first screening for *Histoplasma Capsulatum* may be performed using galactomannan assay, however if the test is positive, confirmation should be obtained by using a *Histoplasma Capsulatum* specific test. The presence of *Leishmania* can be ascertained by direct bone marrow observation.

In addition, search for the following infections is required:

- *Herpes Simplex Virus* (*HSV*), *Herpes Zoster Virus* (*HZV*), *Hepatitis B Virus* (*HBV*), *Hepatitis C Virus* (*HCV*), *Human Immune Deficiency Virus* (*HIV*) by PCR monitoring or serology, at screening and whenever there is a suspicion of infection.
- *EBV, CMV, Adenoviruses* by quantitative PCR, at screening and every 2 weeks as long as NI-0501 is detectable in serum.

A patient with a clinical assessment (including chest X-ray) not indicative of the presence of an active infection, provided that a usable specimen has been taken and the microbiological analysis is ongoing, can be enrolled prior to the availability of the results, if the patient's clinical conditions require a rapid initiation of NI-0501 treatment.

8.6 IMAGING

8.6.1 Abdominal ultrasound

Abdominal ultrasounds, including liver and spleen (longitudinal) measurements, will be performed at screening and every 2 weeks during the study.

8.6.2 Chest X-ray

Chest X-ray will be performed as a measure for detection of pulmonary infections at screening and every 4 weeks during the study. Chest X-ray should be done more frequently in case of clinical suspicion of a pulmonary infection.

8.6.3 Brain MRI

Brain MRI should be performed in case of neurological symptoms occurrence, prior to NI-0501 initiation (or at latest by SD6), and repeated at the end of the study, whenever possible.

8.7 OTHER PROCEDURES

8.7.1 ECG

12-lead ECG will be performed and interpreted locally by the Investigator or delegate for immediate clinical assessment.

At screening, triplicate ECG (three consecutive recordings) is required in order to obtain a stable baseline.

ECG is mandatory at screening, after the first NI-0501 infusion, and at the end of the study, however it should also be performed whenever required based on clinical judgment.

As part of the regulatory requirements for the overall assessment of NI-0501 safety profile, ECGs will be sent for evaluation to a central laboratory designated by Novimmune, and results fully described in the Clinical Study Report.

8.7.2 Cerebrospinal fluid assessment

Lumbar puncture for CSF analysis should be done in case of neurological symptoms occurrence, whenever possible and if coagulation parameters allow, prior to NI-0501 initiation, during the course of the study and at the end of the study, as clinically indicated.

8.8 PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.8.1 Pharmacokinetics

Serum samples for PK analysis will be collected at the visits indicated in the SoA (Table 1 and Table 2). In case of need for prioritization of blood analysis (considering weight and health status of the patient), laboratory safety parameters (which would be done as normal disease monitoring) may need to be prioritized over samples for PK assessments, that in turn will be prioritized over biomarkers exploratory parameters.

On the days of infusion, PK samples should be collected before and after (between 15 and 30 minutes after) the infusion.

After the first NI-0501 infusion, PK samples will be also collected on SD1 (around 24 hrs. post- infusion) and SD2 (around 48 hrs. post-infusion). Additionally, PK samples will be collected on SD5 (around 48 hrs. after the second NI-0501 infusion).

After completion of NI-0501 infusions, samples for PK assessment will be collected until serum NI-0501 concentration are no longer detectable (or until consent is withdrawn), as indicated in the SoA until the EoS visit, and subsequently as described in Section 3.4.

In case of CNS involvement, if lumbar puncture is performed for diagnostic and/or therapeutic purposes, PK analysis in CSF samples may be performed.

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

8.8.2 Pharmacodynamics

Serum samples for PD analysis will be collected at the visits indicated in the SoA (Table 1 and Table 2). In case of need for prioritization of blood analysis (considering weight and health status of the patient), laboratory safety parameters and PK assessments will be prioritized over biomarkers exploratory parameters.

Pharmacodynamics assessments include the measurement of:

- Free IFNγ levels prior to NI-0501 treatment start, and total IFNγ (free IFNγ+bound to NI-0501) during NI-0501 treatment. Samples for total IFNγ measurements will be taken pre-dose on infusion visits, except for the first infusion when free IFNγ will be measured pre-dose and total IFNγ post-dose.
- Chemokines known to be induced by IFNγ (CXCL9, CXCL10). On infusion visits, serum samples will be collected pre-dose only.
- Other potential disease biomarkers (e.g. sCD25, sCD163, IL-18, IL-10, IL-6, TNFα, CXCL11). Serum samples will be collected on SD0 and every 2 weeks during the course of the study.

In case of CNS involvement, if lumbar puncture is performed for diagnostic and/or therapeutic purposes, biomarker analysis in CSF samples may be performed.

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

8.8.3 Immunogenicity

Serum samples for the assessment of ADAs will be collected on SD0 (prior to NI-0501 infusion) and at the End of Study visit, and in case of suspected loss of activity of NI-0501 during the study. Details on sample preparation and handling will be described in a separate laboratory manual.

