Clinical Study Protocol

A Multicenter Study for the Long-term Follow-up of HLH Patients who Received Treatment with NI-0501, an Anti-interferon Gamma Monoclonal Antibody

Study number:	NI-0501-05
Protocol number:	NI-0501-05-US-P-IND#111015
Version:	Version 4.0
Date:	October 31, 2019
P-IND Number:	111015
Sponsor Corporate Address:	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
US Study Coordinator	[redacted]
Chief Medical Officer Sobi Immunology	

Investigator Agreement

Protocol Number: NI-0501-05-US-P-IND#111015

Protocol date and version: October 31, 2019 – Version 4.0

Study drug: NI-0501

Study title: A Multicenter Study for the Long-term Follow-up of HLH Patients who Received Treatment with NI-0501, an Anti-interferon Gamma Monoclonal Antibody

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, and where applicable, from the Competent Authorities, except where necessary to prevent any immediate danger to the patient.

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

_____

Site Principal Investigator's Printed Name

_____ _____

Site Principal Investigator' Signature Date

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NI-0501-05 SYNOPSIS

Title:	A Multicenter Study for the Long-term Follow-up of HLH Patients who Received Treatment with NI-0501, an Anti-interferon Gamma Monoclonal Antibody
Sponsor:	Sobi AG, Switzerland
Study Type:	International, multicenter, long-term, follow-up study of haemophagocytic lymphohistiocytosis (HLH) patients who have received NI-0501 (INN assigned name: emapalumab) in the context of a previous NI-0501 clinical study in which no long-term follow-up is planned. Patients having received NI-0501 under a compassionate use (CU) treatment protocol may also be considered for enrolment, whenever appropriate. NI-0501-05 study is performed both in the US and in Europe according to twin protocols called NI-0501-05-P-IND #111015 and NI-0501-05-EudraCT #2012-005753-23, respectively
Study Population:	HLH patients who have received at least one dose of NI-0501 during a previous NI-0501 clinical study or under a CU treatment protocol. In the event that an appropriate donor has not been identified, at the end of NI-0501 induction treatment in study NI-0501-04, or in case of the need to delay Hematopoietic Stem Cell Transplantation (HSCT) for reasons unrelated to the administration of NI-0501, patients originally enrolled in study NI0501-04 may continue NI-0501 treatment in the context of this protocol upon request of the treating physician after having established a favourable benefit/risk from NI-0501 treatment. Given the fact that patients with different forms of HLH (pHLH or sHLH) can be enrolled in this study, the present protocol has to account for different patient characteristics, namely for: • Patients who have received NI-0501 treatment in the context of a NI-0501 clinical study or a CU treatment protocol, and have received/will receive HSCT. Transplant may have been already performed, or may be performed under this protocol. Long-term follow-up will be conducted up to 1 year post-HSCT (see Table 1). • Patients who have received NI-0501 treatment in the context of an NI-0501 clinical study or a CU treatment protocol, and for whom HSCT is not planned. Patients will enter this study for a long-term follow-up lasting up to 1 year after the last infusion of NI-0501 (see Table 2).

	Different flow charts and Schedules of Assessments (SoA) will be applied, depending on the above patient's characteristics. Patients will enter study NI-0501-05 after the last infusion of NI-0501 or at the end of the short-term follow up in the parent study, depending on the design of the parent study. Whenever some of the visits described in the SoA have been already conducted before entry in study NI-0501-05, the patient will proceed with the next planned visit.
Main Inclusion Criteria:	1. Having received at least one dose of NI-0501 during a previous NI-0501 study or under a CU treatment protocol. 2. Having signed the Informed Consent by the patient or the patient's legal representative(s), as applicable, with the assent of patients who are legally capable of providing it.
Study Objectives:	• To monitor the long-term safety profile of NI-0501 • To assess HLH patients' survival after NI-0501 treatment • To assess duration of response to NI-0501 treatment (i.e. maintenance of HLH control) • To assess post-HSCT outcome measures, if applicable • To assess background disease activity, in patients with secondary forms of HLH • To study the elimination profile of NI-0501 • To evaluate the pharmacodynamic (PD) effects (levels of circulating Total IFNγ, CXCL9, CXCL10) • To assess the profile of relevant HLH biomarkers, e.g., sCD25 • To assess the immunogenicity of NI-0501
Study Drug:	No investigational medicinal product (IMP) will be administered during the course of this long-term follow-up study. However, in the event that, upon request of the treating physician, NI-0501 treatment needs to be prolonged beyond Week 8 in patients originally enrolled in study NI-0501-04, patients will continue receiving NI-0501 in the context of this study. In this case NI-0501 will be managed as the IMP.
Investigating Sites:	All sites where patients have been recruited in NI-0501 clinical studies in which no long-term follow-up is already planned. Sites where patients have been treated under a CU treatment protocol may also be involved (whenever appropriate).
Study Duration and Study End Definition:	• For patients who underwent or will undergo HSCT, the study will continue until data at 12 months post-HSCT are collected • For patients not undergoing HSCT, the study will continue

	until data at 12 months after the last infusion of NI-0501 are collected • Study end is defined as the date of last patient`s last visit
Concomitant Medications	• Any treatment ongoing at the time of study entry will be continued as deemed necessary by the Investigator • Patients receiving prophylactic treatments for infections (e.g. antiviral) at study entry will continue therapy as long as NI-0501 concentrations are detectable in serum • There is no restriction in the use of medications, except for live or attenuated live vaccinations that should be avoided as long as NI-0501 concentrations are detectable in serum. In the event that NI-0501 treatment, upon request of the treating physician, needs to be continued beyond week 8 in patients originally enrolled in study NI-0501-04 and entering the NI-0501-05 study, the use of concomitant medications needs to follow the instructions given in the context of the NI-0501 study in which the patient was recruited.
Study Parameters:	• Vital signs, including body temperature • Physical examination, including liver and spleen sizes • Laboratory parameters: complete blood count, coagulation tests (aPTT, PT, d-Dimers and fibrinogen), erritin, CRP, LDH, glucose, triglycerides, liver, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, total bilirubin and alkaline phosphatases) and renal function tests (creatinine, albumin and urea) • Pharmacokinetics: circulating NI-0501 concentration • Pharmacodynamics: circulating IFNγ levels, CXCL9, CXCL10, and exploratory markers of disease activity (e.g. sCD25) • Anti-drug antibodies (ADAs)
Study Endpoints:	• Safety will be assessed as follows: - Incidence, seriousness, intensity, possible relationship to NI-0501 and outcomes of Adverse Events (AEs) - Evolution over time of vital signs, physical examination and laboratory values over time • Efficacy (as relevant, depending on the different patients' characteristics): • Duration of Response after completion of NI-0501 treatment (assessed according to the definitions set in the parent study) • Survival time up to one year post-HSCT (including survival to HSCT and survival post-HSCT) or one year after last NI-0501 infusion (if transplant is not

	performed) • Post-HSCT outcome indices, e.g. engraftment rate, donor chimerism, incidence of acute and chronic Graft versus Host Disease (GvHD) (it applies to patients who receive HSCT) • Monitoring of background disease activity (it applies to patients with secondary forms of HLH) • Pharmacokinetics: NI-0501 elimination • Pharmacodynamics: IFNγ total • Immunogenicity: presence of ADAs • Exploratory PD parameters/endpoints: e.g. additional markers of disease activity (scD25)
Statistical Analysis	• Duration of Response and Survival time will be presented using Kaplan-Meier curves with medians calculated if available. 95% confidence intervals will be calculated for the median for each of these endpoints • Endpoints based on binary outcomes, including post-HSCT outcome measures, will be converted to proportions and associated 95% confidence intervals calculated.

CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
CBC	Complete blood cell count
CRF	Case report form
CRP	C-reactive protein
eCRF	Electronic case report form
γGT	Gamma Glutamyl Transferase
HLH	Hemophagocytic Lymphohistiocytosis
HSCT	Hematopoietic stem cell transplantation
HZ	Herpes Zoster
ICMJE	International Committee of Medical Journal Editors
IFNγ	Interferon gamma
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IMP	Investigational medicinal product
IRB	Institutional review board
LDH	Lactate Dehydrogenase
NaCl	Sodium Chloride
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMF	Trial Master File
WD	Withdrawal

Table 1: Schedule of Assessments for the Long-term Follow-Up of Patients Who Underwent or Will Undergo HSCT

Assessments		Follow-up pre-HSCT				HSCT	Follow-up post-HSCT						UV [8]
		Baseline visit [1]	Weekly visits pre-HSCT [2]	Pre Conditioning visit [3]			Weekly visits wk 1 – 2 – 3 [4]	D+30 visit [5]	D+60 visit [5]	D+100 visit [5]	6 month visit [6]	1 year visit [6] / WD [7]	
Subject information	Informed consent	X											
	Demographics	X											
	Medical history / relevant treatment	X											
Clinical Assessments	Vital signs	X	X	X	**X**		X	X	X	X	X	X	
	Physical examination[9]	X	X	X	X		X	X	X	X	X	X	
	Duration of response to treatment			X	X			X		X		X	
	Post-HSCT outcome measures[10]						X	X	X	X	X	X	
	Survival	X	X	X	X		X	X	X	X	X	X	
Laboratory	CBC	X	X	X	X		X	X	X	X	X	X	
	Coagulation	X	X	X	X		X	X	X	X	X	X	
	Biochemistry	X	X	X	X		X	X	X	X	X	X	
	Urinalysis	X						X	X	X	X	X	
Search for infections[11]	TB, Adenovirus, EBV, CMV	X[11]	X[11]	X[11]			X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	
Imaging	Chest X ray[11]	X[11]	X[11]	X[11]			X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	
	Abdominal ultrasound[12]	X		X				X		X		X	
AE recording[14]		X	X	X	X		X	X	X	X	X	X	X
Concomitant medications and procedures recording		X	X	X			X	X	X	X	X	X	X
PK/PD (NI-0501 concentrations / total IFNγ & other biomarkers)		X	X	X	X		X	X	X[13]	X[13]	X[13]	X[13]	
Immunogenicity (ADA)		X								X		X	

CBC: complete blood count (white blood cells and subsets, red blood cells including reticulocytes and platelets, hemoglobin and hematocrit). **Coagulation tests:** aPTT, PT, d-Dimers and fibrinogen
Biochemistry: glucose, CRP, ferritin, triglycerides, liver (AST, ALT, γGT, LDH, ALP, bilirubin) and renal function (albumin, creatinine and urea).

1 = Baseline visit: Patients may enter the study at any time-point before or after HSCT, depending on the SoA of the parent study. The required Baseline assessments do not have to be repeated if available from the last visit of a previous NI-0501 clinical study or CU treatment protocol, if occurred within 5 days from the Baseline visit.

2 = Weekly visits pre-HSCT: to be performed weekly up to 4 weeks after last NI-0501 infusion, then bi-weekly until start of conditioning (±2 day window is allowed).

3 = Pre-conditioning visit: if this visit is no more than 48 hrs apart from one of the follow-up visit pre-HSCT, then these visits may be combined following the most demanding SoA.
4 = Weekly visit post-HSCT: a ±2 day window is allowed
5 = D+30, D+60, D+100 visits: a ±1 week window is allowed
6 = 6-mo, 1-yr visits: a ±4 week window is allowed
7 = WD (Withdrawal visit): assessments to be performed in case of premature study discontinuation, performing all assessments as indicated for this last study visit
8 = UV (Unscheduled visit): assessments to be performed as clinically indicated
9 = Physical examination: includes spleen and liver size assessments (in cm from costal grill by palpation)
10 = Post-HSCT Outcome Measures: engraftment rate, donor chimerism, incidence of acute and chronic GvHD
11 = Search for infections and Chest X-ray: TB, Adenovirus, EBV, CMV searches to be performed every 2 weeks as long as NI-0501 is detectable. Chest X-ray only if clinically indicated
12 = Abdominal ultrasound: it has to include longitudinal measure of spleen
13 = PK: as long as NI-0501 serum concentrations are measurable; **PD**: as long as NI-0501 serum concentrations are measurable, thereafter only if clinically indicated
14= AE recording: once NI-0501 is no longer detectable, only SAEs will be recorded

Table 2: Schedule of Assessments for the Long-Term Follow-Up of Patients for Whom HSCT is not Planned

Assessments		Follow-up after last NI-0501 infusion								UV [4]
		Baseline visit [1]	Week 2 visit [2]	Week 3 visit [2]	Day+30 visit [2]	Day+60 visit [2]	Day+100 visit [2]	6 month visit [2]	1 year visit [2] / WD [3]	
Subject information	Informed consent	X								
	Demographics	X								
	Medical history / relevant treatment	X								
Clinical Assessments	Vital signs	X	X	X	X	X	X	X	X	
	Physical examination[5]	X	X	X	X	X	X	X	X	
	Duration of response to treatment				X		X		X	
	Background Disease Activity	X			X		X		X	
	Survival	X	X	X	X	X	X	X	X	
Laboratory	CBC	X	X	X	X	X	X	X	X	
	Coagulation	X	X	X	X	X	X	X	X	
	Biochemistry	X	X	X	X	X	X	X	X	
	Urinalysis	X			X	X	X	X	X	
Search for infections[6]	TB, Adenovirus, EBV, CMV	X[6]			X[6]	X[6]	X[6]	X[6]	X[6]	
Imaging	Chest X ray[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	
	Abdominal ultrasound[7]	X			X		X		X	
AE recording[9]		X	X	X	X	X	X	X	X	X
Concomitant medications and procedures recording		X	X	X	X	X	X	X	X	X
PK/PD (NI-0501 concentrations / total IFNγ & other biomarkers)		X	X	X	X	X[8]	X[8]	X[8]	X[8]	
Immunogenicity (ADA)		X					X		X	

CBC: complete blood count (white blood cells and subsets, red blood cells including reticulocytes and platelets, hemoglobin and hematocrit). **Coagulation tests:** aPTT, PT, d-Dimers and fibrinogen
Biochemistry: glucose, CRP, ferritin, triglycerides, liver (AST, ALT, γGT, LDH, ALP, bilirubin) and renal function (albumin, creatinine and urea).

