A randomized, double-blinded, placebo-controlled, single center, phase I study to evaluate pharmacokinetics, pharmacodynamics and safety of emapalumab after a single intravenous dose in Japanese healthy volunteers.

Final Protocol Number: Sobi.EMAPALUMAB-102

Type of Study: **Phase I**
Compound NI-0501 Sponsor; Swedish Orphan Biovitrum AB
Version 1.0 8 Sep 2020

Sponsor's Medical Director

[redacted]

Signature Date

Principal Investigator

[redacted]

Signature Date

Investigator statement

I have read the protocol entitled "A randomized, double-blinded, placebo-controlled, single center, phase I study to evaluate pharmacokinetics, pharmacodynamics and safety of emapalumab after a single intravenous dose in Japanese healthy volunteers" and the accompanying current IB. I agree to conduct the clinical investigation in compliance with the Final Protocol, Version 1.0 4 Sep ICH harmonized guideline E6(R2): GCP [1], applicable regulatory/government regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki [2]. I will not implement any changes to study procedures or conduct without prior approval from the sponsor and, when applicable, the IRB and Regulatory Authority. I will supervise any individual or party to whom I delegate study-related duties and functions conducted at the study site and ensure qualification of individuals or parties who perform delegated tasks.

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

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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1 Synopsis

STUDY IDENTIFIERS	
Title of study:	A randomized, double-blinded, placebo-controlled, single center, phase I study to evaluate pharmacokinetics, pharmacodynamics and safety of emapalumab after a single intravenous dose in Japanese healthy volunteers.
Clinical study number:	Sobi.emapalumab-102
Type of study:	Phase I; Human pharmacology
STUDY OBJECTIVES	
Primary objective:	To evaluate the pharmacokinetics and pharmacodynamics of emapalumab in healthy Japanese subjects following a single intravenous dose of emapalumab
Secondary objective(s):	To assess safety in healthy Japanese subjects following a single intravenous dose of emapalumab To investigate immunogenicity of emapalumab
STUDY ENDPOINTS	
Primary endpoint:	PK parameters: Cmax, tmax, CEOI, AUClast, AUCinf, %AUCextr, λz, t½, CL, Vss, MRTlast and MRTinf PD biomarkers: Pre-dose circulating IFNγ concentration Total IFNγ concentrations CXCL9 concentration sIL2R concentration
Secondary endpoint(s):	Adverse Events Laboratory parameters The presence of anti-drug antibodies (ADAs) and neutralizing antibodies (nAbs)
STUDY DESIGN AND METHODS	
Study design:	This is a randomized, placebo controlled and double-blinded study to evaluate the PK, PD and safety of a single dose (1 mg/kg) of emapalumab in adult healthy Japanese subjects.
Number of subjects planned:	8

Diagnosis and main criteria for inclusion:	Healthy volunteers, age between 20 to 50 (inclusive)
Assessments for pharmacokinetic (PK) and pharmacodynamics (PD) evaluation:	Serum concentration vs time profiles are obtained for determination of emapalumab PK/PD variables at Study Days 1, 2, 3, 5, 8 and Weeks 2, 4, 6, 10 and 14.
Assessment for safety evaluation:	Adverse events are collected from the time of investigational product administration until last study visit (Week 14) Heart rate, blood pressure, body temperature are assessed at Screening, Study Day -1 prior to the infusion, every 30 minutes after infusion up to 2 hours post infusion, every hour from 4 hours post infusion up to 8 hours post infusion, 10 and 12 hours post infusion, Study Days 2, 3, 5, 8, Weeks 2, 4, 6 and 14. Blood and urine samples for local laboratory analyses of hematology, clinical chemistry and coagulation are collected at Screening, Study Days -1, 1, 2 ,3 ,5 ,8, Weeks 2, 4, 6, 10 and 14 12-lead ECGs are obtained at Screening, prior to the infusion on Study Day 1, after the infusion, and at last study visit (Week 14) A physical examination will be performed at Screening, Study Day -1 and at last study visit (Week 14) Blood samples for central laboratory analyses of ADAs are collected at Study Day -1 pre-infusion and at Week 14.
Test product; dose and mode of administration:	Emapalumab 5 mg/mL for i.v. infusion
Reference product; dose and mode of administration:	Saline 0.9% for i.v. infusion
Duration of treatment(s):	Single dose
Determination of sample size:	No formal sample size calculation. 6 subjects receiving emapalumab are considered sufficient, considering the inter-subject variability in the PK results from earlier studies.
Statistical methods:	No formal statistical hypothesis testing will be performed. All endpoints will be summarized with descriptive statistics and presented individually in listings.

2 Abbreviations and definition of terms

2.1 List of Abbreviations and definitions

Term	Definition
AE	Adverse event
ADA	Anti-Drug Antibodies
BLA	biologics license application
CDASH	Clinical data acquisition standards harmonization
CDISC	Clinical data interchange standards consortium
CEOI	Concentration at end of infusion
CRO	Contract research organization
CRF	Case report form
EOT	End of Treatment
GCP	Good clinical practice
HED	Human Equivalent Dose
HLH	Hemaphagocytic Lymphohistiocytosis
HSCT	Hematopoietic stem cell transplantation
HZ	Herpes Zoster
ICH	International Council for Harmonisation
IRB	Independent review board
IRR	Infusion Related Reaction
IMP	Investigational medicinal product
LOQ	Limit of Quantification
MAA	Market Authorization Application
MAS	Macrophagic
NOAEL	No Observed Adverse Effect Level
ORR	Overall Response Rate
PD	Pharmacodynamics
PK	Pharmacokinetics
SAE	Serious adverse event

sIL2R	Soluble IL2 receptor
SJIA	Systemic Juvenile Idiopathic Arthritis
Sobi	Swedish Orphan Biovitrum AB (publ)
SUSAR	Suspected Unexpected Serious Adverse Reaction

3 Ethics

3.1 Institutional review board

It is the responsibility of the investigator to obtain approval of the study protocol, possible amendments and the written subject information and informed consent form from the IRB. The investigator should file all correspondence with the IRB. Copies of IRB correspondence and approvals should be forwarded to the CRO.

3.2 Ethical conduct of the study

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

3.3 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

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

3.4 Subject information and consent

It is the responsibility of the investigator to, prior to any study-related activities, give each subject , full and adequate verbal and written information regarding the objective and procedures

of the study and the possible risks involved. The subjects must be informed about their right to withdraw from the study at any time. The written subject information and/or informed consent form must not be changed without prior discussion with Sobi. Before any revisions are implemented, the revised written subject information and/or informed consent form must be approved by the IRB.

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

4 Introduction

4.1 Background

4.1.1 Hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome of pathologic immune activation. HLH comprises primary (genetic/familial) HLH and secondary HLH (sHLH), both clinically described as dysregulations of the immune system leading to a profound hypercytokinemia with deleterious consequences on various tissues and organs (3).
Primary HLH (pHLH) is a heterogeneous autosomal recessive disorder characterized by a severe impairment or absence of cytotoxic function by natural killer (NK) and CD8+ T cells with striking activation of the immune system. Primary HLH is mostly seen in infancy and early childhood with an estimated prevalence in Europe of 1/50,000 live births (4). In Japan, as well as ex-Japan, primary HLH is an extremely rare disease with an annual incidence of approximately 0.342/100,000 live births (5) The disease is invariably fatal if untreated, with a median survival of less than 2 months after diagnosis (6, 7).
Typical features of HLH are (8):

- Prolonged fever
- Organomegaly
- Cytopenia
- Hyperferritinemia
- Hypertriglyceridemia
- Hypofibrinogenemia
- Lymphohistiocytic infiltrate, bone marrow hypoplasia, meningeal infiltrate
- Hypercytokinemia.

There is mounting evidence supporting the pivotal pathogenic role of interferon gamma (IFNγ) in the development of both primary (9, 10) and secondary forms of HLH (11-14).