8.9 WITHDRAWAL VISIT

The same procedures described for the EoS Visit should be followed by the Investigator for any patient who is withdrawn prematurely from the study, as soon as possible after the decision to withdraw is made.

For patients who withdraw from the study as a result of their own decision or the decision of their parent/guardian, the Investigator should contact the patient (or parent/guardian) and ask them to attend a withdrawal visit as soon as possible and in any case within 30 days from termination.

Patients who are withdrawn due to a serious adverse event (SAE) should be followed-up until the resolution of the event or until the outcome of the event is known and stable.

8.10 UNPLANNED (UNSCHEDULED) VISITS

Unplanned visits may occur, should the patient need to be assessed or treated for any clinical condition that arises during the study. This may include the evaluation and follow-up of AEs, SAEs or laboratory tests. The assessments (as detailed in the SoA) should always be performed *at minimum*, but additional evaluations may be added according to the clinical judgment of the Investigator.

8.10.1 Unplanned Assessments

Additional samples to assess laboratory parameters and PK/PD may be required for safety reasons and/or for a better characterization of the PK/PD profile.

The number of additional samples taken will depend on the body weight and health status of the patient. Sampling schedule will be proposed by the Sponsor and discussed with the Investigator.

9 STUDY SCIENTIFIC OVERSIGHT

A Scientific Steering Committee (SSC) composed of international experts in pediatric rheumatology as well as in HLH has been involved in the preparation of study design and protocol writing.
The SSC is also to be consulted for the composition of the independent Data Monitoring Committee (iDMC).

The SSC will continue to play an advisory role throughout the course of the study, including the support to the iDMC oversight, and will perform evaluations of the data to support the Sponsor in the interpretation of the results of the study.

Please refer to Appendix C for full details of membership of the SSC.

10 SAFETY MONITORING

10.1 INDEPENDENT DATA MONITORING COMMITTEE

The iDMC, composed of relevant experts (pediatric rheumatologist, pediatric onco-hematologist with experience in HLH, pediatric immunodeficiency/infectious disease specialist, bio-statistician and a specialist in ethics), will oversee the study, with particular regard to the evaluation of safety parameters and benefit/risk profile of NI-0501, reviewing all data generated on an ongoing basis with the aim to ensure that patients are not exposed to unnecessary risks. Some of the iDMC members have been already involved in the oversight of the ongoing NI-0501 studies. Please refer to Section 10.5.1 for further details on the iDMC.

10.2 DESCRIPTION OF SAFETY PARAMETERS

Evaluation of NI-0501 tolerability and safety will be based on the following parameters:

- Adverse events (AEs), with special attention being paid to events temporally related to the infusion of NI-0501 (occurring during the infusions and within 24 hours post infusion) and to the occurrence of infections
- Laboratory parameters, as described in Section 8.4
- Vital signs, as described in Section 8.3.1

- Physical examination with particular attention paid to evolution of signs and symptoms present at baseline, and to any emergent new signs or symptoms (see Section 8.3.2 for more details).

10.3 RECORDING AND REPORTING SAFETY PARAMETERS

10.3.1 Adverse events

Adverse events (AEs) are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the IMP. All AEs reported spontaneously by the patients or his/her relatives or observed by the Investigator or his staff during the clinical study from the signature of the ICF up to and including the EoS visit will be reported on the AE data collection form.

Medical conditions present at screening (before ICF signature) should be recorded in the medical history section of the CRF.

All AEs will be reported in the appropriate section of the CRF.

An AE which occurs between start of screening visit (after ICF signature) and start of first IMP administration will be considered as a pre-treatment AE.

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

However, if a pre-existing medical condition recorded in the medical history worsens (clinically significant change in intensity or frequency), it must be recorded as an AE in the CRF and, depending on the time of its occurrence, will be considered as a pre-treatment AE or a TEAE. If a medical condition, recorded as a pre-treatment AE, worsens it will be recorded in the CRF as a separate TEAE.

For each AE, the following will be assessed and recorded: intensity, relationship to the IMP, action taken regarding the IMP, any treatment received for the event and outcome of AE to date.

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

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

For a given AE, the assessment of its intensity should reflect the highest grade (on the 3 points scale mentioned above) reported during its course (except when the intensity of a pre-treatment AE increases after treatment initiation, as indicated above).

The relationship of the AE to the IMP will be assessed by the Investigator using a “Yes/No” classification. A “Yes” relationship infers that there is a reasonable possibility of causal relationship between the AE and IMP. The expression “reasonable possibility” is meant to convey that there are facts, evidence or arguments to suggest a causal relationship. Conversely, a “No” relationship infers that there is no reasonable possibility of causal relationship between the AE and IMP. Usually it implies that other possible causes have been identified.

In this study NI-0501 is the only IMP.

10.3.2 Serious Adverse Events

An adverse event is considered serious if it:

- results in death (note: death is an outcome, not an event);
- is life-threatening; (note: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe);
- requires in-patient hospitalization or prolongs an existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is an important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of this study, the following will not be considered as serious adverse events:

- Elective hospitalizations or surgical procedures that are a result of a patient's pre-existing condition(s) which has (have) not worsened since receiving IMP. Such events should still be recorded as adverse events in the eCRF;
- Hospitalization as requested per protocol for NI-0501infusion and study visits.