1 = Baseline visit: Patients may enter the study at any time-point, depending on the SoA of the parent study. The required Baseline assessments do not have to be repeated if available from the last visit of a previous NI-0501 clinical study or CU treatment protocol, if occurred within 5 days from the Baseline visit.

2 = Time interval starts from the last NI-0501 infusion. For the allowed time window around visits, please refer to Table 1. These visits may have been conducted as part of the parent study; in such case, they do not need to be repeated.

3 = WD (Withdrawal visit): assessments to be performed in case of premature study discontinuation, as indicated for this last study visit
4 = UV (Unscheduled visit): assessments to be performed as clinically indicated
5 = Physical examination: includes spleen and liver size assessments (in cm from costal grill by palpation)
6 = Search for infections and Chest X-ray: search for infections to be performed every 4 weeks as long as NI-0501 serum concentrations are measurable, thereafter only if clinically indicated. Chest X-ray only if clinically indicated
7 = Abdominal ultrasound: it has to include longitudinal measure of spleen
8 = PK: as long as NI-0501 serum concentrations are measurable; **PD**: as long as NI-0501 serum concentrations are measurable, thereafter only if clinically indicated
9 = AE recording: once NI-0501 is no longer detectable, only SAEs will be recorded

1. STUDY RATIONALE

NI-0501 (assigned INN name: emapalumab) is a fully human immunoglobulin G1 anti-interferon gamma (IFNγ) monoclonal antibody (mAb) which binds and neutralizes IFNγ.

IFNγ is one of the most potent and pleiotropic cytokines of the immune system and it is considered critical for innate and adaptive immunity against viral and intracellular bacterial infections[1].

Haemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by a severe impairment or absence of cytotoxic function by CD8+ T cells, with a striking activation of the immune system, which presents typically as hypercytokinemia and lymphohistiocytic infiltrates[2]. Among the cytokines elevated in HLH patients are: IFNγ, interleukin (IL)-6, IL-10, tumor necrosis factor (TNF) α, IL-8, macrophage colony stimulating factor (MCSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF).

HLH comprises primary forms, genetically determined, and secondary forms, which are consequent to infections, inflammatory/autoimmune diseases or malignancies[3].

Based on data from relevant animal models of HLH[4;5] and from the assessment of IFNγ levels in HLH patients[6], neutralization of IFNγ represents a potential therapeutic objective in this patient population to achieve non-active disease (induction treatment) through a targeted therapy, which might prevent the use of chemotherapy. Of note is that hypercytokinemia and organ infiltration by activated lymphocytes and histiocytes are responsible for all symptoms of HLH patients and are dependent on CD8+ T cells hyperactivity and high IFNγ levels[7-10].

Therefore inhibiting IFNγ is believed to be a viable option for the development of a targeted therapy for HLH, required to be efficacious with no or limited toxicity[11]. IFNγ transient blockade is believed to be potentially less toxic and far less immunosuppressive than VP-16 or ATG, which are currently part of the induction regimen of HLH.

Macrophage Activation Syndrome (MAS) is a secondary form of HLH often observed in patients suffering from a rheumatic disease, such as systemic Juvenile Idiopathic Arthritis (sJIA) and Systemic Lupus Erythematosus (SLE).

MAS, like HLH, is characterized by sustained immune cell activation and an associated cytokine storm of pro-inflammatory cytokines with overproduction of IFNγ and other cytokines.[15, 16]Beyond the demonstration of the safety, tolerability and efficacy of NI-0501 as induction treatment for HLH and as treatment for MAS, there is a need to establish the mid- and long-term safety of NI-0501 treatment and its influence on survival of patients. NI-0501 has been administered to adult Healthy Volunteers (HV) as a single i.v. infusion up to 3 mg/kg without any mid- or long-term adverse events reported during a maximum follow-up of 6 months (study NI-0501-03). At the moment a pilot Phase II study (NI-0501-04) is open for recruitment of patients with primary HLH in whom the disease has reactivated.

Currently, 2 interventional studies are ongoing: an open-label Phase 2/3 study in patients with pHLH (protocol NI-0501-04) and a pilot study in MAS in sJIA patients (protocol NI-0501-06).

In addition, NI-0501 has been administered under a compassionate use treatment protocol to HLH patients that exhausted all available therapeutic options.

Study NI-0501-05 allows a systematic collection of long-term data in patients previously exposed to NI-0501 during the course of the studies mentioned above (and potentially other studies not yet ongoing) or who have received NI-0501 in compassionate use.

2. OBJECTIVES

- To monitor the long-term safety profile of NI-0501
- To assess HLH patients' survival after NI-0501 treatment
- To assess duration of response to NI-0501 treatment (i.e. maintenance of HLH control)
- To assess post-HSCT outcome measures, if applicable
- To assess background disease activity, in patients with secondary forms of HLH
- To study the elimination profile of NI-0501
- To evaluate the pharmacodynamic (PD) effects (levels of circulating total IFNγ, CXCL9, CXCL10)
- To assess the profile of relevant HLH biomarkers, e.g., sCD25
- To assess the immunogenicity of NI-0501

3. STUDY DESIGN

3.1. OVERALL DESIGN

This is an international, multicenter, long-term, follow-up study of HLH patients who have received at least one dose of NI-0501 in the context of a previous NI-0501 clinical study in which no long-term follow-up is already planned. Patients having received NI-0501 under a compassionate use (CU) treatment protocol may also be considered for enrolment, whenever appropriate.

The NI-0501-05 study is performed both in the US and in Europe according to twin protocols called NI-0501-05-P-IND #111015 and NI-0501-05-EudraCT #2012-005753-23, respectively.