No drugs had been specifically developed and approved for the treatment of HLH until

emapalumab was approved in the United States for the treatment of refractory, recurrent or progressive pHLH in November 2018. Nonetheless during the last decades, experts in the field have established guidelines for the management of HLH patients (8, 15, 16)

Despite adoption of the above guidelines, no significant improvement in mortality rates has been seen for primary HLH during the last 20 years. The overall mortality rate for pHLH remains high, around 40%, as shown by the results of the HLH-1994 and of the HLH-2004 studies and as reported for the HIT study (16, 17) . The known short- and long-term toxicities, in particular myelosuppression and immunosuppression, of the current treatment of HLH further contributes to the already high mortality (18, 19).

There is a high unmet need to develop a targeted treatment for HLH that ensures efficacy and less toxicity than available compounds.

4.1.2 Emapalumab

4.1.2.1 Description and Mode of Action

Emapalumab (previously referred to as NI-0501) is a fully human immunoglobulin G1 (IgG1) anti-interferon gamma (IFNγ) monoclonal antibody which binds and neutralizes IFNγ. Emapalumab binds to both free and receptor (IFNγR1)-bound forms of IFNγ.

Since emapalumab is a human IgG1, it retains the characteristics of this immunoglobulin isotype, including the capacity to engage Fcγ receptors and to bind complement.

IFNγ is produced predominantly by NK and NK T cells, as part of the innate immune response, and by CD4 Th1 and CD8 cytotoxic T lymphocyte effector T cells, once antigen-specific immunity develops. IFNγ is one of the most potent and pleiotropic cytokines of the immune system. 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 (20-22).

4.1.2.2 Preclinical data

4.1.2.2.1 Non-clinical pharmacology

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

Due to emapalumab capacity to bind free and IFNγR1-bound IFNγ, studies were performed to investigate the potential of emapalumab to mediate antibody-dependent cell-mediated 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.

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

4.1.2.2.2 Toxicology

Binding and functional data demonstrated Rhesus and 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. Shigella and Campylobacter infections were observed at all dose levels (10 to 200 mg/kg/week) in animals originally harboring gastrointestinal pathogens (Shigella, Salmonella, Campylobacter) prior to emapalumab administration. These findings were assessed to be in line with emapalumab pharmacological effect (i.e., neutralization of IFNγ), given the role played by IFNγ in controlling these pathogens. Subsequently, in a study where cynomolgus monkeys were free from gastrointestinal pathogens at Screening, weekly administrations of emapalumab for 8 consecutive weeks at doses up to 30 mg/kg were well tolerated with no toxicity or gastrointestinal disturbances observed, and no need for antibiotic prophylaxis.

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.

Embryo-fetal development, fertility and early embryonic development as well as peri- and post-natal development studies were performed in mice. No effects on embryo-fetal development, mating or fertility were observed. No effects on sexual maturation, organ weights, learning and memory, reproductive or immunological functions evaluated in the F1 generation mice were observed.

More details are available in the current version, 10.0 dated 24Jan2020, of the Investigator Brochure.

4.1.2.3 Clinical Data

Since the start of the clinical development program for emapalumab, more than 100 patients have received emapalumab in clinical trials and through compassionate use. Furthermore, more than 70 patients have been treated to date in the US following FDA approval, and post-marketing surveillance has not revealed any additional safety concerns with the use of emapalumab

Emapalumab has been granted Orphan Drug Designation in the United States (US) on 26 March 2010 and in Europe (EU) on 09 June 2010. Emapalumab has obtained Breakthrough designation in US on 11 March 2016 and PRIME designation in EU on 26 May 2016.
On 20 November 2018 the FDA approved emapalumab 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.

The FDA approval was based on data from study NI-0501-03, interim data from the pivotal study NI-0501-04 and interim data from the long-term follow-up study NI-0501-05.

Study NI-0501-03 was a phase 1 randomized double-blinded placebo-controlled single ascending dose study, in 20 healthy adult volunteers investigating the safety, tolerability and pharmacokinetic (PK) profiles of single intravenous (IV) administrations of emapalumab took place between September 2011 and January 2013. During this study, 6 subjects received placebo, while 3, 3, 4, and 4 subjects (in total 14 subjects) received emapalumab doses of 0.01, 0.1, 1, and 3 mg/kg, respectively.

Emapalumab PK data from healthy volunteers were evaluated using a population modeling approach. The PK of emapalumab was best described by a two-compartment model (NI-0501-03 - Modelling and Simulation support to NI-0501 PK analysis of study NI-0501-03). In healthy volunteers, emapalumab has the typical PK profile expected for a mAb, with low central and peripheral volumes of distribution (3.02 L and 2.83 L), slow clearance (0.007 L/h) and long distribution and terminal half-lives (1.55 and 25.4 days).

In placebo-treated subjects, mean total IFNγ levels (which represents free IFNγ in the absence of emapalumab) ranged from 60.09 pg/mL to 125.2 pg/mL, showing no visible trend over time. In contrast, in subjects on emapalumab, total IFNγ levels (which to the majority represents IFNγ bound to emapalumab due to the marked emapalumab molar excees of IFNγ) started to increase within 24 hours post-dosing. The maximal mean level of total IFNγ of 1013.6 pg/mL was reached at Week 8 post-dosing for the subjects who received a dose of 1 mg/kg and maximal mean level of 1011.2 pg/mL was reached at Week 4 post-dosing for the subjects who received a dose of 3 mg/kg.

The infusions of emapalumab were 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 Herpes Zoster was reported as a serious adverse reaction in the highest dose group (3 mg/kg). Its intensity was moderate and healed with antiviral therapy. The subject recovered with no sequelae. An increased susceptibility to HZ infections in patients having developed auto-antibodies against IFNγ (23) or having received ustekinumab (a monoclonal antibody which decreases IFNγ production by inhibiting the p40 subunit of IL-12) has been described in the literature (24).

In conclusion, no safety signal emerged from the safety parameters (AEs, clinical laboratory evaluations, vital signs and ECG analysis) collected during the follow-up period extended up to week 44 after emapalumab infusion. The tolerability/safety profile, as well as the PK characteristics observed after administration of emapalumab in healthy volunteers supported the continuation of the development program for emapalumab for the treatment of HLH.

Study NI-0501-04 was designed to investigate the safety and tolerability profile of multiple intravenous (IV) administrations of emapalumab and its efficacy in primary hemophagocytic lymphohistiocytosis (pHLH) patients. The evaluation of the pharmacokinetic (PK) profile and the pharmacodynamic (PD) effects of emapalumab is also an important objective of the study to define the appropriate therapeutic dose regimen for the treatment of pHLH patients. The study has been conducted according to twin protocols in EU and in the US.

Study NI-0501-05 is a long-term, follow-up study that includes patients treated in Study NI-0501-04. Of note, HLH patients who received emapalumab treatment in the pilot NI-0501-06 study (patients with systemic Juvenile-onset Idiopathic Arthritis developing Macrophage Activation Syndrome) and in compassionate use (CU) were also followed-up long-term in this study. The objectives of the long-term follow-up NI-0501-05 study are the long-term monitoring of the safety profile in patients treated with emapalumab, the assessment of survival after emapalumab treatment, the assessment of emapalumab immunogenicity and the evaluation of its elimination profile.

Study NI-0501-04 was completed on 04 January 2019 (last patient last visit, LPLV). Study NI-0501-05 is ongoing; data provided in this CSR are based on a database cut-off date of 31 January 2019, at which date 7 patients originally enrolled in the NI-0501-04 are still ongoing.

Therefore, overall, 45 patients were treated whereof 11 (24.4%) were treated as first-line patients and 34 (75.6%) as second-line patients. A total of 35 (77.8%) patients completed Study NI-0501-04, i.e.,

- completed emapalumab treatment, i.e., received a minimum of 4 weeks of treatment (from SD0 to EOT) unless discontinued subsequently due to lack of efficacy or safety reason, and
- completed the 4-week short-term follow-up or continued treatment in the NI-0501-05 study.