Any serious adverse event (SAE) that occurs during the course of the study, irrespective of the treatment received by the subject and regardless of causality to the study drug, must be communicated by the Investigator to NovImmune, by fax or electronic transmission, within 24 hours of awareness.

For the initial SAE report, the Investigator should report all available case details concerning the patient and the event, using the Novimmune SAE reporting standard form provided to the Investigators.

Novimmune contact information for SAE reporting:

Fax: [redacted]

E-mail: [redacted]

Relevant follow-up information on SAEs should be forwarded to Novimmune as soon as it becomes available. In addition, the Investigator should answer without delay any request for follow-up information or questions Novimmune team may have regarding the reported SAE.

All SAEs must be recorded as an AE in the CRF. They should be reviewed, evaluated and followed through to resolution (or stabilization) by the Investigator.

For any new SAE, the following minimum information is required in the initial report:

- Clear identification of the Investigator, with full contact information or site number
- Subject's identification details (study number, site number, subject's unique study identification number and date of birth),
- IMP administration details (dose and dates)

- Diagnosis of the event (or a brief description of signs/symptoms/clinical course, if the diagnosis is not available) and the date of onset,
- Seriousness criteria.

In addition causal relationship (Investigator's opinion) of the event with the IMP or with the study procedure (e.g. the causality according to the Investigator during screening) should be provided whenever possible in this initial report, otherwise it must be included in a follow-up report.

The Sponsor will also conduct its own assessment on seriousness and causality of all recorded AEs during the study. If the Sponsor becomes aware of an AE, which has not been reported by the Investigator as serious, but is assessed by the Sponsor as serious (e.g. medically important), the Investigator will be asked to report such AEs to the Sponsor as an SAE, according to the timelines and rules described above.

10.3.3 SUSAR reporting

Suspected unexpected serious adverse reactions (SUSARs) are adverse events that are both serious and unexpected (i.e. as per the Investigator's Brochure), and are considered, by the Investigator or the Sponsor, to have a reasonable possibility of causal relationship between the administered IMP and the adverse event.

Some of the SAEs reported by the Investigator may qualify as SUSARs, and such need to be reported in an expedited manner by the Sponsor to Health Authorities and Central Ethics Committees/Independent Ethics Committees/ Research Ethics Boards.

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

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

For Canada, the sponsor is required to inform Health Canada of any serious, unexpected adverse drug reaction that has occurred inside or outside Canada. An adverse drug report must be filed in the cases where the adverse drug reaction is neither fatal nor life-threatening, within 15 days after becoming aware of the information, within 7 days where it is fatal or life-threatening, immediately where possible and, in any event, after becoming aware of the information.

10.3.4 Managing Abnormal Laboratory Test Values

Abnormal safety test values should not be reported as AEs unless specific treatment is given for the abnormality (e.g. a blood transfusion is given for a low haemoglobin) or a laboratory abnormality leads to further investigation and the diagnosis of a new clinical event (e.g. a high white blood cell count is found to be due to incidental leukaemia). In this latter event, the clinical diagnosis should be reported on the AE form, not the laboratory abnormality leading to the diagnosis. Clinically significant abnormal laboratory test value can be qualified as important medical events (see Section 10.3.2) and should then follow the process described in this section.

10.4 FOLLOW-UP OF SAFETY PARAMETERS

10.4.1 Treatment and Follow-up of Adverse Events

Adverse events, especially those for which the relationship to the study drug has been assessed as 'Yes', should be followed-up until the event has returned to baseline status or has stabilised. If a clear explanation is established, it should be recorded on the CRF.

All SAEs must be followed-up until the event has either resolved or reached a stable clinical outcome.

10.4.2 Follow-up of Abnormal Laboratory Test Values

In the event of unexplained clinically relevant abnormal laboratory test values, the tests should be repeated immediately and followed-up until the values have returned to within normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded on the eCRF.

10.4.3 Pregnancy

In the event that a pregnancy occurs during the trial course, it must be reported to Novimmune within 24 hours of awareness. This includes pregnancies occurring in partners of male enrolled patients. All information pertaining to the pregnancy should be reported using the Novimmune Pregnancy form provided to the investigators. Pregnancies should be followed until conclusion to obtain outcome information.

Occurrence of a pregnancy in a study participant will preclude any further IMP administration.

If the patient is withdrawn from the study, the assessments presented in the Schedule of Assessments for EoS are to be performed (see Section 8.9).

10.5 BENEFIT/RISK MANAGEMENT

10.5.1 Safety Surveillance Management

The main responsibility of the DMC is to review all safety and efficacy data as they are generated to ensure that no patient is exposed to unnecessary risk and to continuously assess the benefit/risk profile of NI-0501.

The DMC can recommend treatment discontinuation for individual patients as well as to halt the entire study temporarily or permanently. Predefined stopping rules will guide the DMC review process. For more details, see stopping rules in Section 11.