In the event that an appropriate donor has not been identified by Week 8 or in case of the need to delay transplantation for reasons unrelated to the administration of NI-0501, patients from study NI-0501-04- US-P-IND#111015 can continue receiving NI-0501 treatment beyond the foreseen 8 weeks upon request of the Investigator, providing a favorable benefit/risk has been established. A close monitoring of these patients will be performed in the context of this study (NI-0501-05), according to the schedule of assessment reported in Appendix A, where the end of treatment period visit of the NI-0501-04 study will be the first visit for these patients entering NI-0501-05 study (refer to NI-0501-04-US Study Protocol, Table 2). Due to the probability that, by Week 8, patients may be receiving NI-0501 infusions less frequently than every 3 days, the schedule of assessment, as described in Appendix A, may be adapted to suit the schedule of administration, maintaining the safety and efficacy assessments visits at least on a weekly basis. After NI-0501 discontinuation, patients will be monitored weekly for a period of 4 weeks (4-week follow-up) before entering the long-term follow-up study described above.

Study NI-0501-05 enrolls 2 different groups of patients: patients who underwent or will undergo HSCT, and patients for whom HSCT is not envisioned. The follow-up of these 2 different patients` groups is generally similar. The study design and visits` schedule for each patients`group is specifically described in Sections 3.1.1 and 3.1.2, respectively.

3.1.1. Patients who underwent or will undergo HSCT

This section refers to patients who have received or are planned to receive HSCT after NI-0501 treatment in a previous NI-0501 clinical study or in a CU treatment protocol.

Patients may enter the NI-0501-05 study at any time point after NI-0501 treatment or after completion of the short-term follow-up in the parent study, as applicable.

Patients will undergo:

- **Baseline visit**: it corresponds to the first study visit. The date of informed consent signature has to be recorded. If the last visit that the patient underwent in the parent study required all the assessments to be collected at Baseline in NI-0501-05 and occurred within 5 days from Baseline, data collected during that visit will constitute the baseline for the present study, and the visit will not need to be repeated or will be performed only to cover for any missing assessments. The Baseline visit will be combined with any other study visit depending on when the patient enters this study [for example, if the patient enters the study after having already performed HSCT, the Baseline visit will be combined with the relevant post-HSCT follow-up visit].
- **Weekly visits pre-HSCT**: they have to be performed weekly until HSCT for 4 weeks from the end of NI-0501 treatment. If HSCT occurs beyond this time frame, the additional visits will be performed every 2 weeks until start of conditioning.
- **Pre-conditioning visit**: it should occur up to 3 days prior to the start of conditioning and assessments must be performed prior to the first administration of conditioning drug(s). This visit can be combined with any other follow-up visit before HSCT visit, provided that they are no more than 48 hours apart.
- **Pre-HSCT visit:** it should occur no more than 2 days prior to transplant.
- **Post-HSCT visits:** weekly visits will take place during the first 4 weeks after transplant until Day+30, and subsequently at Day+60, Day+100, 6 months, and 12 months post-HSCT.

For the allowed time windows, please see section 7.

Additional visits (unscheduled) may be required depending on the patient's clinical conditions.

3.1.2 Patients for whom HSCT is not planned

This section refers to patients who have received NI-0501 treatment in the context of an NI-0501 clinical study or under a CU treatment protocol, and for whom HSCT is not planned based on disease characteristics and/or physician's assessment of benefit/risk of the transplant procedure in that individual patient.

Patients may enter the NI-0501-05 study at any time point after NI-0501 treatment (and completion of the short-term follow-up, if required in the parent study).

Patients will undergo:

- **Baseline visit**: it corresponds to the first study visit. The date of informed consent signature has to be recorded. If the last visit that the patient underwent in the previous NI-0501 protocol required all the assessments to be collected at Baseline in NI-0501-05 and occurred within 5 days from Baseline, data collected during that visit will constitute the baseline for the present study, and the visit will not need to be repeated or will be performed only to cover for any missing assessments. The Baseline visit will be combined with any other study visit depending on when the patient enters this study.

- **Follow-up visits after last NI-0501 infusion**: unless already performed in a previous NI-0501 clinical study, weekly visits will take place until Day+30 after last NI-0501 infusion, and thereafter at Day+60, Day+100, 6 months, and 12 months after the last NI-0501 infusion.

Additional visits (unscheduled) may be required depending on the patient's clinical conditions.

For the allowed time windows, please see Section 7.

3.2. STUDY END

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

In case of an ongoing serious adverse event (SAE), patients 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.

4. TARGET POPULATION & ELIGIBILITY CRITERIA

The study population comprises HLH patients who have received at least one dose of NI-0501 in the context of a previous NI-0501 clinical study in which no long-term follow-up is already planned. Patients having received NI-0501 under a CU treatment protocol may also be considered for enrolment where appropriate.

Patients must fulfil the following inclusion criteria:

1. Having received at least one dose of NI-0501 during a previous NI-0501 study or under a CU treatment protocol.
2. Having signed the Informed Consent of this study by the patient or the patient's legal representative(s), as applicable, with the assent of patients who are legally capable of providing it.
3. Having agreed to continue using adequate methods of birth control until 6 months after the last administered dose of NI-0501, when relevant Males with partners(s) of child-bearing potential must agree to take appropriate precautions to avoid fathering a child until 6 months after receiving last dose of NI-0501.

There are no exclusion criteria.

5. PATIENT BACKGROUND TREATMENT AND CARE

There is no restriction in the use of medications for either pre-Transplantation conditioning or for post-Transplantation medical care.

- Any treatment ongoing at the time of study entry will be continued as deemed necessary by the Investigator.
- Patients receiving prophylactic treatments for infections (e.g. antiviral) at study entry will continue therapy as long as NI-0501 concentrations are detectable in serum.
- There is no restriction in the use of medications, except for live or attenuated-live vaccines that should be avoided as long as NI-0501 concentrations are detectable in the serum.

All relevant treatments prescribed to patients (dose, frequency and duration) will be recorded throughout the NI-0501-05 study course.

In the event that, upon request of the treating physician, a patient receives NI-0501 treatment beyond the foreseen duration of the NI-0501 protocol (i.e. Week 8), NI-0501 should be prepared and administered as described in Appendix B of this protocol (Investigational Medicinal Product preparation and handling). With regards to the use of concomitant medications, the recommendations stated in the NI-0501 treatment protocol in which the patient was originally enrolled should be followed by the Investigator, in particular as to the need for prophylactic treatment and restricted use of some other treatments (e.g. refer to NI-0501-04-US Study Protocol, Section 6.3). Each patient receiving NI-0501 treatment for more than 8 weeks should continue to carry a card similar to the one given to him/her during their previous NI-0501 study, but indicating the references of the NI-0501-05 study (i.e. the card giving details on the name of the drug, name of the responsible physician, and the address and telephone number of the study site).

