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

ClinicalTrials.gov ID: NCT03311854

Documentation of statistical methods

Final statistical analysis plan, version 2.0, dated 29 October 2020

Final errata of statistical analysis plan, version 2.0, dated 22 July 2021

Final post-hoc analysis plan, version 1.0, dated 22 April 2021

Sponsor	*Sobi AG*
Protocol Title:	*A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) or Adult-onset Still's Disease (AOSD) developing Macrophage Activation Syndrome/secondary HLH (MAS/sHLH)*
Protocol Number:	*NI-0501-06*
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Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Biostatistician	[redacted] Principal Biostatistician, Premier Research Sign Name: [redacted]	
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Document History

Version	Date	Reason for Amendment
1.0	08-Jun-2019	-
2.0	29-Oct-2020	Updated accordingly to protocol version 2.0. Moreover: • Two sections have been added to describe the impact of COVID-19 (Section 6.1.9) and the safety patient profile analysis (Section 12.1). • A descriptive analysis for presentation at health authority meetings (FDA) has been added (Section 4.2). The following definitions have been added in Section 6.1.7: • Equivalent dose of prednisone. • Glucocorticoids tapering when it is not possible to establish if a patient has been treated for sJIA/AOSD before the study start. • Daily total dose of anakinra, canakinumab, ciclosporin, etoposide, methotrexate, and tocilizumab has been added. • Patients who tapered steroids to ≤1 mg/kg/day of the equivalent dose of prednisone. The following definitions have been amended in Section 6.1.7: • Infection. • MAS remission is defined accordingly to symptoms score <=1. • Suspected and confirmed IRR have

Version	Date	Reason for Amendment
		been combined into IRR. The following definitions have been clarified: • Study day (Section 6.1.7). • TEAE in case of missing or partial dates has been clarified (Section 6.1.8). The following analyses have been added: • Neutralizing antibodies for positive ADA patients (Section 9.5.3). Minor changes not included.

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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Sobi AG protocol number NI-0501-06 (A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) or Adult-onset Still's Disease (AOSD) developing Macrophage Activation Syndrome/secondary HLH (MAS/sHLH)).

The study was being conducted in North America and Europe according to 2 original twin protocols (Version 1.0 dated 19 Oct 2017 for North America and Version 1.1. dated 7 Apr 2017 for Europe) and country-specific versions (to take into account requirements from the national ethics committees). The versions previously in use have been recently amended, in January 2020, and the study is currently being conducted according to protocol version 2.0 (with country specific requirements for France and Italy as previously).

This SAP describes the planned analysis for the combined data of the twin protocols, and a single clinical study report (CSR) will present the results from the protocols.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration, European Medicines Agency, and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP will be included in CSRs, and they may be included in regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to the database lock pertaining to study NI-0501-06.

2. Study Objectives and Endpoints

2.1. Study Objectives

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

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

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

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- Incidence, severity, causality and outcomes of adverse events (AEs) (serious and non-serious), with particular attention being paid to infections.
- Evolution of laboratory parameters, in particular complete blood count (CBC), liver function tests (LFTs), inflammatory markers (ferritin and C-reactive protein [CRP]), and coagulation parameters.
- Number of patients withdrawn due to safety reasons.

2.2.2. Efficacy Endpoints

The efficacy of emapalumab will be evaluated based on the following variables:

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

2.2.3. Pharmacokinetic Endpoints

Non-compartmental pharmacokinetic analysis (NCA) will be applied to calculate the following parameters, as applicable:

- C_{max} (concentration corresponding to T_{max})
- T_{max} (time of maximum observed concentration)
- C_{EOI} (concentration at the end of infusion)
- C_{trough} (concentration just before administration)
- AUC_{τ} (area under curve of a dosing interval)
- AUC_{last} (area under curve from the time of dosing to the last measurable concentration)
- t½ (serum half-life)

Population PK modelling will also be performed to determine the PK properties of emapalumab, but will be described in a separate PK analysis plan and will be reported separately. NCA and population PK analysis will be undertaken to investigate linear and non-linear (TMDD) kinetics.

2.2.4. Pharmacodynamic Endpoints

PK/PD analysis will be performed to describe the relationship between emapalumab and IFNγ and CXCL9, which will be described in a separate PK/PD analysis plan and the outcome of the analyses will be reported separately.

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

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

3. Overall Study Design and Plan

3.1. Overall Design

This is an open-label, single arm, international, multicenter pilot study conducted in Europe and North America.

Emapalumab will be administered intravenously at the initial dose of 6 mg/kg at study day 0 (SD0: initiation of emapalumab treatment), and continued at the dose of 3 mg/kg, every 3 days until SD15, and then twice-a-week for additional 2 weeks, i.e., until SD28.

All patients who have received at least 1 dose of emapalumab will be monitored after the last administration of emapalumab. A short-term follow-up of 4 weeks has to be performed;

therefore, should emapalumab treatment in a given patient need to be prolonged beyond 4 weeks, additional visits will be performed weekly until completion of the 4-week short-term follow-up.

If treatment is shortened (as allowed by the protocol upon achievement of MAS remission), the schedule of visits has to be in any case followed until SD56. Therefore, the last visit for a given patient in the NI-0501-06 study will normally be on SD56 (except in case of prolongation of emapalumab treatment beyond 4 weeks).

3.2. Sample Size

The sample size was not formally calculated. The sample size of approximately 12 evaluable patients (a minimum of 10 sJIA patients) is based on pragmatic considerations, and on the experience acquired from patients with primary HLH treated with emapalumab.

3.3. Study Population

The study population comprises patients of both genders, with sJIA or AOSD, presenting with MAS and having shown inadequate response to high dose intravenous glucocorticoid treatment.

3.4. Treatments Administered

This is an open-label, single-arm study and no randomization is being performed. Emapalumab is administered at the initial dose of 6 mg/kg by infusion over a period of 1 to 2 hours, depending on the volume to infuse. Treatment is continued at the dose of 3 mg/kg every 3 days until SD15, and twice a week thereafter for a total of 4 weeks (i.e., up to SD28).

Treatment may be shortened upon achievement of complete clinical response (i.e. MAS remission), however at least two infusions of emapalumab at the dose of 3 mg/kg have to be administered (i.e. after SD6) before a patient can be considered to achieve MAS remission. In the absence of a trend of improvement in key MAS parameters (including, but not limited to ferritin, LDH, AST/ALT and PLT count) suggestive of lack of response, the emapalumab regimen may be adapted (the frequency between infusions shortened, the dose increased or the treatment prolonged beyond 4 weeks) upon assessment of a favorable benefit/risk profile in that individual patient.

3.5. Method of Assigning Patients to Treatment Groups

This is an open-label, single-arm study. Screening is carried out to enable confirmation of patient eligibility. Eligible patients are administered emapalumab.

3.6. Blinding and Unblinding

There is no need of a blinding and unblinding scheme since this is an open-label, single-arm study.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1 and Table 2.

Table 1: Schedule of assessments: screening and treatment period (from SD-1 to SD28)

Assessments		Protocol Section	Screening (up to one week prior to 1st infusion) SD-1	SD0 Infusion #1[1] Pre	SD0 Infusion #1[1] Post	SD1	SD2	SD3 Infusion #2[2] Pre	SD3 Infusion #2[2] Post	SD5	SD6 to SD28[3] Infusion/Efficacy/Safety visits
Hospitalization[4]		8.1	From SD-1								
Patient information and informed consent		8.2	X								
Medical history including MAS laboratory parameters and MAS treatments		8.2	X								
Concomitant medication (including recording on glucocorticoid tapering when relevant)		8.2	X	X		X	X	X		X	X
MAS diagnosis and Eligibility Criteria[5]		8.2	X								
Prophylactic treatments		8.2	From SD-1								
Clinical assessments	Vital signs	8.3.1	X	X	X[6]	X	X	X	X[6]	X	X[7]
	Physical examination[8]	8.3.2	X	X		X	X	X		X	X
	MAS clinical signs and symptoms[15]	8.3.3	X								X

Assessments		Protocol Section	Screening (up to one week prior to 1st infusion) SD-1	SD0 Infusion #1[1] Pre	SD0 Infusion #1[1] Post	SD1	SD2	SD3 Infusion #2[2] Pre	SD3 Infusion #2[2] Post	SD5	SD6 to SD28[3] Infusion/Efficacy/Safety visits
Laboratory assessments	CBC	8.4	X	X		X	X	X		X	X
	Lymphocyte subset	8.4	X								
	Coagulation (aPTTT, PT, D-Dimers, Fibrinogen)	8.4	X	X		X	X	X		X	X
	Biochemistry	8.4	X	X		X	X	X		X	X
	Serum pregnancy test (if applicable)	8.4	X								X (SD28 only)
	Urinalysis	8.4	X	X[9]							
Search for infections	Mycobacterium Tuberculosis	8.5	X								X[10]
	Atypical mycobacteria, Shigella, Salmonella, Campylobacter, Leishmania, Histoplasma Capsulatum	8.5	X								
	EBV, CMV, Adenoviruses	8.5	X								X[10]
	HSV, HZV, HIV, HBV, HCV	8.5	X								
Procedure	ECG	8.7.1	X[11]		X						