The safety profile of emapalumab is favorable in this fragile, immunocompromised patient population, requiring high number of co-medications and procedures. Infusions were in general well tolerated, no anaphylaxis or severe hypersensitivity reaction have been associated with any emapalumab infusion, the IRRs being mild, self-limiting and not requiring any treatment at any of the doses administered.

Infections caused by pathogens reported to be potentially favored by neutralization of IFNγ occurred in 1 patient with Histoplasmosis disseminated during the course of emapalumab treatment and in 1 patient with Salmonella gastroenteritis during the long-term follow-up after HSCT; both infections resolved.

No patient reported Varicella or Herpes Zoster, including patients who could not receive the recommended anti-viral prophylaxis due to the presence of contraindications.

Emapalumab administration did not appear to be associated with any organ/function toxicity and emapalumab treatment was not discontinued as a result of any cardiac, respiratory, liver or renal events

Study NI-0501-06 is a phase 2 study in sJIA patients with MAS/sHLH who have shown an inadequate response to high-dose glucocorticoid treatment. As of 01 of July 2020, a total of 9 patients have been completed the study. In all 9 patients, complete response was achieved. Systemic glucocorticoids were weaned in all patients. Emapalumab infusions were well tolerated and none of the patients discontinued emapalumab prematurely. A CMV reactivation was reported by investigator as a serious event possibly related to emapalumab, but resolved completely with treatment (25).

For more details on the clinical experience, see Investigator's Brochure version 10.0, 24 Jan 2020.

4.2 Study rationale

The primary objective of the study is to evaluate PK and PD in Japanese Healthy subjects, and the results of this study will be compared with the results of the non-Japanese phase I single-dose study (NI-0501-03). As there is no experience using emapalumab in Japanese subjects it is important to compare the PK and PD of emapalumab data between Japanese and non-Japanese subjects to confirm comparable PK and PD properties.

4.3 Rationale for Herpes Zoster prophylaxis.

One Healthy Volunteer reported Herpes zoster infection of moderate intensity after a single emapalumab infusion of 3 mg/kg during the NI-0501-03 study. The event resolved upon treatment and was considered related to emapalumab (IFNγ neutralization suspected to favor emergence of the infection).

Patients treated with emapalumab are recommended prophylactic treatment with valaciclovir to prevent reactivation of Herpes zoster. Studies with valaciclovir as Herpes zoster prophylaxis have been performed in Japan with prophylactic treatment up to one yea (26). The benefit of valaciclovir prophylaxis is judged to exceed the risks with Herpes zoster reactivation.

4.4 Potential risks and benefits

The healthy volunteers will not derive any therapeutic benefit from participating in the study. However, every effort will be made to minimize potential risk(s) to subjects participating. Emapalumab is approved by FDA since November 2018, for the treatment of patients with primary HLH who have refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.

Since the start of the clinical development program for emapalumab, more than 100 patients have received emapalumab in clinical trials and through compassionate use. Furthermore, more than 70 patients have been treated to date in the US following FDA approval, and post-marketing surveillance has not revealed any additional safety concerns with the use of emapalumab. Based on the analyses conducted to date, no sign of any off-target effect of emapalumab has been detected.

Subjects in the proposed phase I study will receive a single dose of 1 mg/kg, as compared with dose up to 10mg/kg used in other studies with no safety concerns.
Potential risks based on emapalumab's mechanism of action are presented below.

- Infusion related reactions and hypersensitivity
  Up to the 24-Aug-2019, cumulatively, a total of 1290 emapalumab infusion have been administered in clinical trials and 13 of the 62 study subjects (21.0 %) treated had experienced at least 1 IRR. No serious hypersensitivity reactions such as anaphylactic or anaphylactoid reactions have been reported. Patients should, however, not be re-exposed to the investigational treatment in case of hypersensitivity to emapalumab or any of the excipients.
  The most frequently reported IRRs were cutaneous reactions coded drug eruption, rash or erythema or erythematous rash, hyperhidrosis or pyrexia.

- Majority of IRRs were of mild or moderate intensity. IRRs did not prevent administration of the full dose of emapalumab. All IRRs resolved. No specific premedication is required prior to emapalumab administration.

- Infections
  As emapalumab neutralizes IFNγ activity, emapalumab may increase the risk of infections caused by some specific pathogens potentially favored by IFNγ neutralization including mycobacteria (typical and atypical), salmonella, herpes zoster, and Histoplasma capsulatum. Among the 103 subjects treated with emapalumab up to 24-Aug-2019, 1 patient had developed disseminated histoplasmosis which resulted in treatment discontinuation. The infection resolved with adequate antifungal therapy while emapalumab was still at measurable concentrations in blood. One case of Herpes Zoster infection was reported in the phase 1 study in healthy volunteers (study NI-0501-03), as described above. Study specific requirements should be followed for infections screening, prophylaxis and monitoring.

- Immunogenicity
  The development of ADAs can impact both safety and PK properties of a drug. Antibodies against emapalumab have been detected in 1 out of 14 healthy subjects (7.1%) after administration of a single dose of emapalumab. The analyses performed up to the 24-Aug-2019 on HLH subjects treated in the NI-0501-04/05/06 studies have detected the presence of ADAs in 3 of 49 subjects (6.1 %). In none of the subjects was the presence of ADA associated with any AEs or significant changes in the PK profile, and ADA titers were generally low.

  For the most recent information about emapalumab, please refer to the current Investigator´s Brochure. The current risk benefit analysis supports this clinical trial to evaluate PK, PD and safety of emapalumab in Japanese healthy subjects.

5 Study objectives and endpoints

5.1 Primary objective

- To evaluate the pharmacokinetics and pharmacodynamics of emapalumab in healthy Japanese subjects following a single intravenous dose of emapalumab

5.1.1 Primary endpoint

- PK parameters: Cmax, tmax, CEOI, AUClast, AUCinf, %AUCextr, λz, t½, CL, Vss, MRTlast and MRTinf.
- PD biomarkers:
  - Pre-dose circulating IFNγ concentration
  - Total IFNγ concentrations
  - CXCL9 concentration
  - sIL2R concentration

5.2 Secondary objectives

- To assess safety in healthy Japanese subjects following a single intravenous dose of emapalumab
- To investigate immunogenicity of emapalumab.

5.2.1 Secondary endpoints supporting the secondary objective(s)

- Adverse Events
- Laboratory parameters
- The presence of anti-drug antibodies (ADAs) and neutralizing antibodies (nAbs)

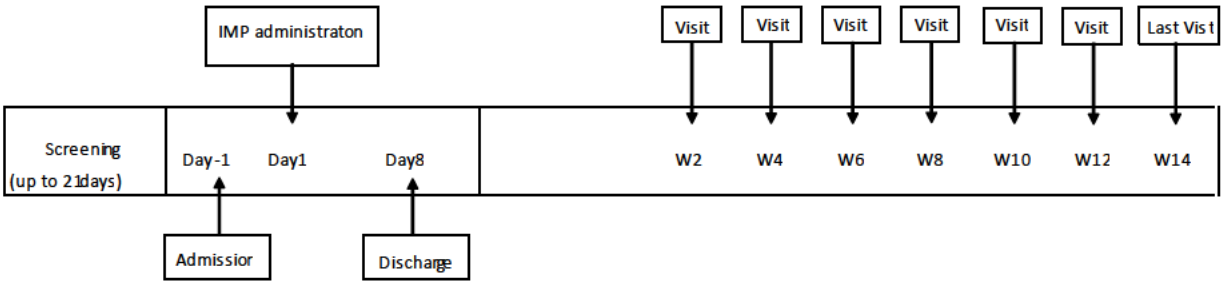
6 Investigational plan

6.1 Overall study design and plan

This is a randomized, placebo-controlled and double-blinded study to evaluate the PK, PD and safety of a single dose (1 mg/kg) of emapalumab in adult healthy Japanese subjects, performed in Japan. The subjects, 8 in total, will be randomized to receive either emapalumab or matching placebo in a 3:1 ratio (emapalumab: placebo).