6. ENDPOINTS

- Safety will be assessed as follows:
  - The incidence, seriousness, intensity, possible relationship to NI-0501 and outcomes of AEs.
  - Evaluation over time of vital signs, physical examination and laboratory values: evolution over time.
- Efficacy (as relevant, depending on the different patients' characteristics):
  - Duration of Response after completion of NI-0501 treatment (assessed according to the definitions set in the parent study)
  - Survival time up to one year post-HSCT (including survival to HSCT and survival post-HSCT) or one year after last NI-0501 infusion (if transplant is not performed)
  - Post-HSCT outcome indices, e.g. engraftment rate, donor chimerism achieved, incidence of acute and chronic Graft versus Host Disease (GvHD) (it applies to patients who receive HSCT)
  - Monitoring of background disease activity (it applies to patients with secondary forms of HLH)
- Pharmacokinetics:
  - NI-0501 elimination profile
- Pharmacodynamics:
  - IFNγ total
  - Exploratory PD parameters/disease markers such as: sCD25, CXCL9, CXCL10
- Immunogenicity:
  - Presence of anti-drug antibodies (i.e. ADAs)

7. STUDY PROCEDURES

The Informed Consent form must be signed by the patient or his/her legal representative prior to any study-related procedures, with the assent of patients who are legally capable of providing it, at the latest at the Baseline visit.

Analyses done on blood samples will favor as much as possible the use of micro-sampling techniques.

When limiting blood drawing is needed, laboratory safety parameters (which would have been done as normal disease monitoring) will be prioritized.

Please refer to the schedule of assessments in Table 1 and Table 2 for an overview of the procedures to be performed during this long-term follow-up study.

If conditioning and/or transplantation have occurred before entry in this follow-up protocol, the corresponding visits will not be performed in the NI-0501-05 protocol. In this case when a patient enters the NI-0501-05 study, he/she will start to be monitored according to the NI-0501-05 remaining visits to be performed in the SOA.

During the study, the following time-windows are allowed around visits:

- Weekly visits pre-HSCT: ±2 days
- Pre-conditioning: if this visit is no more than 48 hrs apart from one of the weekly visit pre-HSCT, then these visits may be combined following the most demanding SoA
- Wk 1-2-3, D+30 post-HSCT: ±2 days
- D+60, D+100 post-HSCT: ±1 week
- 6-mo, 1-yr post-HSCT: ±4 weeks

If HSCT is not performed, the above described time windows apply to the follow-up visits required to occur after the last NI-0501 infusion.

The following assessments will be performed in all patients:

Clinical assessments:
at each visit

- Vital signs: body temperature, heart rate, blood pressure and respiratory rate
- Physical examination with particular attention being paid to:
  - height (at pre-Transplant visit, 100-days, 6-month and 12-month post-Transplant visits), weight
  - occurrence of skin rashes, jaundice, purpura, bleeding, edema
  - signs of infections
  - neurological examination
  - liver and spleen size (in cm from costal grill)

Laboratory:
at each visit

- CBC
- Coagulation tests: aPTT, PT, D-dimers and fibrinogen
- Biochemistry: glucose, ferritin, CRP, AST, ALT, γGT, ALP, LDH, bilirubin, albumin, creatinine, urea, triglycerides
- Urinalysis: glucose, blood, protein, leucocytes, ketones, pH and specific gravity (only at Baseline, D+30, D+60, D+100 visit, 6 months and 1 year/WD visits)

Imaging:

- Chest X-ray if clinically indicated

	▪ Abdominal ultrasound at Baseline, pre-conditioning (as applicable), D+30, D+100 visit and 1 year/WD visits
Search for infections: every 2 weeks, as long as NI-0501 is detectable in serum	▪ Tuberculosis either via polymerase chain reaction [PCR] in any relevant specimen (e.g. blood, urine, broncho-alveolar lavage, gastric aspirate) or by any method agreed to be used in the parent protocol or CU treatment protocol at a given site ▪ Adenovirus, EBV, CMV by quantitative PCR
Pharmacokinetics: at each visit as long as relevant	▪ NI-0501 serum concentration if concentration still detectable at previous visit
Pharmacodynamics/Exploratory Parameters: at each visit as long as NI-0501 is detectable	▪ sCD25, other exploratory markers (e.g. CXCL-9, CXCL-10) ▪ Total IFNγ
Immunogenicity: At Baseline, Day+100 visit, 1 year/WD visit	▪ Presence of anti-NI-0501 antibodies (ADA)
Adverse Events recording at each visit *Relevant concomitant medications and procedures recording* at each visit	▪ Any new AE which has occurred since the last visit should be recorded as well as evolution of ongoing AEs should be checked
Duration of response to treatment: At pre-Conditioning (for patients undergoing HSCT), Day+30, Day+100, 1 year visits	▪ Through assessment of: - HLH disease activity (as defined in the parent protocol in which the patient was originally enrolled)

In addition, *assessment of survival* is to be performed in all patients at each visit.

Background disease activity will be assessed in the relevant population (i.e. patients with secondary HLH) at Baseline, Day+30, Day+100, 1 year visits.

Post-HSCT outcome measures will be collected in the relevant population at each visit post-HSCT.

Unplanned visits may occur should the Investigator need to assess or treat any clinical condition that arises during the study. In the event that, upon the request of the treating physician, NI-0501 treatment needs to be continued beyond Week 8 in patients enrolled in study NI-0501-04, patients will continue receiving NI-0501 in the context of this study at a dose either carried forward from the last administered NI-0501 dose as part of the NI-0501 treatment study the patient was enrolled in, or at an adjusted dose if necessary and depending on NI-0501 PK profile.

NI-0501 infusions will be performed at a dose and frequency which will be determined by the Sponsor based on the observed PK profile of the drug and on the patient's clinical response.

The last dose of dexamethasone administered as part of study NI-0501-04 will be carried forward. If tapering is required, it should be performed in accordance to the general corticosteroid tapering rules, and dose modifications will be recorded in the eCRF.

The stopping rules described in study protocol NI-0501 the patient was part of (e.g. NI-0501-04-US-P-IND-111015, Section 10) still apply for patients on drug to decide whether the patient should continue to receive NI-0501 infusion. If a patient is not receiving anymore NI-0501 infusions in the context of NI-0501-05 study, he remains in the NI-0501-05 as it is an observational study collecting long term data, unless the patient or his/her legal guardian withdraw their consent.

Patients still receiving NI-0501 treatment will be followed-up to monitor safety and efficacy of NI-0501 treatment until treatment discontinuation and will be followed for 4 weeks as described in the NI-0501 treatment protocol they were part of (e.g. NI-0501-04-US-P-IND-111015) and as detailed in the specific Schedule of Assessment for patients continuing to receive NI-0501 beyond Week 8 (see Appendix A). Upon discontinuation of NI-0501 treatment, assessments described above will be performed as part of the long-term follow-up of these patients.