10.5.2 General Benefit/Risk Considerations

10.5.2.1 Potential benefits

Patients presenting MAS secondary to sJIA may not respond to systemic glucocorticoids and have limited alternative therapeutic options. These options are represented by prolonged treatment with high doses glucocorticoids, and administration of CsA or chemotherapy such as etoposide, all options carrying an increased risk of morbidity and mortality. For those non-responders patients, an alternate therapy should aim to obtain remission of MAS with none or limited safety issues.

Three elements strongly suggest that the use of NI-0501 would enable MAS remission:

- In animal model mimicking MAS, administration of an anti-IFNγ enables the recovery/remission of the signs and symptoms associated with hypercytokinemia
- Observational studies have shown a strong correlation between biomarkers (IFNγ as well as IFNγ-induced chemokines) and disease parameters at MAS onset and during disease evolution.

According to the data collected to date in pHLH patients (ongoing NI-0501-04 study), NI-0501 administration has shown the potential to improve or resolve relevant clinical and laboratory abnormalities of HLH, including CNS signs and symptoms when present, allowing patients to proceed to HSCT.

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

Based on these considerations, sJIA patients with MAS having inadequately responded to systemic high dose glucocorticoids are expected to benefit from a targeted therapy with NI-0501 aiming at neutralizing IFNγ and achieving MAS remission.

10.5.2.2 Risks analysis

- Risks related to NI-0501

NI-0501 is a fully human IgG1monoclonal antibody (mAb).
Upon the administration of mAbs, which are proteins, acute infusion reactions can occur. These may happen during the infusion or in the subsequent hours (usually within the first 24 hours)[43,44].

These reactions are either IgE-mediated type I hypersensitivity reactions (anaphylactic reactions), or anaphylactoid reactions not mediated by IgE. True anaphylactic reactions usually do not occur upon initial infusion and require a certain sensitization. In contrast, the pathophysiology of anaphylactoid reactions appears to be secondary to the release of cytokines consequent to a mAb binding to circulating antigen-expressing cells. However, the clinical manifestations of anaphylactic and anaphylactoid reactions overlap, and both may lead to life-threatening conditions, involving cardiovascular, respiratory, central nervous, gastro-intestinal, and cutaneous systems. The management of anaphylactic and anaphylactoid reactions involves immediate administration of oxygen, epinephrine, vasopressors, bronchodilators, corticosteroids, and/or antihistamines.

More than 850 infusions have been administered to HLH patients (either in the context of the NI-0501-04 and NI-0501-05 studies or in patients who have received NI-0501 in compassionate use) up to and including the dose of 10 mg/kg, without any serious or severe infusion related reaction reported. In less than 2% of infusions, mild or moderate transient erythematous rashes localized to the extremities (feet and/or hands) have been reported in a few patients. They occurred in most of the cases during the first infusions of NI-0501 and resolved spontaneously. When administration of NI-0501 has been performed occasionally through a peripheral venous access, infusions were all uneventful.

In the population intended to be enrolled in the study, the risk of developing infusion related reactions compared to previously exposed HLH patients is not expected to be higher. All patients enrolled in this study will continue to receive glucocorticoids concomitantly, and will be monitored during and after the infusion.

When administered to humans, most mAb therapeutics elicit some level of antibody response (anti-drug antibodies or ADAs) against the therapeutic product, as early as after the first exposure. No sign of immunogenicity has been reported in the NI-0501 study in healthy volunteers. The presence of ADAs will be measured during this study as per regulatory recommendations, and the analysis is planned to be performed at the end of the NI-0501-06 study, unless PK or safety concerns possibly related to immunogenicity would justify an interim analysis. Data accumulated so far (in particular PK profiles and

a negative ADA search performed in the first pHLH patient treated with NI-0501) have not led to suspect the presence of ADA.

- Risks related to the target

The impact on the immune defense caused by the neutralization of IFNγ is known from patients with inborn errors of the IL-12/23-IFN-γ circuit, particularly patients with complete or partial IFNγ receptor (R) deficiency, and subjects developing neutralizing auto anti-IFNγ antibodies.

Patients with IFNγ R deficiency are prone to developing mycobacterial infections and, although to a lesser extent, *Salmonella* infections[45,46]. The mean age of the first environmental mycobacterial infection is 3.1 and 13.4 years in patients with complete and partial deficiency, respectively[47]. No systematic prophylaxis has been recommended in these patients.
If an infection occurs, appropriate antibiotherapy based on sensitivity of isolated species is prescribed. Individuals with anti-IFNγ auto-antibodies are also susceptible to develop mycobacterial infections (for the vast majority atypical mycobacterial infections), but also opportunistic infections (e.g. by *Histoplasma Capsulatum, Salmonella*, *Herpes Zoster* virus infections)[4].

Toxicological studies carried out with NI-0501 have shown an increased susceptibility of the monkeys having received NI-0501 to enteral pathogen infections when the pathogen is present into the intestinal tract prior to NI-0501 administration. Presence of infections due to *Shigella, Salmonella* and *Campylobacter* is part of the exclusion criteria.