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

1 Start of emapalumab treatment: loading dose of 6 mg/kg.
2 Continuation of emapalumab treatment: 3 mg/kg every 3 days from SD3 onwards until SD15, and twice-a-week thereafter.
3 After a minimum of two infusions at the dose of 3 mg/kg (i.e. after SD6), emapalumab treatment may be shortened as per Investigator's decision upon achievement of a complete clinical response
(i.e. MAS remission). In this circumstance, efficacy/safety visits have to be in any case performed according to the same schedule until (and including) SD28.
4 Hospitalization: please note that the patients can be discharged from SD15 if their conditions allow, provided that there is no active infections requiring i.v. antimicrobial therapy.
5 Include molecular and functional tests relevant to the diagnosis of primary HLH. Include detailed documentation of inadequate response to high dose i.v. glucocorticoids and MAS treatments
6 Continuous monitoring of HR and SpO2 as well as body temperature and BP recording at regular time points (see Protocol Section 8.3.1).
7 If emapalumab infusions are performed, HR, BP, SpO2, body temperature are to be measured pre-, during, and post-dose (see Protocol Section 8.3.1).
8 Body weight to be recorded prior to infusion and every 2 weeks during the evaluation period for patients weighing less than 10 kg, and every 2 weeks throughout the study for patients weighing
more than 10 kg.
9 If not performed at screening.
10 Abdominal US and Search for infection to be performed on SD15 and SD28; chest X-ray on SD28 only.
11 At screening, three consecutive recordings are required in order to obtain a stable baseline.

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12 Brain MRI & CSF analysis: to be performed in case of neurological involvement prior to emapalumab initiation (or at the latest by SD6 for brain MRI), whenever possible.
13 When emapalumab is administered, PK samples have to be taken before and after the infusion.
14 Total IFNγ only.
15 MAS activity on VAS at all indicated visits. Assessment of clinical parameters as per Protocol Section 8.3.3 at the following visits: SD-1, SD14, SD21, SD28. In addition for cases where emapalumab treatment may be shortened (after SD6 and prior to SD28) due to a complete clinical response, the assessment is also to be made at this corresponding time-point.

Table 2: Schedule of assessments: evaluation period (from SD28 to SD56)

Assessments		Protocol Section	SD35 1st week follow-up	SD42 2nd week follow-up	SD49 3rd week follow-up	SD56[1] 4th week follow-up EoS[2]	Unscheduled Visit (UV)[3]
Hospitalization[4]		8.1					
Concomitant medication (including information on glucocorticoid tapering)		8.2	X	X	X	X	
Clinical assessments	Vital signs	8.3.1	X	X	X	X	X
	Physical examination	8.3.2	X	X	X	X	X
	MAS clinical signs and symptoms[6]	8.3.3	X	X	X	X	
Laboratory assessments	CBC	8.4	X	X	X	X	
	Lymphocyte subset	8.4				X	
	Coagulation (aPTT, PT, D-Dimers, Fibrinogen)	8.4	X	X	X	X	
	Biochemistry	8.4	X	X	X	X	
	Serum pregnancy test					X	
	Urinalysis					X	
Search for infections	Mycobacterium Tuberculosis	8.5		X		X	

Assessments		Protocol Section	SD35 1st week follow-up	SD42 2nd week follow-up	SD49 3rd week follow-up	SD56[1] 4th week follow-up EoS[2]	Unscheduled Visit (UV)[3]
	EBV, CMV, Adenoviruses	8.5		X		X	
Procedure	ECG	8.7.1				X	
Imaging	Abdominal Ultrasound	8.6.1		X		X	
	Chest X-ray	8.6.2				X	
	Brain MRI[5]	8.6.3				X	
Histopathology	CSF analysis (if coagulation allows)[5]	8.7.2				X	
PK	Emapalumab serum concentration	8.8.1	X	X	X	X	
PD 1	IFNγ, CXCL9, CXCL10, sCD25	8.8.2	X	X	X	X	
PD 2	Other markers	8.8.2		X		X	
Immunogenicity (ADA)[6]		88.3				X	

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

Study Exam should be performed, whenever possible.
[6] MAS activity on VAS at all indicated visits. In addition an assessment of clinical parameters as per Protocol Section 8.3.3 at the following visits: SD42 and SD56. For cases where emapalumab treatment may be prolonged beyond SD28, the assessment of the specified clinical parameters is to be made at the time of last infusion and at the follow-up visits corresponding to 2 weeks and 4 weeks after the last emapalumab infusion.

4. Statistical Analysis and Reporting

4.1. Introduction

All study variables in this study are considered to be exploratory, and no hierarchy of endpoints has been specified. The analysis focuses on descriptive statistics and confidence intervals (CIs).

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher).

Continuous (quantitative) variable summaries will include the number of patients (n) with non-missing values, mean, standard deviation, median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of patients who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of patients in the study population, unless otherwise specified.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (standard deviation) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all CIs will be calculated at the 95% CI.

4.2. Interim Analysis and Data Monitoring

An independent iDMC has monitored patient safety during the NI-0501-06 study. The iDMC is composed of relevant experts: pediatric rheumatologist, pediatric onco-hematologists, pediatric immune deficiency/infectious disease specialists, a biostatistician, and a specialist in ethics.

The main iDMC responsibility has been to review safety and relevant efficacy data as they were generated, with the objective of determining the benefit/risk profile of emapalumab treatment in the patients enrolled in the study, thus ensuring that no patient was exposed to unnecessary risks.

The iDMC could recommend treatment discontinuation for individual patients as well as temporary study suspension or study termination.

A PK analysis has been conducted when a total of 5 patients were recruited to assess the appropriateness of the proposed dose regimen.

No formal interim analyses were planned. However, a descriptive summary of the efficacy and safety results from this open label study has been prepared for presentation at health authority meetings (FDA). Some of these preliminary results have been presented at congresses.

5. Analysis Populations

The following analysis populations are planned for this study:

- **All Treated Population (All Treated):** The All Treated Population includes all patients who receive any part of an infusion of study drug. In this study, this population corresponds to the Safety population.
- **Evaluable Population (EVAL)**: The EVAL Population includes all patients in All Treated Population who have received a minimum of 3 consecutive infusions of emapalumab, and for whom the diagnosis of background disease sJIA is confirmed (e.g., no evidence for malignancy-related HLH or primary HLH has emerged after enrollment). Should any deviations be considered to significantly impact on efficacy, the impacted patient(s) should be excluded from the EVAL Population.

Inclusion in the EVAL analysis populations will be determined at a data review meeting before database lock. Sobi will review patient level data and a list of subjects for whom the diagnosis of background disease sJIA is confirmed will be provided to the statistician.

The All Treated Population will be the primary population for safety and efficacy endpoints. The EVAL Population will be secondary for the efficacy analysis.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last observation recorded prior to the first dose of emapalumab will be used as the baseline observation for all calculations of change from baseline.

6.1.2. Adjustments for Covariates

Not applicable.

6.1.3. Multiple Comparisons

Not applicable.

6.1.4. Handling of Dropouts or Missing Data

An additional patient will be recruited for any patient who withdraws from the study for reasons other than safety or lack of efficacy to ensure a sample size of approximately 12 patients across North America and Europe.

No imputation of missing data will be performed. However, for MAS remission, if one or more laboratory data are unavailable within the visit window, the LOCF approach will be used. Partial date assumptions for the definition of TEAEs are described in Section 6.1.8

6.1.5. Analysis Visit Windows

Statistical analyses will be based on scheduled visits as collected in the case report form (CRF) realigned on study days, which are defined based on the date of first emapalumab infusion (SD0) as follows:

Study Day = date of interest – date of first emapalumab infusion.

The following rules will be applied for MAS remission and glucocorticoid tapering.

- For the assessment of MAS remission and glucocorticoid tapering at Week 8, the SD56±5 days analysis period will be considered. Where several such observations occur in this time window, the one closest to SD56 will be selected. If there are 2 such observations that are equidistant from SD56, the observation that is after SD56 will be selected.

- For the assessment of time to MAS remission, see Section 6.1.7.

6.1.6. Pooling of Sites

As relatively few patients are expected in the study, center will not be taken into account in the analyses.

6.1.7. Derived Variables

- Change from baseline = value at current time point – value at baseline.

- Conversion factors: The following conversion factors will be used to convert days into months or years:

    - 1 month = 30.4375 days
    - 1 year = 365.25 days

- Treatment-emergent AE (TEAE) = any adverse event with an onset date/time after the start of the first emapalumab administration.

- Infusion-related reactions (IRRs) = any TEAE that is reported to have occurred within 24 hours after start of infusion and assessed as related to study treatment by the Investigator, excluding the following system organ classes (SOCs): "Infections and infestations," "Congenital familial and genetic disorders," "Neoplasms benign, malignant and unspecified (incl. cysts and polyps)," "Product issues," "Social circumstances," and "Surgical and medical procedures."

  If the onset time of the AE or the start time of the infusion is missing, then an AE with an onset date equal to an infusion date or infusion date + 1 will be considered for the assessment of IRRs.

- Infection: any TEAEs part of the SOC 'infection and infestation'.