8. SAFETY MONITORING

8.1. DESCRIPTION OF STUDY PARAMETERS

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

- Adverse events (AEs), with special attention being paid to the occurrence of infections
- Laboratory parameters:
    - CBC and hemoglobin
    - coagulation tests (aPTT, PT, d-Dimers and fibrinogen)
    - inflammatory markers such as CRP and ferritin,
    - biochemistry: glucose, triglycerides and liver enzymes (AST, ALT, ALP, γGT, LDH, total bilirubin), albumin, creatinine and urea
- Vital signs: body temperature, heart and respiratory rate, blood pressure
- Physical examination and changes over time (see Section 7)
- Immunogenicity: development of anti-NI-0501 antibodies

8.2. RECORDING AND REPORTING SAFETY PARAMETERS

The Safety Reporting Requirements for INDs and BA/BE Studies issued in December 2012 will be followed.

8.2.1. Adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product (IMP). The IMP remains NI-0501 during this study even if the patient is off drug. All AEs reported spontaneously by the patients or his/her relatives or observed by the Investigator or his staff during the clinical study up to and including the end-of-study visit will be reported on the AE data collection form. For all AEs, the following will be assessed and recorded: intensity, seriousness, relationship to test substance, action taken regarding test substance, any treatment received and outcome 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 is not mentioned in the scale, assessment will 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. The relationship of adverse events to NI-0501 will be assessed by the Investigator using a “Yes/No” classification. A “Yes” relationship infers that there is a reasonable suspected causal relationship to NI-0501. The expression “reasonable causal relationship” is meant to convey that there are facts, evidence or arguments to suggest a causal relationship.

All AEs including local and systemic reactions not meeting the criteria for Serious AEs will be captured in the appropriate eCRF section. All AEs occurring while a patient is participating in the study must be documented appropriately, regardless of relationship. All AEs will be followed to adequate resolution.

Any AE that is present at the time that the patient enters the NI-0501-05 study will continue to be monitored in the frame of previous NI-0501 study (for serious AEs, until resolution or until the outcome of the event is known and stable). Therefore it will not be recorded as an AE of the NI-0501-05 study, unless in case of worsening. In this case a new AE will be recorded as a worsening of a previous condition.

8.2.2. Serious Adverse Events

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, 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;

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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.

The term severe is a measure of intensity/severity: thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

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

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

Any serious clinical AE 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.

Sobi AG contact information for SAE reporting:

Fax: [redacted]

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 must be available to answer without delay any request for follow-up information or questions Sobi AG may have regarding the SAE.

All SAEs will be recorded on the appropriate page of the eCRF. They will be reviewed, evaluated and followed through to resolution by a study physician.

If either the Sponsor or Investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting (21 CFR 312.32(a) and 312.32(c)(1)).

8.2.3. SUSAR reporting

Unexpected adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered

These reactions are SUSARs if the following three conditions are met:
1) the event must be serious (see Section 8.2.2 above);
2) there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;

3) the event is not listed as an expected serious reaction in the Reference Safety Information (RSI) of the IB.Under 21 CFR 312.32(c), the Sponsor (directly or through a delegated third party) is required to notify 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 7 calendar days for fatal or life-threatening events and 15 calendar days for all other events, after the Sponsor receives the safety information and determines that the information qualifies for reporting.

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

Sobi AG will also report all SUSARs to the EMA's EudraVigilance database within 15 days, as well as to the relevant National Competent Authorities when required. Fatal and life-threatening SUSARs will be reported within 7 calendar days, with another 8 days for completion of the report.

8.2.4. Managing Abnormal Laboratory Test Values

All safety laboratory tests (hematology and blood biochemistry provided by the site for each visit time-point, should be captured in the database in the laboratory page and should not be reported as AEs even if qualified as `clinically significant` at site, unless specific treatment is given for the abnormality or if qualifying as grade 4 as per WHO recommendations. Treatment does not refer to platelets or RBC transfusions administered during conditioning and post HSCT or when patient has sign of HLH. If a laboratory abnormality leads to a new clinical diagnosis (e.g., high white cell count is found to be due to incidental leukemia), the new clinical diagnosis should be reported as an AE rather than the laboratory abnormality.

8.3. FOLLOW-UP OF SAFETY PARAMETERS

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

8.3.2. 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.

8.3.3. 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 pregnancies should be reported using the Sobi AG Pregnancy form. Pregnancies should be followed until conclusion to obtain outcome information.

No patient will be withdrawn from the study due to pregnancy.

In the event of a pregnancy of a patient still receiving NI-0501, the IMP administration will be discontinued and the patient will enter the 4 week follow-up and then the long-term follow-up periods.

9. BENEFIT/RISK MANAGEMENT

9.1. POTENTIAL BENEFITS

As this study is intended to monitor the long-term safety following the administration of NI-0501, as well as the impact on survival, the main benefit for the patient is to be closely monitored, enabling the early detection of a potential issue.

However, in case the patient would continue to receive NI-0501 in the context of this study after having successfully completed the NI-0501-04 protocol, the expected benefit is to maintain the therapeutic effects of NI-0501 treatment, enabling transplantation to be performed without using immune chemotherapy that has short and long term risks.

9.2. RISKS ANALYSIS

As NI-0501 is a monoclonal antibody and is characterized by a long half-life, the Investigator should be aware of the risks reported below.

9.2.1 Risks related to the target

IFNγ neutralization by NI-0501 clinically mimics that of complete IFNγ deficiency.

Patients with IFNγ R deficiency are prone to developing mycobacterial infections and, although to a lesser extent, *Salmonella* infections[12;13].

The mean age of a first infection is 3.1 and 13.4 years in patients with complete and partial deficiency, respectively. No systematic prophylaxis has been recommended in these patients.

If infection occurs, appropriate antibiotic treatment based on sensitivity of isolated species is prescribed. In this patient population infections usually respond to antibiotics, however they often relapse when antibiotics are discontinued[14].

Toxicological studies carried out with NI-0501 have shown an increased susceptibility to enteral pathogen infection when the pathogen is already latent in the intestinal tract. However this risk is considered to be of limited relevance to humans.

To date, NI-0501 has been administered to Healthy Volunteers (14 subjects) in a single ascending dose study, which confirmed the absence of off-target toxicity. However, a reactivation of *herpes zoster* (HZ) virus was observed in one healthy volunteer at a dose of 3 mg/kg, and it may have been due to the pharmacological effect of the drug. Although it is difficult to draw firm conclusions from this one case, prophylaxis against HZ for all patients, as long as the activity of NI-0501 is measurable, is to be maintained in the context of this study.