A reactivation of *Herpes Zoster* virus after the single NI-0501 infusion at 3 mg/kg, was observed in one healthy volunteer in the NI-0510-03 study with a non-uneventful course and full recovery.

Preliminary data on infections collected in patients treated with NI-0501 to date allow the following conclusions to be drawn:

- Active infections, in particular bacterial and viral infections (among them EBV or CMV infections, which are often the trigger of the HLH), were present at the first administration of NI-0501in some of them. During NI-0501 administration these infections resolved with appropriate antimicrobial treatment and while achieving control of HLH.
- Some HLH patients treated in second line after immune-chemotherapy developed infections during the course of NI-0501 treatment. A long and profound generalized immune suppression caused by HLH treatments administered prior to the initiation of NI-0501 constitutes a higher risk for infection development. However in the presence of a satisfactory control of HLH, and upon appropriate anti-microbial treatment, infections have usually resolved.
- Patients treated in first line or after a limited exposure to glucocorticoids or chemotherapy seem to develop less infections during the course of NI-0501.
- Systematic search for tuberculosis was negative and no atypical mycobacteria were detected in any of the patients. Stool/blood cultures were negative for *Salmonella*, *Shigella* or *Campylobacter* in all patients. No *Herpes Zoster* infection has been reported.
- Only one infection reported (disseminated histoplasmosis in a patient with a severely compromised immune status and suspected to carry the pathogen prior to the administration of NI-0501) was reported as a serious adverse reaction as it is one of the few pathogens known to be favored by IFNγ neutralization. However the patient recovered from it rapidly after the administration of an effective antifungal treatment.
- The severity and duration of neutropenia, a hallmark of HLH as well as a potential consequence of previous HLH treatments, seemed to contribute significantly to the development of infections.

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

- Risk related to the study population

Most of the patients are expected to have already received at least glucocorticoid treatments as well as having possibly been previously treated by sJIA specific therapies, some of them for a relatively long time depending on the duration of their underlying rheumatic disease; therefore they may carry variable degree of toxicities caused by those treatments. The data collected to date in pHLH patients who have been heavily pretreated by immune-chemotherapy show that administration of NI-0501 does not aggravate toxicities of previous therapies while showing, in general, a favorable impact on HLH activity.

All information collected on disease severity and previous treatments will be taken into account for the analysis of adverse events.

Toxicities of concomitant treatments, authorized or recommended during the administration of NI-0501, may also potentially expose the patients to adverse events; however their benefits may outweigh their risks. No safety concern related to the concomitant administration of NI-0501 with other treatments (e.g., antimicrobial agents, anti-hypertensive drugs) has been reported so far. Corticosteroids have already been administered with anti-IFNγ therapy in Crohn's Disease without any particular safety concerns[48]. Of interest, tapering of glucocorticoids had no impact on safety and tolerability of NI-0501 infusions and has shown benefit for patients with steroids-related hypertension and generalized immunosuppression.

Although the risk that the NI-0501 treatment will not be able to control the disease may exist, the close monitoring and the stopping rules of the study ensure that, in this event, NI-0501 treatment will be discontinued and the patients will rapidly receive rescue treatments according to the standard clinical practice at the participating sites. The risks of administering alternate therapy after having received NI-0501 seems to be low, since no particular safety concerns were observed during treatment with NI-0501.

10.5.2.3 Risk minimization measures

In view of the expected benefits and previous experience gathered with patients exposed to NI-0501 the above listed risks are considered to be manageable in this patient population, if adequate minimization measures are put in place. An overview of specific measures to minimize the subject's risk is provided below:

- Study designed with rheumatologists experienced in the treatment of sJIA and MAS, forming the SSC.
- Patients are hospitalized in specialized centers for the treatment of MAS, and therefore with all necessary emergency assistance equipment.
- Inclusion/exclusion criteria: patients with malformations or severely altered functions (either due to the disease stage or to a concomitant disease), as well as patients with evidence of patent or latent TB infections or active mycobacteria*, Shigella, Salmonella, Campylobacter, Histoplasma Capsulatum* or *Leishmania* infections, will not be included in the study (for details see Section 4.1).
- Although unlikely to be observed based on preliminary results gathered from patients treated with NI-0501 up to 10mg/kg, Infusion Related Reactions (IRRs) will be detected and managed in due time through patients' monitoring during and after drug infusions. Each of the specialized centers will have physicians adequately trained in IRR management.
- Recommendations on prophylaxis for Herpes Zoster virus for all patients and Tuberculosis for a defined subpopulation (see Section 6.2) in the protocol to avoid occurrence of these infections.

- The monitoring for specific infections, known to be favored by IFNɣ neutralization, will continue after NI-0501 discontinuation as long as serum NI-0501 levels are detectable.
- Close monitoring of potential infections through careful physical examination, laboratory parameters, active search for EBV, CMV, Adenoviruses, detection of tuberculosis
- Study safety surveillance by an independent Data Monitoring Committee

The Development Risk Management Plan addresses risks, identify signals for early detection of safety concerns and propose mitigating actions. It will be part of the study documentation shared with Investigators and any relevant third party involved in the study.