- Duration of exposure (days) = date last study drug intake – date first study drug intake + 1

- Study Day = date of interest – date of first emapalumab infusion.

  This SAP follows the protocol assumption that the day of the first infusion is SD0. Starting with 0, rather than with 1, can cause trouble for SDTM programming since it is not compliant with the SDTM Implementation Guide[4]. SDTM data set will include two ways in counting the study day: starting with zero as in the protocol and starting with 1 as reccommended by the SDTM Inplementation Guide[4].

- Cumulative administered dose of emapalumab (mg/kg) = sum of administered emapalumab doses (mg/kg)
- Average administered dose of emapalumab (mg/kg) = (cumulative dose of emapalumab)/(number of doses)
- Equivalent dose of prednisone

  The Systemic Glucocorticoids data are collected into two modules of the paper CRF:

  - the 'Systemic Glucocorticoids from SD-3 until SD15" log
  - the 'Concomitant Medication' log

For the analysis of systemic glucocorticoid dose tapering, conversion to prednisone-equivalent dose may be required, if different glucocorticoids have been administered. Furthermore, the glucocorticoid dose will be expressed as prednisone-equivalent mg/kg body weight/day.

Steps to calculate the prednisone equivalent dose (mg/kg/day):

1) Select systemic glucocorticoids where route is IV or oral from the 'Systemic glucocorticoids from SD-3 until SD15' form. Reported doses in the 'Systemic glucocorticoids from SD-3 unit SD15' form are daily doses and the number of doses per day is set to 1.

2) Select concomitant medications with ATC code H02B (Glucocorticoids) from the 'Concomitant medication' form with IV or oral route of administration. Calculate the frequency per day as follows (this list should not be seen as exhaustive):

Frequency	Description	Number of doses per day
OB, QD	Once a day	1
BID	Twice a day	2
TIB	Three times a day	3
QID	Four times a day	4
QW	Every week	1/7
2xW	Twice per week	2/7
3xW	Three times per week	3/7
NxW	N times per week	N/7
EVERY 2 WEEKS	Every 2 weeks	1/14
QM	Every month	1/30.4375
QAD	Every other day	0.5
Once	Single intake	1/(stop date – start date +1)
PRN	As needed	0
Other	Other	0
UNK	Unknown	0

CI	Continuous infusion	0
Note: Administration of glucocorticoids with 'as needed', 'other', or 'unknown' frequency will not be included in the calculation of the equivalent dose.		

3) If the dose unit is not mg, then the following conversion will be done: 1 g = 1000 mg, 1 mcg = 0.001 mg. IV and oral routes of administration are equivalent.

4) Select the weight in kg from the physical examination visit closest to the glucocorticoids administration date.

5) Calculate the equivalent dose of prednisone using the following formula:

$$Equivalent\ dose\ \text{(mg/kg/day)} = \frac{Conversion\ Factor * Dose(mg) * Number\ of\ doses\ per\ day}{Weight\ (kg)}$$

where the conversion factor is:

1 for prednisone

1.25 for methylprednisolone

1 for prednisolone

- Glucocorticoids tapering = glucocorticoids permanently tapered
    - to the same (or lower) dose being administered before the occurrence of MAS (in patients already on treatment for sJIA/AOSD

      or
    - by at least 50% of the equivalent dose of prednisone administered at emapalumab treatment start (in those patients who present with MAS at sJIA/AOSD onset).

  The daily equivalent dose of prednisone will be compared with the daily equivalent dose of prednisone at SD0.

If it is not possible to establish if a patient has been treated for sJIA/AOSD or not before study start for all patients, or if it is not possible to retrieve glucocorticoids dose administered before the occurrence of MAS for all patients who already are treated for sJIA/AOSD, the glucocorticoids tapering endpoint will be changed. In this case the endpoint will be: "glucocorticoids permanently tapered at any time during the study by at least 50% of the equivalent dose of prednisone administered at emapalumab treatment start (SD0).

If glucocorticoid dosing data are unavailable at a given time point, the assumption that dose has not been further tapered from the previous available observation will be made. Glucocorticoid doses will be calculated as (prednisone-equivalent) mg/kg/day.

- MAS remission = resolution of clinical signs and symptoms according to the Investigator (MAS clinical signs and symptoms score ≤ 1) AND normalization of laboratory parameter relevant to MAS as follows:
    - White blood cell count (WBC) and platelet count above the lower limit of normal (LLN)
    - Lactate dehydrogenase (LDH) below 1.5 upper limit of normal (ULN)
    - Alanine aminotransferase/aspartate aminotransferase (ALT/AST) below 1.5 ULN
    - Fibrogen higher than 100 mg/dL
    - Ferritin level decreased by at least 80% from values at screening or baseline (whichever is higher) or below 2000 ng/mL, whichever is lower

  If one or more laboratory data are unavailable within the visit window, the LOCF approach will be used.

- MAS remission by week 8 = patients who meet MAS remission conditions in the period SD56 ± 5 days regardless the time of first MAS remission or its duration.

- Survival:

  Time to death = date of death – date of first emapalumab infusion + 1

  Patients who survive to the end of the study will be censored at the date of last contact. In case in which a patient withdrew consent the censoring date will be the date of withdrawal of consent.

- Time to MAS remission:

date of first MAS remission – date of first emapalumab infusion + 1

Time to the first MAS remission will be calculated from the date of first emapalumab infusion until the date of first MAS remission. Patients who do not meet the criteria of MAS remission will be censored at the date of last contact.

The MAS remission evaluation is based on a combination of assessments, including Investigator assessment and laboratory findings. The latest date of assessments, within the visit window of ± 3 days around the planned day of the visit, will be used for the calculation of the time to MAS remission.

- Time to achievement of permanent glucocorticoids tapering:

  date of glucocorticoids tapering – date of first emapalumab infusion + 1

  Time to achievement of glucocorticoids tapering will be calculated from the date of first emapalumab infusion until the date in which the target level of glucocorticoid dose reduction is permanently achieved. Patients who do not meet the criteria of glucocorticoids tapering will be censored at the date of last contact.

- The total daily dose of anakinra, canakinumab, ciclosporin, etoposide, methotrexate, and tocilizumab will be calculated for each subject using the same unit of measurement provided in the concomitant medication log.

  Total daily dose = dose * Number of doses per day

  Where the number of doses per day are derived using the same approach for the calculation of the equivalent dose of prednisone equivalent.

- Glucocorticoids tapering to ⩽1 mg/kg/day of the equivalent dose of prednisone:

  Achievement of permanent glucocorticoids tapering and last equivalent dose of prednisone is ⩽1 mg/kg/day.

6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but rather in the data listings only.

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

For TEAEs:

- If an AE with partial time occurs on the same day of the first infusion then the AE will be considered a TEAE.
- If an AE has missing date then the AE will be considered a TEAE.
- If partial dates of AE occur, the convention for replacing missing dates for the purpose of discriminate TEAE is as follows:
    - If just day is missing then the AE will be considered a TEAE when the mm/year of AE is the same of after the mm/year of the first infusion;
    - If just month is missing then the AE will be considered a TEAE when the year of AE is the same or after the year of the first infusion.

6.1.9. COVID-19

A Coronavirus Disease 2019 (COVID-19) Continuity Plan has been written to mitigate the negative effects of the COVID-19 pandemic on the conduct of this clinical trial.

The impact of COVID-19 on this clinical trials and trial participants will be extensively described both in tables and listings and in the CSR.

The following aspects will be summarized when due to COVID-19:

- Changes to treatment dispensation
- Changes to treatment administration
- Changes to visit windows to accommodate delays for some assessments
- Protocol deviations
- Missing efficacy endpoints Missing visits

7. Study Patients and Demographics

7.1. Disposition of Patients and Withdrawals from the study

The number of patients for each of the following categories will be presented in a table:

- All Treated Population
- Evaluable Population
- Completed patients
- Withdrawn from the study after start of treatment

- Reason of early study termination

Percentages will be calculated using the number of patients in the All Treated Population.

The total number of screening failures and the reasons for screen failure will be presented in a separate table.

In addition, assignment to analysis populations, the study completion status, and the reason of withdrawal from the study, and the screening failures will be listed.

7.2. Protocol Deviations

Protocol deviations will be identified and classified at the data review meeting.

Protocol deviations will be medically reviewed. Protocol deviations, especially related to occasional lack of adherence to the schedule of assessments or visit timings (primarily attributable to optimization in the clinical management of this fragile children population), will not be presented.

In particular, the following situations will not be considered as protocol deviations:

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

Relevant protocol deviations categorized as major and minor will be tabulated in a summary table. Individual major and minor protocol deviations will be listed by patient.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, sex, race, country of origin, height, weight, and body surface area (BSA) will be presented.

The MAS features present at the time of diagnosis of the current episode, the overall level of MAS activity, the functional testing related to HLH if available, and the optional genetic testing results, if available will be tabulated.

This analysis will be conducted for the All Treated Population and for the EVAL Population.

The number and percent of patients reporting various medical histories, grouped by MedDRA SOC and preferred term (PT) will be tabulated for the All Treated Population.

All demographics and baseline characteristics will be displayed in the data listings.