In addition, as of 30 June 2017, NI-0501 has been administered to 34 patients (16 M, 18 F) in study NI-0501-04. Infections reported by HLH patients during or after administration of NI-0501 are commonly observed in immunocompromised patients or described in pediatric population (seasonal viral infections). They did not prevent initiation of NI-0501 treatment when present prior to the first infusion, and did not result in the discontinuation or dose decrease of NI-050, except in one patient who has experienced a disseminated histoplasmosis which has resulted into treatment discontinuation; infection resolved with proper antifungal treatment. Infections resolved when treated appropriately and not associated with a refractory disease status. Severe infections were generally reported in patients with previous recent significant exposure to immunosuppressive treatments as they added an additional risk factor for infection development.

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

For patients originally enrolled in study NI-0501-04 who will continue receiving NI-0501 \ (Section 3.1), the risk analysis described in the NI-0501-04 study protocol will apply unless new information is available. This information will be part of the Development Safety Risk Management Plan.

9.2.2 Risk related to the study population

Most of the patients are expected to be children of a young age, affected by a life-threatening disease. They may have already received the conventional treatment regimen for HLH. All information collected with regards to disease stage and previous treatments will be taken into account for the analysis of AEs. Duration of NI-0501 treatment will also be taken into account. Concomitant medications given during or after the administration of NI-0501 may also potentially expose patients to AEs; however their benefits may outweigh their risks.

At present, the potential impact of NI-0501 treatment on conditioning and Transplantation is unknown.

9.2.3 Risk minimization measures

The risks listed above, in view of the expected benefits, are considered to be manageable in this patient population, if adequate prevention and minimization measures are put in place. The following specific measures have been introduced to minimize the patient's risk:

- Patients are cared for in specialized centers for the treatment of HLH, which are used to managing severely immuno-compromised patients
- Prophylaxis for *herpes zoster* to avoid occurrence of these infections will be administered as long as deemed necessary, either because of residual NI-0501 activity or because of the patient's current treatment
- Close monitoring of potential infections through careful physical examination and monitoring of laboratory parameters

The NI-0501 Development Safety Risk Management Plan will address 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.

Risk minimization measures as described in corresponding protocol section of the NI-0501 study the patients were part of (e.g. section 9.5.2.3 of NI-0501-04-US-P-IND#111015 protocol) still apply in the event that patients continue receiving NI-0501 treatment beyond the foreseen 8 weeks in study NI-0501-04, upon request of the Investigator, providing a favourable benefit/risk has been established.

10. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

Full details of all statistical aspects and planned statistical analyses will be specified in a separate Statistical Analysis Plan (SAP), which will be finalized prior to the locking of the study database. This section contains an overview of the planned methods of analysis.

Statistical methods will focus on summarizing the data collected, using appropriate graphical and tabular presentations. For measurements of continuous endpoints, summary statistics will include n, mean, median, standard deviation, minimum and maximum values. Duration of Response and Survival time will be presented using Kaplan-Meier curves with medians calculated if available. 95% confidence intervals will be calculated for the median for each of these endpoints. Endpoints based on binary outcomes, including post-HSCT outcome measures, will be converted to proportions and associated 95% confidence intervals calculated.

Data collected in this study may be analyzed on multiple occasions as the study proceeds, in order to facilitate the development program for NI-0501 and to optimize the dissemination of information which may help patient care. The timing and nature of these interim analyses cannot be specified in advance and will depend on the numbers of patients recruited into the study and the nature of the outcomes seen.

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.

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

All PD data will be summarized using appropriate graphical and tabular presentations. Exploratory statistical models may be fitted, and correlation analyses undertaken, to investigate the relationships between PD data, other biomarkers and other endpoints recorded in the study.

Other exploratory analyses of data collected in this study, including summaries for various subsets of patients, may also be conducted, including comparisons with appropriate historical data extracted from published literature, from external databases, and from other studies, if considered appropriate.

No imputations of missing data will be performed.

11. ETHICAL AND LEGAL ASPECTS

11.1. 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 authorised 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 outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) 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.

11.2. INVESTIGATOR'S RESPONSIBILITIES

The Investigator should 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. 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 authorized representative) who have signed an informed consent document to enter the study. Patients not participating in the NI-0501-05 study, despite having participated in a previous NI-0501 protocol, must have the reason(s) recorded in their source documents and the study participant log.

In the event that N-0501 treatment needs to be prolonged beyond Week 8, the treating physician has to comply with local requirements and regulations. The Investigator should maintain source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete.

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

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

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 patient' records (e.g. medical/hospital records, office charts, hospital charts, and study-related charts) for source data and other types of verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

11.3. CONSENT

Before being admitted to the clinical study, the patient must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent document that includes both information about the study and the consent form will be prepared and given to the patient. This document will contain all ICH, GCP, and locally required regulatory elements (whichever are most stringent). The document must be in a

language understandable to the patient 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 summarizes the content of the Patient Information Sheet and is used to obtain the dated signature from the patient as evidence of the patient's agreement to 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 in the clinical trial center's Trial Master File (TMF).

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

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

11.4. 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 authorization 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.

11.5. PROTOCOL AMENDMENTS

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

11.6. 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 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 initiate the NI-0501-05 study at any site which has already participated in a previous NI-0501 clinical trial or a CU treatment protocol, as soon as Sobi AG, or their authorized representative, has received documentation on all ethical and legal requirements for starting the study at this site.

Sobi AG can only supply NI-0501 to an Investigator of an initiated site and for patients requiring, as per the treating physician's request, to continue receiving NI-0501 beyond the 8-week treatment in study NI-0501-04.

This documentation must also include a list of the members of the IRB and their occupations and qualifications. If the IRB 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 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). Before the first patient is enrolled in the study, all ethical and legal requirements must be met.

The IRB 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 and, if applicable, between a coordinating Investigator and the IRB. This statement also applies to any communication between the Investigator (or coordinating Investigator, if applicable) and regulatory authorities.

Before any documents are given to patients or their legal representative, they must first be reviewed and approved by Sobi AG, and upon approval by Sobi AG, submitted to and reviewed and approved by the competent IRB. These include but are not limited to the informed consent form, patient information sheet, assent form, advertisements, training materials, etc.

11.7. ONGOING INFORMATION FOR IRB

If required by legislation or the IRB, the Investigator must submit to the IRB:

- 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 subjects.

11.8. 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, regulatory authorities).

11.9. 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
- Composition of the IRB
- 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, if applicable
- Record of any body fluid 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's TMF.

11.10. LIABILITY AND INSURANCE

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

11.11. 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 clinical trial and for one year following the completion of the study.

11.12. 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.

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

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.

12. MONITORING AND AUDITING

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

12.1. 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 study related documents (e.g. IRB correspondence, investigational product and supplies shipment manifests if applicable, monitoring logs, or correspondence with Sobi AG and with any of its representatives for this study, etc).