Figure 1 shows the study design.
Study subjects will be screened within 21 days prior to administration of investigational medicinal products (IMP). An additional visit will take place within 96 hours prior to IMP infusion for collection a PCR test for SARS-CoV-19. Eligible subjects will be admitted to the clinical unit the day before drug administration (Study Day -1). On Day 1 of the admission period subjects will receive a single dose of emapalumab (1 mg/kg) or placebo administered as a 1-hour infusion. Subjects will be discharged from the unit on Day 8. PK samples will be collected for up to week 14 in order to measure the emapalumab serum levels during at least 3 times the terminal half-life (a total of approximately 3 months). All subjects will be followed-up on regular visits for a minimum of 14 weeks after single infusion of emapalumab. In addition, any subject with ongoing SAEs at study completion will be followed-up until resolution.

Figure 1 Study Design



6.2 Dosing Strategy

Since more than 100 patients have been treated and there are no significant safety concerns, a sentinel dosing strategy is not planned for the study. The investigator will evaluate safety and tolerability data (AEs, laboratory data, vital signs, and ECG) continuously in the study and determine if it remains acceptable to continue dosing.

In case emergency unblinding of IMP is required, the investigator will have access to randomization codes (in sealed envelopes).

6.3 Stopping Rules

The trial may be prematurely terminated if warranted on safety grounds. The severity of the observed events shall be graded as mild, moderate or severe.
Dosing will be stopped in the event of:

- One or more subjects demonstrate an immediate infusion reaction that fulfils the following criteria:
  - Severe and
  - does not respond to symptomatic treatment, and
  - has a duration of more than 2 hours

- Two or more subjects report a severe treatment emergent AE or a severe laboratory safety test result
- One or more subjects develop a treatment emergent serious (life-threatening or fatal) AE at any time during the study
- The investigator considers the AE profile or the laboratory safety assessment to indicate an unacceptable risk to the well-being of trial subjects

The study may be terminated by the sponsor at any time for any reason. This may include reasons related to benefit-risk, practical, regulatory or medical reasons.

6.3.1 Stopping Rules for individual subject

As per the judgement of the investigator:

- In the event of any severe events, administration of IMP to the individual subject must be discontinued.
    - If an event, considered to be mild or moderate, occurs during the infusion, the subject shall be treated as the investigator deems appropriate and may continue receiving the single infusion.
    - In the event of appearance of mild or moderate local infusion site reactions during the infusion, the infusion rate may be lowered. However, infusion time should not exceed two hours.

Subjects for whom IMP administration has stopped will be followed-up as per protocol.

6.3.2 Emergency Treatment

This study will be conducted at a single center (Phase I Unit) under the supervision of the principal investigator. The Phase I Unit is equipped with emergency care facilities to provide a safe environment for the study. Subjects in this study will be hospitalized from the day before treatment until 8 days after and immediate access to medical staff and equipment necessary for emergency treatments are available.

In case of hypersensitivity reaction, immediate treatment is given at the discretion of the investigator. Depending on symptoms, this may e.g., be antipyretics such as acetaminophen (paracetamol), corticosteroids or additional antihistamines, epinephrine and bronchodilators in case of severe hypersensitivity reactions (e.g. anaphylaxis) Necessary equipment for resuscitation must be available during study drug infusion.

6.4 Discussion of study design, including the choice of control groups

The study is designed to investigate safety, PK/PD in Japanese healthy subjects. The investigator, study subjects and sponsor will be blinded to treatment allocation (placebo vs. active) to avoid reporting, assessment and allocation biases.

6 subjects are considered sufficient, considering the inter-subject variability in the PK results in the NI-0501-03 study and 2 placebo is considered a reasonable number of subjects.

6.5 Selection of study population

6.5.1 Inclusion criteria

A subject must fulfill the following criteria in order to be included in the study:

1. Healthy Japanese (male and female) subjects between 20 and 50 years (inclusive).
2. Body weight greater than 45 kg (female) or 50 kg (male) and a body mass index (BMI) >18 kg/m2 and < 30 kg/m2 (BMI= weight (kg) / height (m)²)
3. Vital signs in the following range:
    - Axillary body temperature: 35.2 – 37,5
    - Heart rate (after at least 3 minutes of rest, measured in the supine position): 40-100 bpm
    - BP < 140/80, mean of 3 readings after 15 minutes rest
4. Haemoglobin level equal or above 11 g/dL in females and 13 g/dL in males.
5. Subject having C-reactive protein (CRP) levels within the normal range (local laboratory range).
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant **having agreed to use highly effective methods of contraception** during dosing and for 6 months after receiving IMP.

   Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient, otherwise highly effective methods to be applied.
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS),

or other forms of hormonal contraception that have comparable efficacy (failure rate <1%).

- In case of use of oral contraception women should have been stable on the same brand (or generic equivalent) for a minimum of 3 months before taking study treatment.

  Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago.

7. Signed informed consent.

6.5.2 Exclusion criteria

The presence of any of the following will exclude a subject from inclusion in the study:

1. Any clinically significant abnormality in the results of the safety laboratory tests. Subjects presenting a minor deviation from laboratory ranges could be enrolled if the investigator judge it to be non-clinically significant
2. Any clinically significant abnormality on the screening electrocardiogram (ECG), as judged by the investigator
3. History or clinical evidence of any disease and/or existence of any surgical or medical condition that might interfere with the absorption, distribution, metabolism or excretion of the study drugs
4. Actual presence or occurrence of any bacterial, viral, parasitic or fungal infection within the 4 weeks preceding IMP infusion
5. Positive results from serology examination for Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV), syphilis (TP-antigen and RPR) or pregnancy
6. Positive stool test for Shigella or salmonella infection.
7. Positive results from Sars-CoV-19 screening within 96 hours prior to randomization
8. History or clinical evidence suggestive of active or latent tuberculosis at screening. (i.e. test positive to the IFN γ -release assay)
9. History or presence of any severe allergic reactions
10. Suspected hypersensitivity to any component of the drug formulation.
11. History or presence of any malignancy
12. History or presence of drug or alcohol abuse
13. Subject with a smoking history within the last 6 months prior to the time of screening
14. Immunization with a live vaccine within 6 weeks prior to receiving IMP and 12 weeks after IMP infusion

15. Experience of collected blood corresponding to any of the following
    - Component blood donation within 2 weeks before the screening test and within 2 weeks before the first study drug administration
    - Collection of 200 mL or more of blood (blood donation, etc.) from 4 weeks before the screening test until admission
    - Collection of 400 mL or more of blood (blood donation, etc.) from 12 weeks before the screening test until admission
16. Usage of any prescription drugs within 2 weeks or over-the-counter medication including herbal supplements (with the exception of multi-vitamins) within 1 week before IMP administration without prior approval from the investigator
17. Positive pregnancy test at screening or Day -1
18. Any circumstances or conditions, which, in the opinion of the investigator, may affect the subject's full participation in the study or compliance with the protocol
19. Enrollment in another concurrent clinical interventional study, or intake of another IMP, within four months or 5 half-lives (of the other IMP) prior to inclusion in this study

6.5.3 Withdrawal of subjects from treatment or study

6.5.3.1 Withdrawal from treatment

As this is a single dose study withdrawal from treatment is not applicable.

The IMP administration of a subject should be prematurely stopped if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the subject. These subjects will continue to participate in the study and will not be considered as treatment withdrawals.

If the IMP administration of a subject is prematurely stopped the reason should be clearly described in the relevant sections of the CRF. If the dosing is prematurely stopped because of an AE, the reason should always be stated as 'adverse event' irrespective of whether this was the investigator's or the subject's decision.

6.5.3.2 Withdrawal from study

Whenever possible and irrespective of the reason for withdrawal, a subject that has received a partial or full dose of IMP should be examined as soon as possible. Relevant samples should be obtained, and all relevant assessments should be completed, preferably according to the schedule for the week 14 visit (Table 3). The CRF should be completed as far as possible. Date and reason for the study withdrawal should be clearly described in the CRF. If a subject is removed from the study because of an AE, the reason for study withdrawal should always be stated as 'adverse event' irrespective of whether this was the investigator's or the subject's decision.