7.4. Exposure and Drug Administration

Investigational product administration will be summarized in terms of the number of doses received, average dose and cumulative dose per kg, and duration of exposure, from the first dose to the last dose of treatment.

This analysis will be conducted for the All Treated Population.

Drug administration and infusion details will be listed by patient and presented for the All Treated Population.

8. Efficacy Analysis

8.1. Efficacy Analysis

The following binary efficacy endpoints will be described using counts, proportions, and exact Clopper-Person 95% CI:

- Patients achieving MAS remission by Week 8 after initiation of emapalumab treatment
- Patients for whom at any time during the study glucocorticoids can be tapered
- Patients who tapered steroids to ≤1 mg/kg/day of prednisone equivalent dose
- Patients withdrawn from the study due to lack of efficacy

The following time-to-event efficacy endpoints will be analyzed descriptively:

- Time to first MAS remission
- Time to achievement of permanent glucocorticoids tapering
- Survival time

Summaries will include for each observed time, the survival estimate, failure rate, number of events and the number of patients remaining, also called population at risk. The median, lower quartile and upper quartile estimates of time-to-event and their 95% CI will be tabulated in a separate table. A Kaplan–Meier graph will be presented for each time-to-event endpoint.

The efficacy analysis will be based on the All Treated Population. Efficacy analyses will be repeated for the EVAL Population.

8.2. MAS Clinical Signs and Symptoms

Descriptive summaries of the overall level of disease activity, clinical signs and symptoms by visit will be tabulated and patient-level data will be displayed in listing.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, changes from baseline in clinical laboratory values, changes in vital signs, electrocardiogram (ECG), physical examination results, pregnancies, and emergence of anti-drug antibodies.

All safety analyses will be performed on the All Treated Population.

9.1. Adverse Events

A summary table will present the number and percent of patients reporting:

- Any AEs
- Treatment-emergent AEs (TEAEs)
- Non-TEAEs
- Serious AEs (SAEs)
- TEAEs leading to study treatment withdrawal
- TEAEs resulting in death

The table will show the number of events for each category.

All AEs, TEAEs, and SAEs will be coded using the latest version of MedDRA.

Summaries of the incidence (number and percentage of patients reporting the TEAE and the number of the TEAE) of TEAEs will be displayed by:

- PT
- SOC and PT
- SOC, PT and maximum severity
- SOC, PT and relationship to study drug

TEAEs related to study drug will be displayed by SOC and PT in a separate table for readability.

Summaries of the incidence of non-TEAEs will be displayed by PT.

In the case of multiple occurrences of the same TEAE in the same patient, each patient will only be counted once for each PT. However, all multiple occurrences will be included in the number of events. In the summaries showing severity and relationship to the study drug, the event with the maximum severity or strongest relationship will be reported. If a

particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = severe, relationship = related).

By-patient AE data listings with all AEs will be displayed. Adverse events that are not treatment emergent will be flagged.

9.1.1. Treatment-Emergent Adverse Events Leading to Study Treatment Discontinuation

The number and percentage of patients reporting the TEAE and the number of the TEAE leading to study treatment discontinuation, by SOC and PT will be tabulated for the All Treated Population.

By-patient data listing of TEAEs leading to study treatment discontinuation will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Serious adverse events will be tabulated by:

- PT
- SOC and PT.

By-patient data listing of AEs with a fatal outcome will be displayed. Serious adverse events will be described in a separate listing.

9.1.3. Infusion-related Reactions

The number and percentage of patients reporting IRRs and number of the events by PT will be tabulated in total and by maximum severity.

In the case of multiple occurrences of the same TEAE in the same patient, each patient will only be counted once for each PT. In the case of different severities of the multiple occurrences of the same IRR in the same patient, the worse severity will be used for analysis.

A by-patient listing of all IRR will be displayed.

9.1.4. Infections

The number and percentages of patients reporting infections and number of events, displayed by MedDRA PT, and will be tabulated in total and by maximum severity.

A by-patient listing of all infections will be displayed with date of sampling, pathogen, source, type of investigation, result (positive, negative, numerical value and units), and the AE it was linked to.

9.2. Clinical Laboratory Evaluations

The number of patients with clinical laboratory values below, within, or above the normal range by time point and in relation to baseline will be tabulated for each clinical laboratory analyte (shift table). Denominator of the percentages will be the number of patients in the All Treated Population.

Clinical chemistry and hematology results will be presented in separate tables.

Urinalysis results will not be tabulated. Abnormalities in urinalysis results assessed as medically relevant will be recorded as AEs and analyzed as described in Section 9.1.

Pregnancy test results will be tabulated by visit.

All laboratory values will be displayed in the data listings and those that are outside the normal range will be flagged, along with corresponding normal ranges.

9.3. Vital Signs

Descriptive summaries of actual values by study day and time point will be calculated for systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), oxygen saturation (%), and highest daily body temperature (Celsius).

During an infusion, day time points include:

- pre-dose assessment
- assessments during infusion at 15 minutes, 30 minutes, 45 minutes, 1 hour 15 minutes, 1 hour 30 minutes, 1 hour 45 minutes, and at the end of infusion and
- post-dose assessments at 1 hour, 2 hours, 3 hours, 4 hours, and 24 hours

For each infusion day, the post-infusion changes from pre-dose will be calculated and displayed in summary tables for systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), oxygen saturation (%), and highest daily body temperature (Celsius). From infusion #2 onwards the table will show the following time points: pre-dose, end of infusion, and post-dose assessments at 1 hour, 4 hours, and 24 hours, if applicable.

All vital signs will be provided in data listings. For systolic blood pressure, any reduction of ≥30% from baseline will be flagged.

9.4. Electrocardiograms

By-patient listing of all abnormal ECG results will be displayed.

9.5. Further Safety Evaluations

9.5.1. Physical Examination

By-patient listing of all abnormal findings will be displayed in each body system: general appearance, skin and mucous, ears/nose/throat, pulmonary, cardiac, gastro-intestinal, neurological, and other.

Abnormalities related to physical examination assessed as medically relevant will be recorded as AEs and analyzed as described in Section 9.1.

9.5.2. Pregnancy Outcome

Abnormalities related to pregnancy outcome assessed as medically relevant will be recorded as AEs and analyzed as described in Section 9.1.

9.5.3. Immunogenicity – anti-drug antibodies (ADAs)

A list of patients who developed ADAs and neutralizing antibodies will be presented, including information about the findings and timing of occurrence.

Descriptive summaries of ADA findings (neutralizing antibodies) will be tabulated when available.

9.5.4. Other Exploratory Analyses

Other exploratory analyses of safety data, including summaries for different subsets of patients, may be conducted. Any unplanned exploratory analysis performed will be clearly identified as such in the final CSR.

Data in the following CRF forms will be included in listings only:

- Imaging
- Brain magnetic resonance imaging (MRI)
- Cerebrospinal fluid (CSF) analysis
- Hospitalization
- Concomitant procedures
- Transfusion

9.6. Concomitant Medication

Concomitant medications by ATC level 2 will be summarized descriptively using counts and percentages. Concomitant medication administered for the treatment of sJIA will be also summarized and presented separately.

Concomitant use of biologics will be also summarized and presented separately.

Glucocorticoids administered since the date of MAS diagnosis will be summarized and presented separately as prednisone-equivalent mg/kg/day.

Medications that start prior to initiation of study drug will be considered prior medications, whether or not they were stopped prior to treatment. Any medications that are continuing or start post-dose will be considered to be concomitant. Medications that start prior to initiation of study drug and continue post-dose will be considered both prior and concomitant. If the start/stop dates of a medication are partially or completely missing, then the medication will be assumed to be concomitant if it cannot be definitely shown that it was not administered during the treatment period. Missing dates will not be replaced.

Concomitant medications and systemic glucocorticoids use from SD-3 until SD15 will be presented in separate listings.

Medications will be coded using anatomical therapeutic chemical (ATC) classification level 2 (World Health Organization Drug Dictionary [WHO-DD] Version 2019).

10. Pharmacokinetic/Pharmacodynamic Analysis

PK and PK/PD analyses will be conducted separately and are not included in this SAP.

However, descriptive summaries of circulating emapalumab and PD parameter, including marker levels, will be tabulated and included in this SAP. By-patient listing of circulating emapalumab, PD parameters, and marker levels will be displayed.

11. Changes from Planned Analysis

The Safety analysis set coincides with the All Treated Population and it is not listed in the analysis populations section. The EVAL Population has been added to check the robustness of the efficacy results. The Per-Protocol analysis set has been removed due to the small sample size and the introduction of the EVAL population.

Infusion-related reaction has been added in the safety endpoints (Section 2.2.1).

The glucocorticoids tapering endpoint has been modified when it is not possible to establish whether a patient have been treated for sJIA/AOSD or not before study start for all patients or when it is not possible to retrieve glucocorticoids dose administered before the occurrence of MAS for all patients who already are treated for sJIA/AOSD. In this case the endpoint is "Number of patients for whom, at any time during the study, glucocorticoids can be tapered by 50% (or more) of the dose administered at emapalumab treatment start.

IL-10, sCD163, TNFa and IL-18 may be analysed and/or reported separately.