Stopping rules have been also developed to ensure individual patient safety and determine whether the study should be put on hold or terminated prematurely.

11 STOPPING RULES

11.1 AT PATIENT LEVEL

11.1.1 Investigator's or Patient's Decision to Discontinue

An Investigator can decide at any time during the study to discontinue the treatment for an individual patient based on his/her own medical judgment, taking into account the individual benefit risk ratio for his/her patient. In addition, the patient (or their legal representative) can decide at any time to withdraw from the study.

In any case the decision to withdraw or be withdrawn will have no impact on the patient's care and further treatments administered to him/her after withdrawal.

Patients who are withdrawn from the study will receive alternative treatments according to the standard of care at the site.

11.1.2 Decision to Discontinue Treatment due to Safety Reason or Lack of Efficacy

11.1.2.1 Treatment Discontinuation for a Safety Reason

A patient must be discontinued from study treatment if a SAE occurring after NI-0501 administration is:

1. considered by the Investigator to be related to NI-0501 (with guidance from the iDMC if needed)

   AND

2. is a life-threatening event.

All other AEs will be judged by the DMC on a case-by-case basis taking into account the disease evolution (such as signs of improvement in HLH) and the possibility of managing the AE and ensuring that no patient is exposed to unnecessary risks.

11.1.2.2 Treatment Discontinuation for Lack of Efficacy

A patient should be discontinued from study treatment for lack of efficacy in the event of any of the followings:

- Rapid worsening of MAS representing immediate risk for the patient and requiring the use of a salvage therapy.
- No Response to NI-0501, provided that there is evidence of IFNg neutralization.

However, upon request by the Investigator to continue NI-0501 treatment in the absence of therapeutic alternatives, the iDMC can authorize it after a thorough review of the patient's data and confirmation of lack of risks for the patient.

11.1.3 Systemic and local reaction to NI-0501 infusion

In case of clinical relevant changes in vital signs compared to pre-infusion values, the rate of NI-0501 infusion may be decreased or the infusion temporarily interrupted, if deemed necessary by the Investigator.

A decision to definitely stop the infusion should only be taken in case of very severe systemic reactions and be based on the evolution of patient status after appropriate symptomatic measures, e.g. oxygenation, and upon physician's own medical judgment.

All changes in the infusion rate should be recorded on the Infusion Worksheet: each time with the rate modification.

Unless related to a hypersensitivity reaction, the occurrence of local issues related to the infusion (such as catheter displacement, obstruction or product extravasation) should be managed through the identification of a new venous access as soon as possible to complete the infusion. All relevant information needs to be recorded in the Infusion Worksheet, including the volume of IMP potentially lost (in order to calculate the quantity of drug infused), and the time at which the infusion was stopped and restarted.

11.2 AT STUDY LEVEL

11.2.1 Suspension of Recruitment

Recruitment may be suspended in the following situations:

- Any occurrence of death or life-threatening SAE related to the drug
- At the iDMC's own request as an outcome of their regular study review.

Patients already enrolled in the study should continue receiving NI-0501 as per protocol unless decided otherwise by the Investigator.

The suspension will allow the iDMC to analyse the data already generated and consider a recommendation.

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

- To resume recruitment without any change
- To implement minimisation measures that may require protocol amendment
- To implement conditions for study termination, e.g. next occurrence of a particular serious drug reaction or at the next patient worsening or reactivation

11.2.2 Study Termination

11.2.2.1 Study Termination for Safety Reason

Occurrence of two deaths suggesting a reasonably possible relationship with continuous exposure to NI-0501 and occurring in similar conditions will trigger the decision to terminate the study.

This process will involve both the DMC and the Investigator. The management of patients already enrolled in the study will also be part of the DMC recommendations.

11.2.2.2 Study Termination for Absence of a Demonstrated Benefit

The decision to terminate the study due to absence of a demonstrated benefit will be one of the responsibilities of the iDMC, based on the ongoing review of the individual patient data and benefit/risk analysis.

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

12 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

Full details of all planned analyses will be specified in separate documents describing PK/PD and Statistical Analyses, which will be finalized prior to the locking of the study database. This section contains an overview of the planned methods of analysis with regard to safety and efficacy variables.

12.1 SAMPLE SIZE

The sample size of 5 patients is based on pragmatic considerations, and on the experience acquired from primary HLH patients treated with NI-0501.

12.2 ANALYSIS SETS

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

12.2.1 Safety Analysis Set

The safety analysis set will include all patients who receive any part of an infusion of study drug.

12.2.2 Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will coincide with the Safety Analysis Set.

12.2.3 Per-Protocol Analysis Set

The per-protocol analysis set will consist of all ITT patients who complete the study without major violations of the study protocol. Detailed listing of major protocol deviations will be defined in the SAP prior to locking of the final database.

12.3 STATISTICAL AND ANALYTICAL METHODS

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

All study variables are considered to be exploratory in this study, and no hierarchy of endpoints has been specified, as the objective of this pilot study is to confirm that the proposed dose regimen is adequate in this patient population.