A subject for whom the treatment blind is broken at the request of the investigator should not by default be withdrawn from the study.

6.5.4 Replacement of withdrawn subjects

Subjects who withdrawn from the study after IMP administration will not be replaced. Subjects who withdraw from the study prior to IMP administration will be replaced to ensure that 8 subjects, i.e. 6 who receive emapalumab and 2 who receive placebo.

6.5.5 Specific restrictions/requirements

The subjects will need to comply with the following restrictions:

- The subjects should follow local guidance to minimize risk of Covid-19 infection , between the PCR test for SARS-CoV-19 and the admission to the phase I unit, to avoid getting infected
- The subjects need to fast 8 hours (water allowed) prior to each visit as food may affect the results of some of the laboratory tests that are being performed
- The subjects should avoid eating poppy seeds or food containing poppy seeds (for example poppy seed bread) in the 24 hours before any urine testing
- The subjects need to avoid alcohol intake 48 hours prior to admission to the clinical unit on Study Day -1
- Subjects should refrain from donating plasma for at least 12 weeks after study completion
- Subjects should refrain from smoking during the course of the study

6.6 Treatments

The different treatment groups are;

Arm A: Emapalumab
Arm B: Placebo (saline)

One randomization list will be prepared by CRO. The ratio between the treatment groups is 3:1, i.e., the 6 subjects will be randomized to emapalumab, and 2 subjects will be randomized to placebo/saline.

6.6.1 Treatments administered

Table 1 describes the investigational medicinal products.

Table 1 Investigational medicinal products

Treatment	Investigational product	Dosage form	Route	Daily dose	Dosage regimen
A	Emapalumab	Solution	i.v. infusion	1 mg/kg	Single dose
B (placebo)	Saline	Solution	i.v. infusion	NA	Single dose

6.6.2 Identity of investigational medicinal products

Emapalumab and placebo (saline) will be supplied to the study site as open label supplies.

Possible deficiencies related to the handling and quality of the IMP(s) should be reported to the study monitor and also directly to complaints@sobi.com.

6.6.2.1 Emapalumab

The IMP emapalumab is delivered as a sterile concentrate for infusion, prefilled in single use glass vials which require a dilution prior to administration. The concentrate of emapalumab in the solution is 5 mg/mL. The solution contains no antimicrobial preservative, and therefore each vial must be used only once.

The nominal composition of the emapalumab sterile concentrate for infusion (per mL) is as presented in Table 2.:

Table 2 Composition of emapalumab sterile concentrate

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

Emapalumab should be stored between 2 and 8°C in a secure area at the study site. Further instructions on handling and storage of emapalumab are available in the Pharmacy manual.

Labeling will comply with national regulatory requirements.

6.6.2.2 Placebo

For emapalumab there is no matching placebo available, instead saline will be used. Once diluted, there is no visual differences between emapalumab and saline solution. However, visual

changes can be detected between emapalumab and saline prior to dilution. Therefore, a carefully monitored process with an unblinded site pharmacist will be developed and described in detail in the Pharmacy Manual. The unblinded pharmacist will prepare emapalumab, or saline, for infusion.

Saline should be stored between 2 and 8°C in a secure area at the study sites. Further instructions on handling and storage of saline are available in the Pharmacy manual.

Labeling will comply with national regulatory requirements.

6.6.2.3 Herpes Zoster prophylaxis

Prophylaxis for Herpes Zoster will start at Study Day -1 and be taken up to the visit at week 14. The prophylaxis will be provided by Sobi. Table 3 shows information of prophylaxis.

Table 3 Prophylaxis to be provided

Investigational product	Dosage form	Route	Daily dose	Dosage regimen
Valaciclovir	tablet	oral	1000 mg	500 mg twice daily

6.6.3 Methods of assigning subjects to treatment groups

A single intravenous dose of 1 mg/kg is considered relevant for this Phase 1 study in Japanese healthy subject to bridge to the global Phase 1 study NI-0501-03 where single dose administration of 0.01, 0.1, 1 and 3 mg/kg were administered.

Because the PK of emapalumab in healthy adults is linear, one dose level is sufficient for a comparison between Japanese and non-Japanese. Also, a single dose is sufficient to compare PK between Japanese and non-Japanese, since the PK of emapalumab does not show any time-dependency upon repeated-dose since administration.

The global Phase 1 study (NI-0501-03) in 20 healthy adult volunteers investigated the safety, tolerability and PK profiles of single IV administrations of emapalumab. During this study 6 subjects received placebo, while 3, 3, 4, and 4 subjects (in total 14 subjects) received emapalumab doses of 0.01, 0.1, 1, and 3 mg/kg, respectively. All IMP infusions were uneventful, and most AEs were singular occurrences and no trend in relation to increasing emapalumab dosage was observed.

The PK analysis of emapalumab in the NI-0501-03 study revealed the expected profile for an IgG1 with a long half-life (around 22 days), a slow clearance (≤ 0.1 mL/kg/hr) and a low volume of distribution (< 65 mL/kg on average). The serum concentrations following 1 mg/kg were

pharmacologically relevant since Cmax (32 200 ng/mL) was approximately 50 times the IC50 (603 ng/mL) for significant neutralization of IFNγ.

Considering the scaling factor from the Non-human primate to human (x0.32). 30 mg/kg (NO AEL) which was very well tolerated in monkeys, with no adverse clinical signs or organ toxicity reported, correspond to a HED of 10 mg/kg, therefore the 30 mg/kg in monkey is 10-fold higher than the starting dose in human of 1 mg/kg
Taken these aspects into account, a single intravenous dose of 1 mg/kg emapalumab has been selected for the Phase 2-3 study in pHLH thus this dose is selected also for this study in Japanese healthy subjects.

6.6.4 Selection and timing of dose for each subject

IMP will be administered by i.v. infusion over a period of 1 hour, as a single dose of 1 mg/kg.

The following information will be recorded in the CRF for each IMP administration: date, start and end time, total volume infused, and, if infusion was interrupted, reason for interruption.

The subject should receive the designated volume of the infusion material through an infusion pump over 1 hour (could be extended to up to 2 hours in case of high volume or mild to moderate reactions as per 6.3.1). A 0.2 μm filter must be included in all infusion lines.

Full instructions for the preparation of IMP, including dilution steps and method for administration, are available in the pharmacy manual.

6.6.5 Blinding and unblinding

6.6.5.1 Blinding

This study will be performed in a double-blind fashion. The investigator and study staff, the subjects, the monitors, Sobi staff, and the contract research organization (CRO), involved in the conduct of the study will remain blinded to the study treatment until database closure. However, as saline will be used as placebo, emapalumab/saline must be prepared by an unblinded Pharmacist or other appropriately qualified staff member, specifically authorized by the investigator/pharmacist and appropriately licensed to perform the task. A carefully monitored process with an unblinded site pharmacist will be applied to ensure the blinding of the study. The unblinded pharmacist will prepare emapalumab, or saline only, for infusion. The pharmacist must be independent and not involved in any other study activities.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential, and accessible only to authorized persons.

6.6.5.2 Unblinding

6.6.5.2.1 Unblinding for finally analyses

Full randomization information will be made available for data analysis only after database closure in accordance with Sobi SOPs.

6.6.5.2.2 Unblinding for SUSARs

When a SUSAR occurs for a subject participating in the study, Sobi Global Pharmacovigilance & Patient Safety will request the unblinding of the treatment assignment. The randomization code will not be communicated to the site staff, or to the Sobi study team; unblinded SUSAR information will be provided to respective Health Authorities only. SUSARs will be reported to investigators and independent ethics committees (IECs) or institutional review boards (IRBs) in a blinded fashion.