The following have been added:

- safety patient profile reports (Section 12.1)
- descriptive summaries of neutralizing antibody in case of positive ADA results (Section 9.5.3)
- Number and percentage of patients who tapered steroids to ≤1mg/kg/day of the equivalent dose of prednisone (Section 6.1.7)

No other changes from the analyses specified in the protocol are planned.

12. Other Planned Analysis

12.1. Patient Profile Report

A graphical display of the evolution of laboratory parameters and medications administered, collected for an individual patient and also known as patient profile report, will be presented.

For each individual patient a PDF document will include the following data:

- Header: subject identification number, sex, study site, date of birth, age at screening.
- Administered dose (mg) of emapalumab by study day.
- Equivalent dose of prednisone (mg/kg/day) by study day.
- CXCL9 by study day.
- Laboratory test results by study day:
- C-Reactive protein (mg/dL)
- Ferritin (ng/dL)
- Triglycerides (mg/dL)
- ALT/GPT (IU/L)
- AST/GOT (IU/L)
- LHD (IU/L)
- White blood cell (x1000/mcL)
- Platelets (x1000/mcL)
- D-Dimer (mcg/mL)

A niddle plot, i.e., a plot in which data points are connected by a vertical line that connects to a horizontal baseline, will be used for the prescribed dose of emapalumab. A connected scatterplot, i.e., a plot in which data points are represented by a dot and connected by straight line segments, will be used for the equivalent dose of prednisone and potentially other sJIA/MAS treatments and relevant laboratory test results. The header and the plots for the prescribed dose and the equivalent dose of prednisone will be repeated at the beginning of each page.

The first page will include the CXCL9 data and in order the plots of the following laboratory test results: ALT/GPT (IU/L), AST/GOT (IU/L), and LHD (IU/L).

The second page will include in order the plots of the following laboratory test results: Ferritin (mcg/L), WBC (x10^9/L), platelets (x10^9/L), and D-Dimer (mcg/mL).

The third page will include in order the plots of the following laboratory test results: triglycerides (mmol/L) and C-Reactive protein (mg/dL).

The X-axis of all plots will show the study day ranging from -14 to 70 for all patients.

Laboratory normal ranges will be included in the plots when available.

An example of patient profile report document is presented in Section 15.2.

The same plots will be produced in RTF format with the header, the prescribed dose of emapalumab, and the equivalent dose of prednisone available only on the first page.

Additional data, i.e. laboratory test results or concomitant medications, may be added to the patient profile report.

13. References

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.

2. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm

3. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf

4. CDISC. SDTM Implementation Guide: Human Clinical Trials, Version 3.2, 2013. https://www.cdisc.org/standards/foundational/sdtmig

14. Tables, Listings, and Figures

All tables, listings, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

14.1. Planned Table Descriptions

The following are planned summary tables for protocol number NI-0501-06. The table numbers and page numbers are placeholders only and will be determined when the tables are produced.

Table 3: Demographic Data Summary Tables and Figures

Table/Figure Number	Population(s)	Table/Figure Title / Summary	Supporting Listing
14.1 Demographics and Baseline Characteristics			
Table 14.1.1	All Treated	Study Populations and Patient Disposition	16.2.1.1 16.2.1.2
Table 14.1.2	Screen Failures	Reason of Screening Failure	16.2.1.3
Table 14.1.3.1	All Treated, EVAL	Summary of Demographics and Baseline Characteristics	16.2.4.1
Table 14.1.3.2	All Treated, EVAL	MAS Features Present at the Time of Diagnosis of the Current Episode	16.2.4.5
Table 14.1.3.3	All Treated, EVAL	Overall Level of MAS Activity	16.2.4.6
Table 14.1.3.4	All Treated, EVAL	Functional Testing Related to HLH	16.2.4.7
Table 14.1.3.5	All Treated, EVAL	Genetic Testing	16.2.4.8
Table 14.1.3.6	All Treated	Medical History by System Organ Class and Preferred Term	16.2.4.2
Table 14.1.4	All Treated	Protocol Deviations	16.2.2.1

Table 4 Efficacy Data

Table Number	Population(s)	Table Title / Summary	Supporting Listing
14.2 Efficacy Data			
Table 14.2.1	All Treated, EVAL	MAS Remission, Glucocorticoid Tapering, and Lack of Efficacy	16.2.6.1 16.2.1.2
Table 14.2.2.1	All Treated, EVAL	Statistical Analysis of Time to MAS Remission: Event-free Estimates by Day	16.2.6.1
Table 14.2.2.2	All Treated, EVAL	Statistical Analysis of Time to MAS Remission: Median and Quartile Estimates of Time to MAS Remission	16.2.6.1
Table 14.2.3.1	All Treated, EVAL	Statistical analysis of Time to Glucocorticoid Tapering: Event-free Estimates by Day	16.2.6.1
Table 14.2.3.2	All Treated, EVAL	Statistical Analysis of Time to Glucocorticoid Tapering: Median and Quartile Estimates of Time to Glucocorticoid Tapering	16.2.6.1
Table 14.2.4.1	All Treated, EVAL	Statistical Analysis of Time to Death: Survival Estimates by Day	16.2.6.1
Table 14.2.4.2	All Treated, EVAL	Statistical Analysis of Time to Death: Median and Quartile Estimates of the Survival Time	16.2.6.1
Table 14.2.5	All Treated, EVAL	MAS Clinical Signs and Symptoms	16.2.4.6

Table 5 Safety Data

Table Number	Population(s)	Table Title / Summary	Supporting Listing
14.3 Safety Data			
14.3.1 Displays of Adverse Events			
Table 14.3.1.1	All Treated	Summary of All Adverse Events	16.2.7.1
Table 14.3.1.2.1	All Treated	Treatment-Emergent Adverse Events by Preferred Term	16.2.7.1
Table 14.3.1.2.2	All Treated	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	16.2.7.1
Table 14.3.1.3	All Treated	Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term	16.2.7.1
Table 14.3.1.4	All Treated	Treatment-Emergent Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term	16.2.7.1
Table 14.3.1.5	All Treated	Treatment-Emergent Adverse Events Related to the Study Drug by System Organ Class and Preferred Term	16.2.7.1
Table 14.3.1.6	All Treated	Non-Treatment-Emergent Adverse Events by Preferred Term	16.2.7.1
14.3.2 Other Serious and Significant Adverse Events			
Table 14.3.2.1.1	All Treated	Serious Treatment-Emergent Adverse Events by Preferred Term	16.2.7.2
Table 14.3.2.1.2	All Treated	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	16.2.7.2
Table 14.3.2.2	All Treated	Treatment-Emergent Adverse Events Leading to Study Treatment Discontinuation by System Organ Class and Preferred Term	16.2.7.3
Table 14.3.2.3	All Treated	Infusion-related Reaction by Preferred Term	16.2.7.1
Table 14.3.2.4	All Treated	Infections by Maximum Severity and Preferred Term.	16.2.9.14

Table Number	Population(s)	Table Title / Summary	Supporting Listing
14.3.5 Laboratory Data Summary Tables			
Table 14.3.5.1	All Treated	Shift Table of Clinical Chemistry Results	16.2.8.1
Table 14.3.5.2	All Treated	Shift Table of Hematology Results	16.2.8.2
Table 14.3.5.3	All Treated (women)	Pregnancy Test Results	16.2.8.4
14.3.6 Other Safety Data Summary Tables			
Table 14.3.6.1	All Treated	Vital Sign Results	16.2.9.1
Table 14.3.6.2.1	All Treated	Concomitant Medications by ATC Level 2 and Preferred Term	16.2.9.3
Table 14.3.6.2.2	All Treated	Concomitant Medications Administered for the Treatment of sJIA by ATC Level 2 and Preferred Term	16.2.9.3
Table 14.3.6.2.3	All Treated	Concomitant use of Biologics by ATC Level 2 and Preferred Term	16.2.9.3
Table 14.3.6.2.4	All Treated	Glucocorticoids Administered Since the Date of MAS Diagnosis	16.2.9.3
Table 14.3.6.3	All Treated	Summary of Exposure	16.2.5.1

Table 6 Pharmacokinetic/Pharmacodynamic Data

Table Number	Population(s)	Table Title / Summary	Supporting Listing
14.4 Pharmacokinetic and Pharmacodynamic Data Summary Tables			
Table 14.4.1	All Treated	Summary of Pharmacodynamic Parameters	16.2.10.1
Table 14.4.2	All Treated	Summary of Circulating Emapalumab	16.2.10.1
Table 14.4.3	All Treated	Summary of ADA Parameters	16.2.10.1

14.2. Planned Listing Descriptions

The following are planned data and patient data listings for protocol number NI-0501-06.

In general, one listing will be produced per CRF domain.

All listings will be sorted by site and patient number.

All calculated variables will be included in the listings.

In all listings, a blank line will be placed between each patient. Within a data listing, if an item appears repetitively (e.g., patient number), then only the first occurrence will be displayed.

In data listings, the information for a patient will be kept on a single page if possible, rather than splitting it across multiple pages.