12.2. ON-SITE AUDITS

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

12.3. 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 and/or the scientific value of the study, Sobi AG must be notified within 24 hours.

13. DOCUMENTATION AND USE OF STUDY FINDINGS

13.1. DOCUMENTATION OF STUDY RESULTS

All required information must be entered in the CRFs provided to record data for each subject. 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 in the CRF will be entered into the study database. If the Investigator authorizes 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 authorized representative before these individuals start completing CRF information.

The CRF pages must be reviewed and signed by the Investigator named in the study protocol or by a designated sub-investigator. Sobi AG will ensure that the CRF copies left with the Investigator (print-outs and/or CD-ROM) have never been under the direct or indirect control of Sobi AG.

13.2 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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15.APPENDICES

Appendix A - Schedule of Assessment for patients still continuing NI-0501 treatment

Appendix B - Investigational Medicinal product administration and handling

APPENDIX A – SCHEDULE OF ASSESSMENTS FOR PATIENTS STILL CONTINUING NI-0501 TREATMENT

Assessments		NI-0501 infusion visit	Efficacy/Safety visit[12]	Follow-Up post NI-0501 completion				
				Week 1[13]	Week 2[13]	Week 3[13]	Week 4 or Withdrawal[13&14]	Unscheduled visit (UV)
Laboratory procedures	Safety[1]		X	X	X	X	X	
Clinical assessment	Vital signs[2]	X	X	X	X	X	X	X[9]
	Continuous cardiac monitoring/pulse oxymetry[3]	X						
	Physical Examination[4]	X	X	X	X	X	X	X[9]
Procedure	ECG	X at the last infusion day only[10]					X[11]	
Search for infections	TB[5], Adenoviruses, EBV, CMV[6]		X at least every 2 weeks		X		X	
Imaging	Chest X-ray		X every 3 weeks	X if not performed at previous visit			X	
PK[7]		X pre and post inf. every 2 infusions			X		X	
PD[7, 8]		X post inf. every 2 infusions			X		X	
ADA (Immunogenicity)							X	

Please note: timing of the assessments may be adapted/adjusted depending on NI-0501 schedule of administration

1 = Safety: CBC and hemoglobin; coagulation tests (aPTT, PT, and fibrinogen); inflammatory markers such as CRP and ferritin; biochemistry: glucose, triglycerides and liver enzymes, total bilirubin, albumin, creatinine and urea, as well as urinalysis (protein, glucose, blood, ketones, leucocytes, pH and specific gravity).

2 = Vital signs: Temperature, heart rate, blood pressure, respiratory rate and skin aspect (rash, coloration and sweating). Oxygen saturation at infusion visits only. At infusion visit, to be measured pre infusion, during infusion about every 15 minutes until completion of infusion, and 4 hours post infusion. Patients can be discharged 4 hours after infusion upon decision of the treating physician.

3 = Continuous cardiac monitoring/pulse oxymetry: pre infusion, during infusion, and post infusion up to 4 hours after infusion

4 = Physical Examination: Particular attention paid to height (at last infusion visit and at week 4 or withdrawal visit), weight (at each infusion visit and at week 4 or withdrawal visit as well as at unscheduled visits), occurrence of edema or ascites, occurrence of signs of infections (e.g. tonsillitis, lymphadenopathies, cough and/or dyspnea), neurological examination, liver and spleen size (in cm from costal grill).

5 = TB: search for tuberculosis mycobacteria by either PCR in any relevant specimen (e.g. blood, urine, broncho-alveolar lavage, gastric aspirate) or any method agreed to be used in the parent protocol or CU treatment protocol at a given site

6 = Adenoviruses, EBV, CMV: search by quantitative PCR

7 = PK and PD: sampling times may be adjusted if required

8 = PD will look at IFNγ circulating levels and potential markers of disease activity (e.g. sCD25, CXCL10, CXCL9, CXCL11, IL-10…).

9 = Vital signs and physical examination will be performed *at minimum*, but additional assessments may be added according to the clinical judgment of the Investigator.

10 = ECG: to be done on the last NI-0501 infusion day as long as an ECKG has NOT been performed within the past 4 weeks.

11 = ECG: to be performed at the Week 4 follow-up visit. In case of withdrawal prior to this Week 4 follow-up visit, an ECG is to be done at the withdrawal visit as long as an ECG has NOT been performed within the previous 4 weeks.

12 = Efficacy/safety visits should occur every 6 days but can be combined with infusion visits, if infusion are separated by no more than 7 days

13 = Assessments can be performed within 24h before or after the planned time-point during **the follow-up Period.** If the conditioning starts during the short term follow-up period and is not separated by more than 48h from a weekly follow-up visit, then the follow-up visit and the pre conditioning visit may be combined and all assessments scheduled for each individual visit should be performed. The same process applies if the Transplant occurs during the short term follow-up period. Then the patient will start to be monitored for the long term follow-up period according to the remaining visits to be performed in the SOA presented in table 1.

14 = If a patient withdraws or is withdrawn at any time from the study, he/she will be asked to attend one last visit (i.e. equivalent to Week 4 visit) so that all final assessments can be performed.

APPENDIX B - INVESTIGATIONAL MEDICINAL PRODUCT (IMP) PREPARATION AND HANDLING

Description of the Investigational Medicinal Product (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 Sobi AG and supplied to study sites in 2 mL-filled and 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.

Dosing Regimen

NI-0501 will be administered by infusion over a period of one hour (or more depending on the volume to infuse) at a dose either carried forward from the last administered NI-0501 dose as part of the NI-0501 treatment study the patient was enrolled in, or at an adjusted dose if necessary and depending on NI-0501 PK profile.

NI-0501 infusions will be performed at a dose and frequency which will be determined by the Sponsor based on the observed PK profile of the drug and on patient's clinical response.

IMP Handling

Packaging and Labeling

NI-0501 will be supplied to study sites in glass vials. Labeling and packaging will be prepared to meet local regulatory requirements.

IMP Supply

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

IMP Receipt and Storage

The NI-0501 vials will be transported with temperature deviation alarms (TempTale 4 or equivalent device) in order to ensure consistent temperatures during transit. When the study drug is received at the site, the Investigator, Pharmacist or appropriate delegate will check for accurate delivery and absence of temperature deviation alarm.

The study drug is to 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, responsible study monitor or contract research organisation (CRO). Affected vials should not be used and quarantined until the Sponsor has authorized their use.

Regular inspections of the NI-0501 vials are required (please refer to the study specific drug/pharmacy manual for more details).

IMP Preparation, Administration, Accountability and Destruction

Full instructions for the preparation, administration, accountability and destruction of NI-0501 will be further described in a study specific drug/pharmacy manual.