Emergency unblinding

The investigator, study staff, sponsor staff and CRO must remain blinded to the subject's study treatment assignment. The identity of the study treatment may be revealed only if the subject experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. The decision to break the code must be made by the investigator. Whenever it is possible and if it does not interfere with (or does not delay) any decision in the best interest of the subject, the investigator is invited to discuss the intended code-break with the sponsor. If the treatment blind is broken, the reason and the date should be recorded on the code envelope and signed by the investigator.

6.6.6 Prior and concomitant therapy

Prophylaxis for HZ virus infection has to be in place from the day before emapalumab infusion until W14 (i.e. after at least 2 times the terminal half-life of emapalumab levels in serum).

Each healthy volunteer will be supplied with commercially available Valaciclovir by the study site. Site will be provided with this, either locally purchased/supplied by pharmacy or by sponsor as per local regulations.
Valaciclovir will be labeled in local language and comply with legal requirements.

Other therapy considered necessary for the subject's welfare may be given at the discretion of the investigator. All such therapy must be recorded in the CRF. No other concomitant medication can be used concomitantly with the IMP in this study.

6.6.7 Documentation of IMP handling

Product accountability records will be kept. The pharmacy and investigator must maintain accurate records demonstrating date and amount of IMP(s) received, to whom and by whom administered or dispensed (subject-by-subject accounting), and accounts of returned IMP(s) and any IMP accidentally or deliberately destroyed. All unused IMP will be counted. At the end of

the study, any remaining IMP(s) will be returned to Sobi for destruction or destroyed locally. In either case, a certificate of destruction must be issued.

6.7 Pharmacokinetic, pharmacodynamic and safety assessments

6.7.1 Study schedule

Table 4 describes the study schedule.

Table 4 Schedule of Events

Assessments		Screening Visit (21 days)	Study Day -1	Treatment – Study Day							Study Days 2-8				Follow-up Wks 2, 4, and 6 (±2 days for all visits)	Follow-up Wks 8, 10, and 12 (±2 days for all visits)	Study Completion Visit (w14-±2 days) or withdrawal (WD)	Unscheduled Visit
				1							2	3	5	8				
				Pre-infusion	1h post start	2h post start	4h post start	8h post start	10h post start	12h post start								
Subject Information	Informed Consent	X																
	Demographic	X	x															
	Medical history	X																
	Eligibility criteria	X	x	x														
	Randomization			x														
Physical Examination	Vital Signs[1]	X	x		every 30 min		every hour		every 2h		x	x	x	x	x		x	x
	12-lead ECG	X		x			x										x	
	Physical Examination[2]	X	x														x	x
	Body weight	X	x														x	
Laboratory procedure	Viral serology and Infections[3]	X																
	Microbiology testing for shigella and salmonella bacteria (stool)	X																
	s-HCG	X	x															
	Hematology/Chemistry[4]	X	x				x				x	x	x	x	x	x[5]	X	x
	Urine Pregnancy Test[6]														x	x	x	
	Urinalysis[7]	X	x				x				x	x	x	x	x		x	x
	TB testing (Quatiferon/T-spot)	X																

Assessments		Screening Visit (21 days)	Study Day -1	Treatment – Study Day							Study Days 2-8				Follow-up Wks 2, 4, and 6 (±2 days for all visits)	Follow-up Wks 8, 10, and 12 (±2 days for all visits)	Study Completion Visit (w14-±2 days) or withdrawal (WD)	Unscheduled Visit
				1							2	3	5	8				
				Pre-infusion	1h post start	2h post start	4h post start	8h post start	10h post start	12h post start								
	PCR – SARS-Cov-19[8]	X																
	Alcohol and drug screen		x															
PK				x	x[9]	x	x	x	x		x	x	x	x	x	x	x	
PD				x	x	x	x	x	x		x	x	x	x	x		x	
Immunogenicity				x													x	
SAE/AE		X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medication				x	x	x	x	x	x	x	x	x	x	x	x	x	x	

1. Body weight and height will be collected at Screening, and body weight at Study Day -1 and Week 14
2. A full physical examination will be performed at screening. And at Week 4 visit. At all other visits brief physical examinations will be performed, only if indicated.
3. Viral serology for HBsAg, HCV,HIV and syphilis (unless performed within 12 weeks prior to screening evaluation and no clinical suspicion of such infections)
4. Blood Haematology measurements, taken under fasting condition except from screening, should follow Table 5.
5. Only at week 10
6. Urine pregnancy test is to be performed with a dipstick at week 4, 8, 12 and study completion
7. Urine analyses are to include the assessments according to Table 5.
8. A PCR test for SARS-CoV-2 should be collected within 96 hours of IMP administration.
9. At end of infusion

6.7.1.1 Visit 1 screening

After the informed consent has been signed, the subjects will be assigned a screening-ID, the screening-IDs will be assigned in consecutive order. The investigator should keep a log of the subjects screened for the study and the reasons for non-eligibility.

Subjects should be screened according to study eligibility criterias.

Screening evaluations should be completed within 21 days prior to IMP administration as per the schedule of events (Table 3). Within 96 hours of the IMP administration, a PCR test for SAR-CoV-19 should be performed, the test result must be available prior to the IMP administration.

Should any of the tests be out of the range specified for this study, subject(s) may eventually be asked to return to the Phase I Unit to provide an additional sample for repeat testing.

Some subjects may be asked to be *"reserved participants"* as additional participants may be needed to replace screened subjects (e.g. non-attendance, subject exclusion or last minute withdrawal).

6.7.1.2 Study Day -1

Once all screening results are available and the subject meets all inclusion criteria, and none of the exclusion criteria, subjects will be admitted to the Phase I Unit on the morning of Study Day -1 and will undergo study specific procedures as per the schedule of events (Table 3). Prophylaxis treatment against Herpes Zoster should be initiated.

6.7.1.3 Treatment – Study Day 1 Assessments

Pre-infusion

Prior to the administration of IMP on the morning of Study Day1, the subjects will be assigned a randomization number and undergo study specific procedures as per the schedule of events (Table 4)

Post-infusion

Once the assessments and procedures listed above have been performed and the eligibility if the subjects is once again confirmed, the subject will be randomized, be assigned a randomization ID and thereafter receive an i.v. infusion of emapalumab or placebo/saline according to the IMP administration instructions (Pharmacy manual). Subsequent to the start of IMP administration, the subjects will undergo study specific procedures as per the schedule of events (Table 4)

All subjects will be discharged on Study Day8 post-infusion provided that no safety issues have emerged.

6.7.1.4 Follow-Up visits (Study W2, W4, W6, W8, W10, W12)

All assessments and procedures will be performed according to the schedule of events (Table 4). The time window for the visits on week 2, 4, 6, 8, 10, and 12 is ± 2 days.

6.7.1.5 Study completion visit (W14) or withdrawal

At the last visit (Study completion visit) the subjects will undergo assessment and procedures according to the schedule of events (Table 4). The time window for this visit is ± 2 days.

The same assessment and procedures should be conducted at a withdrawal visit for any subject who withdraws prematurely or is withdrawn by the investigator. The withdrawal visit should be scheduled within 30 days of termination.

Subjects withdrawn due to a SAE should be followed-up until resolution of the event or until the outcome is known and stable.

In order to measure the emapalumab serum levels during at least 3 times the terminal half-life (a total of approximately 3 months) PK samples will be taken up to week 14.

6.7.1.6 Unscheduled Visits

In the event of unscheduled visits, a non-exhaustive list of assessments and procedures which may be performed can be found in the schedule of events (Table 4).

6.7.2 Medical history

A relevant medical and surgical history, including current medical status and allergies should be collected at the screening visit and recorded in the CRF.

6.7.3 Prior and Concomitant Medication

Details on the subject's prior medications (including over-the-counter and herbal medications) within 3 months of the screening visit, should be collected at the screening visit. As no concomitant medication is allowed, adequate time (depending of half-life and mechanism of action) should have elapsed since the use of previous medication to ensure no residues of the medication

6.7.4 Demography

The subject's age at screening, gender, race, body weight and body length will be collected at screening and recorded in the CRF. The body weight recording will be repeated at Study Day -1.