Table 6: Planned Data Listings

Data Listing Number	Population	Data Listing Title / Summary
16.2 Patient Data Listings **16.2.1 Patient Disposition**		
Data listing 16.2.1.1	All Treated	Assignment to Analysis Populations
Data listing 16.2.1.2	All Treated	Study Completion Status
Data listing 16.2.1.3	Screen Failures	List of Reasons for Screening Failure
16.2.2. Protocol Deviations		
Data listing 16.2.2.1	All Treated	Protocol Deviations
16.2.3 Patients Excluded from the Evaluable Set		
Data listing 16.2.3.1	All Treated	List of Patients Excluded from EVAL Population
16.2.4 Demographics and Other Characteristics		
Data listing 16.2.4.1	All Treated	Demographic Data
Data listing 16.2.4.2	All Treated	Medical History
Data listing 16.2.4.3	All Treated	Prior Medications
Data listing 16.2.4.4	All Treated	sJIA and MAS History
Data listing 16.2.4.5	All Treated	MAS Diagnosis (Current Episode)
Data listing 16.2.4.6	All Treated	MAS Clinical Signs and Symptoms
Data listing 16.2.4.7	All Treated	Functional Testing Related to HLH
Data listing 16.2.4.8	All Treated	Genetic Testing
16.2.5 Drug Exposure		
Data Listing 16.2.5.1	All Treated	Drug Administration
Data Listing 16.2.5.2	All Treated	Infusion
16.2.6 Efficacy Listings		
Data listing 16.2.6.1	All Treated	MAS Remission, Glucocorticoid Tapering, and Mortality
16.2.7 Adverse Event Listings		
Data listing 16.2.7.1	All Treated	Adverse Events
Data listing 16.2.7.2	All Treated	Serious Adverse Events

Data Listing Number	Population	Data Listing Title / Summary
Data listing 16.2.7.3	All Treated	Treatment-Emergent Adverse Events Leading to Study Treatment Discontinuation
Data listing 16.2.7.4	All Treated	Adverse Events Leading to Death
16.2.8 Laboratory Data Listings		
Data listing 16.2.8.1	All Treated	Clinical Chemistry Results
Data listing 16.2.8.2	All Treated	Hematology Results
Data listing 16.2.8.3	All Treated	Urinalysis Results
Data listing 16.2.8.4	All Treated (Women)	Pregnancy Test Results
Data listing 16.2.8.5	All Treated	Other Laboratory Measurement Results
16.2.9 Other Clinical Observations and Measurements		
Data listing 16.2.9.1	All Treated	Vital Signs
Data listing 16.2.9.2	All Treated	Physical Examination Results
Data listing 16.2.9.3	All Treated	Concomitant Medications
Data listing 16.2.9.4	All Treated	Concomitant Procedure
Data listing 16.2.9.5	All Treated	Systemic Glucocorticoids from SD-3 until SD15
Data listing 16.2.9.6	All Treated	ECG Results
Data listing 16.2.9.7	All Treated	Imaging: Abdominal Ultrasound
Data listing 16.2.9.8	All Treated	Imaging: X-Ray
Data listing 16.2.9.9	All Treated	Brain MRI
Data listing 16.2.9.10	All Treated	CSF Analysis
Data listing 16.2.9.11	All Treated	Hospitalization
Data listing 16.2.9.12	All Treated	Serum PK/PD/ADA
Data listing 16.2.9.13	All Treated	Transfusion
Data listing 16.2.9.14	All Treated	Infections
Data listing 16.2.9.15	All Treated	Infusion-related Reactions
Data listing 16.2.9.16	All Treated	ADA Findings
16.2.10 Pharmacokinetic and Pharmacodynamic Measurements		
Data listing 16.2.10.1	All Treated	Pharmacodynamic Measurements
Data listing 16.2.10.2	All Treated	Pharmacokinetic Measurements

14.3. Planned Figure Descriptions

The following are planned summary figures for protocol number NI-0501-06. The figure numbers and page numbers are placeholders only and will be determined when the figures are produced.

Table 7 Planned Figures

Figure Number	Population	Figure Title / Summary	Supporting Listing
Figure 14.2.1	All Treated	Vital Sign Profiles: Systolic Blood Pressure	16.2.9.1
Figure 14.2.2	All Treated	Vital Sign Profiles: Diastolic Blood Pressure	16.2.9.1
Figure 14.2.3	All Treated	Vital Sign Profiles: Heart Rate	16.2.9.1
Figure 14.2.4	All Treated	Vital Sign Profiles: Temperature	16.2.9.1
Figure 14.2.5	All Treated	Vital Sign Profiles: Oxygen Saturation	16.2.9.1
Figure 14.2.6	All Treated	Statistical Analysis of Time to MAS Remission: Kaplan-Meier Curve	16.2.6.2
Figure 14.2.7	All Treated	Statistical Analysis of Time to Glucocorticoid Tapering: Kaplan-Meier Curve	16.2.6.2
Figure 14.2.8	All Treated	Statistical Analysis of Time to Death: Kaplan-Meier curve	16.2.6.2

Moreover, a patient profile report will be produced for each individual. The PDF document including the patient profile will be named pp_<*subjectid*>.pdf. .

15. Tables, Listings, and Listing Shells

15.1. Standard Layout for all Tables, Listings, and Figures

Table and listing shells are provided as a separate document.

Note that programming notes may be added if appropriate after each TLF shell.

The final statistical tables will be produced in the format of the shells and will additionally include “double” page numbering in the format “page xx of yy.” The first page numbering will count all pages of the document continuously and the second numbering will count the pages for each table separately.

The standardized layout of tables and listing will include information about source data, program path and name, date and time of program execution, and date of database.

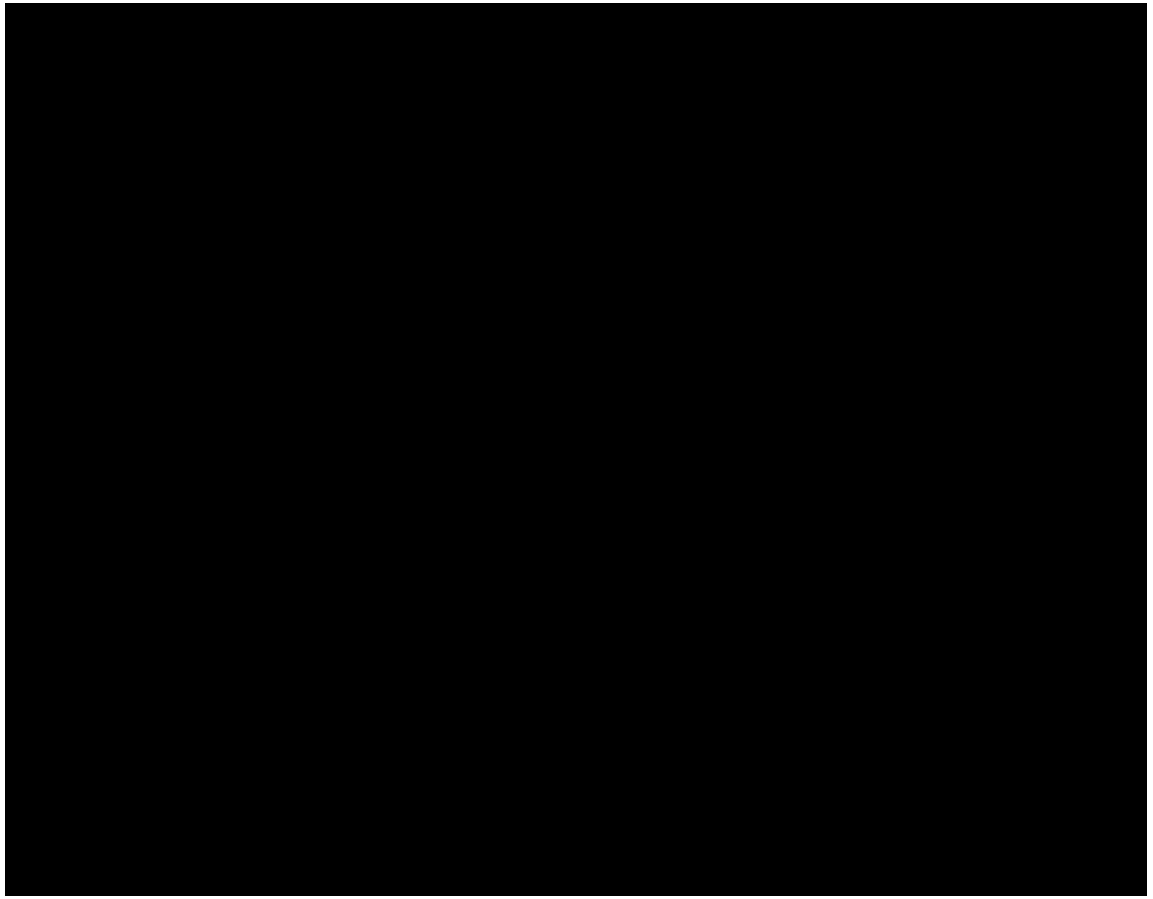
The final statistical output will be provided as fully bookmarked pdf file, including a table of contents.

No shells are provided for figures. However, an example of a patient profile report is provided in Section 15.2.

15.2. Planned Patient Profile Shells

The planned patient profile shells are presented in Figure 1.