Analysis will focus on descriptive statistics and confidence intervals. As this is a pilot study, statistical methods will focus on summarizing the data collected using descriptive statistics and on appropriate graphical presentations.

12.3.1 Efficacy Data

Graphical and tabular summaries will be prepared for each of the MAS distinct features, e.g. *fever; splenomegaly; WBC; platelet counts; liver function test (in particular ALT/AST); fibrinogen; ferritin; LDH.*

For binary endpoints (MAS remission by Week 8, number of patients who taper glucocorticoids, number of patients who discontinue due to lack of efficacy), 95% confidence intervals will be calculated for proportions.

For time to event endpoints (time to MAS remission, time to achievement of glucocorticoids tapering and time to death), Kaplan-Meier curves will be calculated and summary statistics, such as medians, proportions event-free at various time points will be calculated and presented, and 95% confidence intervals calculated where possible.

12.3.2 Safety Data

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

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

For each clinical laboratory test, individual patient values will be listed and summarized and change from pre-treatment baseline values calculated and summarized. Summaries of marked abnormalities and shift tables will be tabulated for each laboratory test.

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

12.3.3 Pharmacodynamic Data

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

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

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

12.3.4 Immunogenicity Data

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

12.3.5 Missing Data

No imputations of missing data will be performed. However, the following rules will be applied to ensure that all patients can be included in the final analysis:

- patients who are withdrawn from the study prior to Week 8 because of safety concerns or poor efficacy will be classified as non-responders from the time of their withdrawal in all analyses of response status, and their data will be censored at time of withdrawal in all time-to-event analyses. For continuous endpoints in such patients, all analyses for time points beyond the point of withdrawal will exclude missing data for these patients.

12.4 INTERIM ANALYSIS

No interim analysis is planned.

12.5 WITHDRAWAL AND REPLACEMENT

12.5.1 Patients

Additional patients will be recruited into the study if patients are withdrawn from the study for reasons other than safety or lack of efficacy to ensure a sample size of a minimum of 5 evaluable patients in North America.

12.5.2 For Centers

Centers may be closed down for the following administrative reasons: excessively slow recruitment, poor protocol adherence.

PART II

13 ETHICAL AND LEGAL ASPECTS

13.1 GOOD CLINICAL PRACTICE

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

13.2 INVESTIGATOR'S RESPONSIBILITIES

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

The Investigator is responsible for keeping a record of all patients (or their legally authorised representative) who sign an informed consent document and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in their source documents and the study-screening log.

The Investigator, or a designated member of the Investigators' staff, must be available during monitoring visits, audits and inspections to review data, resolve queries and allow direct access to patients' records (e.g. medical/hospital records, office charts, hospital charts, and study related charts) for source data and other type of verification. The Investigator must ensure timely and accurate completion of CRFs and queries. The Investigator must make himself/herself personally available during at least one monitoring visit per month, in order to address questions and to generally demonstrate his/her direct oversight of the conduct of the study.

The Investigator must allow regular visits at the site when patients are enrolled, to be not less than one 2 day visit every 14 days. In addition, the Investigator must ensure that all source data, including but not limited to medical records and hospital charts are available for review by the monitor for at least 30 days after a study day.

13.3 CONSENT

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

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

If applicable, since minors are involved in the trial, assent must be obtained from the minor and informed consent from at least one of the parents or as mandated by local rules (individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedures involved in the research). The language used in the Assent Form is adapted to the maturity level of the minor involved in the trial. Since minors of different age groups are likely to be entered into the trial different versions of the Assent Form will be provided. The modalities for obtaining informed consent from the parents and Assent from the minor will be defined at the site initiation visit and documented at the clinical trial center.

The Investigator, or designee, will obtain consent for participation in the study in writing. The written informed consent will be obtained prior to conducting any study-related procedures or tests, although procedures or tests that are done as a part of routine medical care and conducted before consent can be used for the purposes of screening. The patient's consent (or the consent of the patient's legally authorized representative) must be confirmed at the time of consent by the personally dated signature of the person conducting the informed consent discussions. A copy of the signed consent document must be given to the patient or their legally authorized representative. The Investigator will retain the original signed consent document.

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

13.4 CONFIDENTIALITY AND DATA PRIVACY

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

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

13.5 PROTOCOL AMENDMENTS

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

13.6 APPROVAL OF THE CLINICAL STUDY PROTOCOL AND AMENDMENTS

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

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

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

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

All documents handed over to patients or their legal representative will be reviewed by Novimmune prior to submission to the competent Regulatory Authorities and to IRB/IEC. This includes but is not limited to the informed consent form, patient information sheet, assent form, advertisements, training materials, etc.

13.7 ONGOING INFORMATION FOR IRB/IEC

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

- Information on SAEs or SUSARs as per local applicable rules and timelines;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to patients.