6.7.5 Pharmacokinetics

PK blood samples, to measure serum levels of emapalumab, will be collected for all subjects receiving study treatment.

At Study Day 1 sampling should be done pre-dose and at end of infusion, 2, 4, 8, and 10h post dose. PK samples will thereafter be collected on all study visits. It should be noted that a separate i.v. line will have to be used when collecting the PK samples, i.e. not the same i.v. line as used for the i.v. infusion of study treatment.

The date and time of blood sampling will be recorded in the CRF.

Samples will be sent to central laboratory for analysis. The procedures for blood collection, processing into serum, storing and transporting to the central laboratory as well as the laboratories responsible for the analysis are fully described in the laboratory manual.

6.7.5.1 Bioanalytical method

The PK measurements will be performed at [redacted]

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

Further details regarding the PK serum samples analysis will be described in a bioanalytical plan which will be agreed and signed between the Sobi Clinical Representative and the bioanalytical Laboratory before any biological sample is dispatched to the bioanalytical Laboratory.

6.7.5.2 Pharmacokinetic calculations

Emapalumab serum concentration-time data, based on actual administered dose and actual relative time-points, will be evaluated by Non compartmental analysis. The following PK parameters will be calculated as applicable: Cmax, tmax, CEOI, AUClast, AUCinf, %AUCextr, λz, t½, CL, Vss, MRTlast and MRTinf. PK modelling may also be conducted using compartmental analysis and/or non-linear mixed effects modelling as appropriate, based on the PK results from this study only alternatively based on these results pooled with other PK data e.g. From study NI-0501-03.

6.7.6 Pharmacodynamics

Blood samples for determination of CXCL9, IFNγ and sIL-2R will be collected according to Table 4. It should be noted that a separate i.v. line will have to be used when collecting the PD samples, i.e. not the same i.v. line as used for the i.v. infusion of study treatment.

The date and time of sampling will be recorded in the CRF.

Samples will be sent to central laboratory for analysis. The procedures for blood collection, processing into serum, storing and transporting to the central laboratory as well as the laboratories responsible for the analysis are fully described in the laboratory manual.

6.7.6.1 Bioanalytical methods

The PD measurements will be performed at [redacted]

The measurements of the biomarkers in human serum samples will be performed using a validated Sandwich sequential ECLIA on Meso Scale Discovery (MSD) Platform. All the samples are to be dispatched under frozen conditions to the bioanalytical Laboratory and will be analyzed within established timeframe stability.

All the details regarding the PD serum samples analysis will be described in a bioanalytical plan which will be agreed and signed between the Clinical Representative and the bioanalytical Laboratory before any biological sample is dispatched to the bioanalytical Laboratory.

6.7.6.2 Calculations

The PD biomarkers (Total IFNγ, CXCL9 and sIL2R serum levels) will be described descriptively, and the change from base-line levels will be derived.

6.7.7 Immunogenicity

Immunogenicity samples will be collected for all subjects Study Day 1 – pre-infusion, and at the study completion visit. The date and time of blood sampling will be recorded in the CRF. Samples will be sent to central laboratory for analysis. The procedures for blood collection, processing into serum, storing and transporting to the central laboratory as well as the laboratories responsible for the analysis are fully described in the laboratory manual.

All the ADA and any Nab analyses will be performed at

[redacted]

using validated methods. All the details regarding these analyses will be described in a sample analysis plan which will be agreed and signed before any biological serum sample is dispatched to LGC.

Safety assessments

6.7.7.1 Adverse events

6.7.7.1.1 Definitions

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

AEs include:

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

Abnormal laboratory values or test results should be reported as adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,

- they are considered clinically significant,
- they require therapy or
- they result in dose reduction, interruption or permanent discontinuation of IMP administration.

Overdose, misuse, and abuse of the IMP should be reported as an AE and, in addition, IMP errors must be documented in the IMP log of the eCRF.

6.7.7.1.2 Intensity of adverse events

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

- Mild

  The event may be noticeable to the subject. It does not influence daily activities, and usually does not require intervention

- Moderate

  The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- Severe

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

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

If an AE occurs during the screening period (i.e. after signature of informed consent up to IMP initiation) and worsens after IMP initiation or during the follow-up period, a new AE form must be entered with the appropriated intensity.

A mild, moderate, or severe AE may or may not be serious (see Section 6.7.7.2.1 for definition of SAE). Medical judgment should be used on a case-by-case basis.

6.7.7.1.3 Relationship to investigational medicinal product

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

6.7.7.1.4 Adverse event reporting

All AEs occurring after IMP initiation and up to end-of study (EOS) must be recorded on specific AE forms of the eCRF.

6.7.7.1.5 Follow-up of adverse events

All AEs should be followed until they are resolved, or the investigator assesses them as stable, or the subject's participation in the study ends, i.e., last scheduled visit (Study Completion).

All AEs assessed by the investigator as related to the IMP should continue to be followed until they resolve or until the investigator assesses them as "stable", including after EOS. In the latter case, no changes to eCRF are made.

6.7.7.2 Serious Adverse Events

6.7.7.2.1 Definitions of SAE

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

- Results in death.
- Is life-threatening (i.e., at immediate risk of death).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect (i.e., in an offspring to the study subject).
- Is a medically important AE.

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

The following reasons for hospitalization are exempt from being reported:

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

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

6.7.7.2.2 Reporting of SAEs

During screening, administration of IMP and follow-up period

All SAEs occurring after study start (i.e., signing of informed consent) up to EOS must be reported on the SAE form and recorded in the AE pages of the eCRF.

After EOS

New SAEs occurring after the EOS must be reported to the Sobi safety department within 24 hours of the investigator's knowledge of the event, only if considered by the investigator as causally related to previous exposure to the IMP.

6.7.7.2.3 Follow-up of SAEs

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

6.7.7.2.4 Reporting procedures

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

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

SAE forms must be emailed to Sobi safety department and Sobi Study Physician (contact details are provided on the SAE form). The investigator must complete the SAE form in English, must assess the causal relationship of the event to IMP and sign the report.

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

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

The reference safety document to assess expectedness of a suspect serious adverse reaction and for reporting by the sponsor to Health Authorities, ECs/IRBs and investigators is the reference safety information section of the current version of the Investigator Brochure (IB).

6.7.7.2.5 Pregnancy

There are no data from the use of emapalumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see IB).

Females of childbearing potential should not get pregnant during the study and should agree to use appropriate contraception (see Section 6.5.1).

6.7.7.2.6 Reporting of pregnancy

Any pregnancy occurring after IMP administration up to the EOS must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Sobi pregnancy form and e-mailed to the Sobi safety department.

6.7.7.2.7 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion, and its outcome must be reported to the Sobi safety department.

Such follow-up information will only be entered in the sponsor's safety database, and hence will not affect study closure. Table 5 presents the laboratory assessments.

Table 5 Laboratory Assessments

Biochemistry	**Hematology**
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Direct Bilirubin Total Bilirubin Uric acid Alkaline phosphatase Total Protein Albumin Prothrombin Time/International Normalized Ratio (PT-INR) Fibrinogen Complement C3/C4 Cardiac troponin Creatinine C-reactive protein (CRP) Electrolytes (Sodium, Potassium, Calcium) Glucose Lipids (fasting (except screening) triglycerides, HDL, LDL) BUN/Urea	Hemoglobin Hematocrit Platelet count White blood cells Red blood cells Differential blood count Immunoglobulin levels Coagulation profile (APTT) **Urinalysis (dipstick)** Erythrocytes, Leukocytes Glucose Ketones pH Protein Sediment (only if positive results are obtained for Protein, Erythrocytes and leukocytes measurements) Urine pregnancy test **Additional testing at screening** TB screening (Quantiferon/T-spot) PCR SARS-CoV-2 Viral serology and infections HBV, HCV, HIV and syphilis) Microbiology testing (stool) for shigella and salmonella bacteria s-HCG Drug screen; Benzodiazepines, cocaine, methamphetamines, marijuana, barbiturates, morphine, Phencyclidines and tricyclic antidepressants

All laboratory samples will be analyzed at the local laboratory of the phase I unit according to their standard routines.