Figure 1: Patient Profile Shells



Appendix 1: Premier Research Library of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
AOSD	adult-onset Still's disease
ATC	anatomical therapeutic chemical
ALT	alanine aminotransferase
ASA	American statistical association
AST	aspartate aminotransferase
AUC	area under the curve
BSA	body surface area
CBC	complete blood count
CEOI	concentration at the end of infusion
CI	confidence intervals
Cmax	concentration corresponding to Tmax
CRF	case report form
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSR	clinical study report
Ctrough	concentration just before administration
CXCL9	Chemokine (C-X-C Motif) Ligand 9

Abbreviation	Definition
CXCL10	Chemokine (C-X-C Motif) Ligand 10
DMC	data monitoring committee
ECG	electrocardiogram
EVAL	evaluable
HLH	Hemophagocytic lymphohistiocytosis
IL	interleukin
INFγ	Interferon gamma
IMP	Investigational medicine product
LDH	lactate dehydrogenase
LFT	liver function tests
LLN	lower limit of normal
LOCF	last observation carried forward
MAS	macrophage activation syndrome
MedDRA	medical dictionary for regulatory activities
MRI	magnetic resonance imaging
NCA	non-compartmental pharmacokinetic analysis
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SAS®	a software system used for data analysis
sCD25	soluble CD25 (i.e soluble IL-2 receptor)
sCD163	soluble CD163
SD	study day
sHLH	secondary HLH
sJIA	juvenile idiopathic arthritis
SOC	system organ class
t1/2	serum half-life
TEAE	treatment-emergent adverse event
TLF	table listing figure
Tmax	time of maximum observed concentration
TMDD	target-mediated drug disposition
TNFα	tumor necrosis factor alpha
US	ultrasound
ULN	upper limit of normal
WBC	white blood cell
WHO-DD	world health organization drug dictionary

Errata of Statistical Analysis Plan

Sponsor	*Sobi AG*
Protocol Title:	*A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of emapalumab, an anti-interferon gamma (anti- IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) or Adult-onset Still's Disease (AOSD) developing Macrophage Activation Syndrome/secondary HLH (MAS/sHLH)*
Protocol Number:	*NI-0501-06*
Premier Research PCN:	*NOVI 176557*
Document Version:	*Final Version 2.0*
Document Date:	*22-Jul-2021*

Approvals

Role	Signatures
Biostatistician	Print Name: [redacted] Senior Biostatistician, Premier Research
	Sign Name: [redacted]

Role	Signatures
Sobi AG Representative	Print Name: [redacted] Statistical Science Director, Sobi
	Sign Name: [redacted]

Document History

The errata of the statistical analysis plan (SAP) describes the last changes compared to signed statistical analysis plan version 2.0 (dated on 29-OCT-2020) reported for Sobi AG protocol number NI-0501-06 (A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) or Adult-onset Still's Disease (AOSD) developing Macrophage Activation Syndrome/secondary HLH (MAS/sHLH)).

The changes identified in this document will be included in the clinical study report (CSR), in regulatory submissions, or future manuscripts. Post-hoc exploratory analyses are not part of this document and should be specified in a separate document, if any. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The changes described hereafter will be submitted to file prior to the database lock pertaining to study NI-0501-06.

Version 1.0 (Dated 19 April 2021):

Not applicable – first version.

Version 2.0 (Dated: 22 July 2021):

Section 6.1.5 – Analysis Visit Windows/ Assessment selection: New rules added for selection of assessments used in outputs where multiple records exist within a visit window.

Section 6.1.7 - Derived variables/ MAS remission: Updated visit windowing rules for MAS remission and time to MAS remission to be in line with assessment selection rules.

Section 6.1.7 – Derived variables/ Definition of Biologics: Updated from L03AC to L04AC due to typo when defining medications.

Section 6.1.7 – Derived variables/ Steps to calculate the prednisone equivalent dose (mg/kg/day) and total daily doses of anakinra, canakinumab, ciclosporin, etoposide, methotrexate, and tocilizumab: Wording added to clarify prednisone equivalent dose and total daily doses should be calculated from study day -180 and until the end of the study.

Section 6.1.8 - Data Adjustments/Handling/Conventions/ Handling partial or missing start/stop dates for equivalent daily dose of prednisone, and daily total doses of anakinra, canakinumab, ciclosporin, etoposide, methotrexate, and tocilizumab: Clarified derivation of medication imputed dates and when to calculate equivalent dose of prednisone and total daily dose when start date is missing and end date is not missing.

Section 7.2 – Protocol Deviations: Implemented new terminology used in categorization of deviations referenced in the ICH E3 Q&A R1 and ICH GCP E6 R2 and update to terminology in output displays to align.

Section 6.1.8 - Data Adjustments/Handling/Conventions and Section 9.1 – Adverse Events: Correction to MedDRA version used in coding.

Summary of Amended Sections

SAP Section(s)/ Purpose	Initial text from SAP version 2.0	Rationale / Updated text
Section 6.1.5 – Analysis Visit Windows / Assessment selection	No rules specified for the selection of assessments where multiple assessments may be eligible for tables except for Week 8 assessment.	Rules for selection of assessments used in Week 8 assessment of MAS remission provided in section 6.1.5, however no information provided for other safety and efficacy analysis and timepoint. / *"In case there are two (or more) assessments from a subject within the visit window, the assessment with the date closest to the expected visit date will be used for the efficacy and safety analysis. In the event that two assessments are available and equidistant from the expected visit date, the result from earliest assessment will be used. If there are still two or more assessments recorded during the same day, the earliest measurement before the emapalumab infusion will be used (not applicable for the assessment of MAS remission at Week 8). If there is no treatment on the selected day, the earliest assessment of the selected day will be selected (not applicable for the assessment of MAS remission at Week 8). If there is no possibility to identify the earliest assessment, the assessment with the earliest sequence number will be used."*

<table>
<tr><th>SAP Section(s)/
Purpose</th><th>Initial text from SAP version 2.0</th><th>Rationale
/
Updated text</th></tr>
<tr><td>Section 6.1.7 - Derived variables/
New Age group variable</td><td>No age group was defined in the SAP version 2.0.</td><td>Results will be posted and published in Eudra CT and predefined age group should be displayed as per template, therefore age group variable will be created and presented in the demographic table.
/
The new age group variable will be defined as follows
<table>
<tr><th>Age Group</th><th>Definition</th></tr>
<tr><td>Newborns (0-27 days)</td><td>0 ≤ (Date of informed consent – Date of Birth) ≤ 27</td></tr>
<tr><td>Infant and toddlers (28 days - 23 months)</td><td>28 ≤ (Date of informed consent – Date of Birth) and age in years = 1</td></tr>
<tr><td>Children (2-11 years)</td><td>2 <= age in years <= 11</td></tr>
<tr><td>Adolescents (12-17 years)</td><td>12 <= age in years <= 17</td></tr>
<tr><td>From 18-64 years</td><td>18<= age in years <= 64</td></tr>
<tr><td>From 65-84 years</td><td>65 <= age in years <= 84</td></tr>
<tr><td>Over 85 years</td><td>85 <= age in years</td></tr>
</table></td></tr>
</table>

Section 6.1.7 - Derived variables/ IRR with missing start date	"If the onset time of the AE or the start time of the infusion is missing, then an AE with an onset date equal to an infusion date or infusion date + 1 will be considered for the assessment of IRRs."	Describe how completely missing AE start date will be imputed for an IRR assessment. / Corrected to *"If the onset time of the AE or the start time of the infusion is missing, then an AE with an onset date equal to an infusion date or infusion date + 1 will be considered for the assessment of IRRs. If the onset date of the AE is completely missing, the AE will be considered as IRR (most conservative approach)."*
Section 6.1.7 - Derived variables/ Infection definition	"Infection = any TEAEs part of the SOC 'infection and infestation'"	Infection definition updated to a broader search strategy for all potential infections with emapalumab use. / Updated to *Infection = All AEs in the SOC "Infections and infestations" or in the HLGT "Microbiology and serology investigations".*
Section 6.1.7 - Derived variables/ Selection of systemic glucocorticoid dose	"Select concomitant medications with ATC code H02B"	Selection should be applied on ATC code H02AB. The ATC level 4 H02AB correctly and specifically corresponds to GLUCOCORTICOIDS, whereas in the SAP version 2.0, selection by code H02B is an error, as this code does not include plain glucocorticoid products, but only combinations (CORTICOSTEROIDS FOR SYSTEMIC USE, COMBINATIONS).