13.8 CLOSURE OF THE STUDY

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

In addition, the Investigator or Novimmune has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Lack of screening or recruiting activities
- Significant non-compliance with contractual enrolment timelines and targets
- Persistent GCP non-compliance
- Inaccurate, incomplete or delayed data collection
- Persistent failure to adhere to the study protocol
- Persistent failure to provide requested follow-up information for data queries

13.9 RECORD RETENTION

The investigator will ensure that essential records are kept in a secure archiving facility for the retention period stipulated in the study contract. Essential documents include, but are not limited to, the following:

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

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

13.10 LIABILITY AND INSURANCE

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

13.11 FINANCIAL DISCLOSURE

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

13.12 DISCLOSURE OF PROTOCOL AND STUDY RESULTS AND PUBLICATION POLICY

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

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

Novimmune will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Novimmune will support publication of multicenter trials only in

their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the trial.

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

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

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

14 MONITORING AND AUDITING

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

14.1 STUDY MONITORING AND SOURCE DATA VERIFICATION

As part of the responsibilities commensurate with participating in the study, the investigator agrees to maintain and have available for monitoring, adequate case records (accurate source documents and CRFs) for the patients treated under this protocol. In addition, the investigator agrees to maintain all administrative documents (e.g. IEC correspondence, investigational product and supplies shipment manifests, monitoring logs, or correspondence with Novimmune and with any of its representative for this study).

14.2 ON-SITE AUDITS

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

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

14.3 SERIOUS GCP BREACHES

Novimmune is required to report a serious GCP Breach within 7 days to applicable health authorities. Therefore, should an Investigator become aware of a possible serious GCP breach, e.g. a protocol violation, or non-reporting of critical safety information that has the potential of jeopardizing patients' safety, Novimmune must be notified within 24 hours.

15 DOCUMENTATION AND USE OF STUDY FINDINGS

15.1 DOCUMENTATION OF STUDY RESULTS

A CRF (including electronic data capture) is used in this study and a specific CRF will correspond to each patient.

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

The CRF must be reviewed by the Investigator named in the study protocol or by a designated sub-investigator, and final signature will be required.

15.2 USE OF COMPUTERIZED SYSTEMS AT THE CLINICAL TRIAL CENTER

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e. in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

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

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17 APPENDICES

Appendix A – Literature reference for sJIA diagnosis: "Operational case definition of new onset sJIA used in development of treatment plans"

Appendix B – Literature reference for MAS diagnosis: "2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis"

Appendix C – Membership of the Scientific Steering Committee (SSC)

Appendix D – Estimated blood volumes to be drawn during the study

APPENDIX A: Operational Case Definition Of New Onset sJIA Used In Development Of Treatment Plans (designed by Childhood arthritis and rheumatology research alliance)

(DeWitt EM et al. *Arthritis Care Res 2012*)[49]

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 erythematous 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

[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:

1. ILAR specifies that the duration of *quotidian* fever has to be 3 days (the total duration of fever is two weeks in both).
2. ILAR specifies six weeks' duration of arthritis.
3. 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 B: 2016 Classification Criteria For Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: A European League Against Rheumatism/American College Of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative

(Ravelli A et al. *Ann Rheum Dis 2016*)[22]

Classification of macrophage activation syndrome in systemic juvenile idiopathic arthritis

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 C: Membership Of The Scientific Steering Committee (SSC)

- [redacted]
- [redacted]
- [redacted]
- [redacted]

APPENDIX D: Estimated Blood Volumes To Be Drawn During The Study

Assessments		Screening	NI-0501 Treatment period						Evaluation period	EoS
		SD-1	SD0	SD1	SD2	SD3	SD5	Infusion Visits[1] SD6 to SD28	SD35 – SD42 – SD49	SD 56 Week 8
Laboratory assessments	- CBC (including Lymphocyte subset)	1	1	1	1	1	1	1	1	1
	- Coagulation, Fibrinogen	1	1	1	1	1	1	1	1	1
	- Biochemistry	2	2	2	2	2	2	2	2	2
	- Serum pregnancy test (if applicable)	0.5								0.5
	-*Search for EBV, CMV, Adenoviruses, Mycobacteria*	0.5						0.5[2]	0.5[3]	0.5
	-*Search for HSV, HZV, HIV, HBV, HCV*	0.5								
	-*Search for other pathogens (if needed)*	1								
Subtotal per visit		6.5	4	4	4	4	4	4/4.5[2]	4/4.5[3]	5
Subtotal per month								59.5		17.5
PK	- NI-0501 serum concentration		1	0.5	0.5	1	0.5	1	0.5	0.5
PD 1	- IFNγ, CXCL9, CXCL10, sCD25		1	1	1	1	1	1	1	1
PD 2	- Other biomarkers		1					1[2]	1[3]	1
Immunogenicity (ADA)			0.5							0.5
Molecular diagnosis (if consent for genetic testing is given)		(3)								
Subtotal per visit		(3)	3.5	1.5	1.5	2	1.5	2/3[2]	1.5/2.5[3]	3.0
Total per month (maximum)								**90.5**		**26.0**
TOTAL OVERALL STUDY (maximum)										**116.5**

[1] Assumes worst case scenario in terms of blood volumes, i.e. NI-0501 treatment is continued until SD28 (total of 10 infusions). If treatment is shortened, the amount of blood to be drawn would be less.

[2] At SD15 and SD28.

[3] At SD42.