Clinically significant laboratory values should be reported as AEs (see Section 6.7.7.1.1 for details).

6.7.7.3 Vital signs

Vital signs (body temperature, heart rate, and semi-supine systolic and diastolic blood pressure will be measured at all study visit at timepoint indicated the schedule of events (Table 3) and recorded in the CRF.

Clinically significant abnormal vital signs values should be reported as AEs (see Section 6.7.7.1.1 for details).

6.7.7.4 Physical examination

A complete physical examination will be performed at screening and at the Study Completion Visit. At all other visits brief physical examinations will be performed, only if indicated.

The complete physical examination will be performed by a physician and will include examination of the following: general appearance, eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid/neck, lymph nodes, and neurological/psychiatric. Each component will be recorded as "normal" or "abnormal" at each visit. Abnormalities should be described.

If any abnormalities are reported at baseline they should be recorded as medical history. New or worsening of abnormalities should be reported as AEs (see Section 6.7.7.1.1 for details).

6.7.7.5 Electrocardiograms

A 12-lead ECG recording will be performed at screening, at Study Day1 pre-infusion and at 4h post-infusion, and at the study completion visit. The ECG assessments will be performed at the phase I unit and will be reported as "normal" or "abnormal" in the CRF. Any abnormalities should be specified. Abnormalities reported at screening should be recorded as medical history.

Clinically significant abnormal ECG findings should be reported as AEs (see Section 6.7.7.1.1 for details).

6.7.7.6 Pregnancy Test

Female of childbearing potential will have a serum pregnancy test taken at screening and Study Day -1 and then urine pregnancy tests monthly (week 4, 8 and 12) and at study completion, week 14. The outcome of the test will be reported as "positive" or "negative" in the CRF.

7 Quality control and quality assurance

This study will be conducted in compliance with this protocol, study specific procedures, Sobi's and the CRO's SOPs, the ICH Guideline for GCP (1), and applicable regulatory requirements.

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

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

Monitoring visits to the study site will be performed periodically during the study, to help ensure compliance with the protocol, study specific procedures and applicable regulatory requirements. Source documents will be reviewed for verification of agreement with data in CRFs. All subject informed consent forms will be reviewed. The investigator or institution guarantees access to source documents by Sobi, its representatives, and appropriate regulatory agencies.

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

It is important that the investigator(s) and the(ir) relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

8 Statistical plan

8.1 Determination of sample size

This is a phase I study to evaluate the pharmacokinetics and pharmacodynamics of emapalumab in healthy Japanese subjects following single dose administration of emapalumab.
No formal sample size calculation was made but the sample size was chosen based on previous experience in phase I studies. Also, 6 subjects receiving emapalumab are considered sufficient, considering the inter-subject variability in the PK results in the NI-0501-03 study and 2 placebo is considered a reasonable number of subjects. In study NI-0501-03 CV for inter-subject variability was within 30% for PK parameters such as Cmax and AUC % based on 4 subjects at a dose level of 1 mg/kg emapalumab.

8.2 Definition of study populations

All analyses will be conducted on the modified intention-to-treat (mITT) population which will comprise all randomized subjects who received an infusion of IMP and have at least one blood draw to determine PK and PD.

The Safety population will comprise of all patients who received an infusion of IMP.

8.3 Overall statistical and analytical plan

8.3.1 General statistical issues

A study specific statistical analysis plan (SAP) containing a detailed description of all analyses to be conducted will be developed and finalized prior to database lock. Suitable tabular and graphical summaries will be prepared for individual data and for appropriate summary statistics, and all data will be listed. No formal statistical hypothesis testing will be performed. All endpoints will be summarized with descriptive statistics and presented individually in listings.

8.3.2 Demographics and baseline characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics.

8.3.3 Analysis related to primary objective

8.3.3.1 Analysis of pharmacokinetic parameters

The pharmacokinetic analysis will primarily be conducted using non-compartmental procedures and results of PK parameter will be presented by descriptive statistical methods.

PK modelling may also be used based on naïve pooled compartmental modeling and/or non-linear mixed effects modeling compartmental analysis may be used as deemed appropriate.

PK results may be compared with other studies e.g. study NI-0501-03, but will not be presented in the report for this study.

8.3.3.2 Analysis of pharmacodynamic parameters

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

8.3.4 Analysis related to secondary objective

8.3.4.1 Adverse events

Reported AEs during the study will be coded using MedDRA. The incidence of AEs will be summarized in frequency tables by IMP, system organ class, preferred term, relationship to IMP and maximum severity. Separate tabulations will be performed for serious and non-serious AEs.

8.3.4.2 Laboratory Parameters

Abnormal laboratory values will be listed and their incidence, severity and relationship to the IMP will be tabulated for the IMP groups. Change from baseline will be summarized by IMP group. Individual changes (shift tables), individual clinically significant abnormalities and severity grading (mild, moderate, severe) will also be presented.

8.3.4.3 Anti-drug antibodies

The number and percentage of patients with ADA at baseline and at the post-baseline assessment will be summarized.

8.3.5 Analysis of safety and tolerability data

8.3.5.1 Vital signs and physical Examination

Abnormal values from physical examination findings and vital signs will be summarized descriptively over time.

8.3.5.2 Infusion reactions

The incidence and severity of infusion related reactions will be analyzed (including the need for medication)

8.3.6 Interim analysis

No interim analysis will be performed.

8.3.7 Multiple comparison/multiplicity

As no formal hypothesis testing will be performed adjustment for multiple comparisons will not be applicable in this study.

8.3.8 Handling of missing data

No imputations of missing data will be performed.

9 Data collection, handling and record keeping

9.1 Data standards

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

9.2 Case report form

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

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

9.3 Source data

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

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

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

9.4 Protocol Deviations

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

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

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

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

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

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

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

9.5 Database closure

Prior to database closure, all tasks or criteria defined in the data management plan must be completed and documented. The study database must be locked before breaking of the blind and before generation of any results. The database lock will be approved by relevant study personnel and all edit accesses will be removed. The study database can only be unlocked in case critical errors, affecting the main conclusions of the study, are discovered.

9.6 Record retention

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

All documents and data relating to the study will be kept securely by the investigator in a secure file and/or electronically. The storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search and retrieval. The data will be available for evaluation and/or audits from Health Authorities, Sobi or Sobi's representatives.

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

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

10 End of study

The end of this study is defined as the date of last subject out, i.e., the last subject's last visit.

11 Sponsor's discontinuation criteria

Sobi reserves the right to discontinue the study prior to inclusion of the intended number of subjects but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating subjects within 10 days. All study materials must be collected and all the CRFs completed to the greatest extent possible.

12 Dissemination and publication of results

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

Sobi is committed to publishing study results in a complete, accurate, balanced, transparent and timely manner. Sobi follows the principles of the International Committee of Medical Journal Editors (ICMJE) recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals including criteria for authorship (27).

The data from this study will be considered for reporting at a scientific meeting or for publication in a scientific journal. The sponsor will be responsible for these activities and will work with the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues. The results of the study, or any part thereof, shall not be published without the prior written consent and approval of Sobi, such consent and approval not to be unreasonably withheld.

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Appendix 1 Additional Protocol Signatures

Sponsor's Clinical Program Leader

[redacted]

Signature

Date

Sponsor's Statistician

[redacted]

Signature

Date

Appendix 2 Study Administrative Structure

Study center:	[redacted]
Monitoring:	[redacted]
SAE reporting:	[redacted]
Data management:	[redacted]
Statistics:	[redacted]
Pharmacokinetics:	[redacted]
Investigational products (production):	[redacted]
Investigational products (packaging and labeling):	[redacted]
Clinical laboratory:	[redacted]
PK/PD analyses:	[redacted]
Bioanalysis:	[redacted]