		/ Corrected to "*Select medications with ATC Level 4 code H02AB*"
Section 6.1.7 – Derived variables/ Steps to calculate the prednisone equivalent dose (mg/kg/day)	"4) Select the weight in kg from the physical examination visit closest to the glucocorticoids administration date."	Further clarification on which assessment should be selected if observations are equidistant and prior to first treatment administration. / Under the Steps to calculate the prednisone equivalent dose (mg/kg/day), corrected to: *"4) Select the weight in kg from the physical examination visit closest to the glucocorticoids administration date. If there are 2 such observations that are equidistant from the glucocorticoids administration date, the first observation will be selected. Prior to first treatment administration, the weight at screening will be selected."*
Section 6.1.7 – Derived variables/ Steps to calculate the prednisone equivalent dose (mg/kg/day) and total daily doses of anakinra, canakinumab, ciclosporin, etoposide, methotrexate, and tocilizumab	No specification of time frame for calculation of equivalent prednisone dose or total daily doses of anakinra, canakinumab, ciclosporin, etoposide, methotrexate, and tocilizumab.	To add detail on when equivalent daily dose of prednisone, and daily total doses of anakinra, canakinumab, ciclosporin, etoposide, methotrexate, and tocilizumab will be derived. / Specifications added: *"Equivalent daily dose of prednisone, and daily total doses of anakinra, canakinumab, ciclosporin, etoposide, methotrexate, and tocilizumab will be derived from study day -180 until the end of the study."*

Section 6.1.7 - Derived variables/ Conversion factor for derivation of equivalent dose of prednisone	"where the conversion factor is: 1 for prednisone 1.25 for methylprednisolone 1 for prednisolone"	The use of dexamethasone was not considered initially and should be added as administered to some patients. / Corrected to *"where the conversion factor is:* *1 for prednisone* *1.25 for methylprednisolone* *1 for prednisolone* *6 for dexamethasone"*
Section 6.1.7 - Derived variables/ MAS remission	"The MAS remission evaluation is based on a combination of assessments, including Investigator assessment and laboratory findings. The latest date of assessments, within the visit window of ± 3 days around the planned day of the visit, will be used for the calculation of the time to MAS remission."	To clarify assessment handling for the MAS remission. Currently in the SAP, it specifies "If one or more laboratory data are unavailable within the visit window" but no details on the visit windows. / Updated to: *"The MAS remission evaluation is based on a combination of assessments, including Investigator assessment and laboratory findings, and will only be calculated if the Investigator assessment has been performed. The earliest date of assessments, within a visit window of ± 3 days, will be used in the calculation of the individual assessments feeding into MAS remission. See Section 6.1.5 for further details on assessment selection. The latest date of the combination of assessments within a visit window will be used for the calculation of time to MAS remission and MAS remission."*

Section 6.1.7 – Derived variables/ Definition of Biologics	No specification of biologics concomitant used is specified in the SAP version 2.0.	Concomitant use of relevant biologics will be also summarized per section 9.6 however no specification was provided under section 6.1.7. / Specifications added: *"Relevant concomitant biologics medications will be defined as medications from ATC 4 levels L04AB, L04AC."*
Section 6.1.8 - Data Adjustments/Handling/Conventions/ Handling partial or missing start/stop dates for equivalent daily dose of prednisone, and daily total doses of anakinra, canakinumab, ciclosporin, etoposide, methotrexate, and tocilizumab	No details regarding how to handle partial or missing start/stop dates for equivalent daily dose of prednisone, and daily total doses of anakinra, canakinumab, ciclosporin, etoposide, methotrexate, and tocilizumab	To add detail on how to handle partial or missing start/stop dates for equivalent daily dose of prednisone, and daily total doses of anakinra, canakinumab, ciclosporin, etoposide, methotrexate, and tocilizumab. / Imputation of partial/missing medication start or stop dates for equivalent daily dose of prednisone and daily total doses of anakinra, canakinumab, ciclosporin, etoposide, methotrexate, and tocilizumab: -Partial medication end date • If only month and year are available, medication end date will be imputed to the last day of the corresponding month • If only year is available, medication end date will be imputed to the 31st of December of the corresponding year -Partial medication start date • If only month and year are available, medication start

		date will be imputed to the 1st day of the corresponding month • If only year is available, medication start date will be imputed to the 1st of January of the corresponding year. -Medication start and end dates are both missing, then the record of the medication will not be considered (i.e. no derivation of equivalent dose of prednisone or daily dose of anakinra, ….). -Medication end date is missing (and medication start date not missing) • When medication end date is missing and "Ongoing" is not ticked ▪ If medication start date < Study day -180, then this record will not be considered (i.e. no derivation of equivalent dose of prednisone or daily dose of anakinra, ….). ▪ If Study day -180 ≤ medication start date < Study day 0, then medication end date is set to medication start date. ▪ If medication start date ≥ Study day 0, then medication end date is set to end of study date of

		the corresponding patient. • When "Ongoing" is ticked, then medication end date is set to end of study date of the corresponding patient unless medication start date > end of study date then set to medication start date of the corresponding patient. -Medication start date is missing (and Medication end date is not missing) • If medication end date < Study day -180, then this record will not be considered (i.e. no derivation of equivalent dose of prednisone or daily dose of anakinra, ….). • If medication end date ≥ Study day -180, then the medication start date will be set to the medication end date. Note: medication end date if available should have priority over the ongoing flag.
Section 6.1.8 - Data Adjustments/ Handling/ Conventions/ Handling < LLOQ, > ULOQ	No details regarding how the laboratory data below or above the limit of quantification will be handled.	Imputation rules to be applied to shift table when laboratory data below or above the limit of quantification. Laboratory listings will present data as collected. / Imputation rules added: "Values below the lower limit of quantitation (i.e. < LLOQ) for individual values will be imputed to zeros when summarizing for

		descriptive statistics. Values above the upper limit of quantitation (i.e. > ULOQ) for individual values will be imputed to ULOQ values when summarizing for descriptive statistics."
Section 7.2 – Protocol Deviations / Correction	"Relevant protocol deviations categorized as major and minor will be tabulated in a summary table. Individual major and minor protocol deviations will be listed by patient."	Change in category terminology (applicable to the classification of deviations from a study conduct perspective) to align with references in regulations ICH E3 Q&A R1 and ICH GCP E6 R2. / Corrected to: *"Relevant protocol deviations categorized as important and non important will be tabulated in a summary table. Individual important and non important protocol deviations will be listed by patient."*
Section 7.3 - Demographics and Other Baseline Characteristics / New Age group variable	"Summary statistics for age, sex, race, country of origin, height, weight, and body surface area (BSA) will be presented."	Pre-defined age group, as defined per Eudra CT publishing template, was added (see Section 6.1.7) and will be summarized in the demographic table. / Updated to: *"Summary statistics for age (as continuous and categorical variables), sex, race, country of origin, height, weight, and body surface area (BSA) will be presented."*
Section 9.1.2 – Deaths and Serious Adverse Events/ Correction	"Serious adverse events will be tabulated by:"	Corrected to: *"Serious TEAEs will be tabulated by:"*
Section 6.1.8 – Data	Section 6.1.8 states "Adverse events will be coded using the latest version of the Medical Dictionary	Correction of the MedDRA version.

Adjustments/ Handling/ Conventions and Section 9.1 – Adverse Events / Correction	for Regulatory Activities (MedDRA)." Section 9.1 states "All AEs, TEAEs, and SAEs will be coded using the latest version of MedDRA."	/ Corrected to: *Section 6.1.8: "Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0."* *Section 9.1: "All AEs, TEAEs, and SAEs will be coded using MedDRA version 23.0."*
Section 9.3 – Vital signs/ Temperature presented per route	No details regarding how the temperature will be presented.	As temperature could be measured at different location, summary statistics and change from baseline should consider the location/route. / Sentence added: *"Highest daily body temperature will be presented by route; shift tables will display baseline and post-baseline body temperatures from the same route."*
Sections 9.6 – Concomitant Medication / Remove of Concomitant Medications Administered for the Treatment of sJIA analysis	"Concomitant Medications Administered for the Treatment of sJIA will be also summarized and presented separately."	A number of medications can be administered to treat both sJIA and MAS. The investigators may record either sJIA or MAS (or both) as indication for their use. A summary table presenting only medications administered to treat sJIA may provide partial and potentially misleading information. All concomitant medications with their reported indications will be presented in listings. It was decided that the following sentence will be removed: *"Concomitant medication administered for the treatment of sJIA will be also summarized and presented separately."*

Section 9.6 – Concomitant Medication/ WHO-DD version correction	"Medications will be coded using anatomical therapeutic chemical (ATC) classification level 2 (World Health Organization Drug Dictionary [WHO-DD] Version 2019)."	Correction of the WHO-DD version / Corrected to: *"Medications will be coded using anatomical therapeutic chemical (ATC) classification level 2 (World Health Organization Drug Dictionary [WHO-DD] Version March 2020)."*
Section 12.1 – Patient profile report/ Removal of DOB	"Header: subject identification number, sex, study site, date of birth, age at screening."	As described for Section 15.2, Date of birth (DOB) is protected information under the GDPR, therefore the DOB was removed from the patient profile. / Corrected to: *"Header: subject identification number, sex, study site, age at screening (years)."*
Section 14.1, Table 5 – Safety Data/ Remove of Concomitant Medications Administered for the Treatment of sJIA table	Concomitant Medications Administered for the Treatment of sJIA by ATC Level 2 and Preferred Term	As detailed for Section 9.6, the table on Concomitant Medications Administered for the Treatment of sJIA by ATC Level 2 and Preferred Term will be removed. / Remove Table 14.3.6.2.2 from the list of Tables.
Section 14.1, Table 5 – Safety Data/ Update Concomitant use of Biologics	"Concomitant use of Biologics by ATC Level 2 and Preferred Term"	Display by ATC level 4 instead on ATC level 2 as selection of medications are based on ATC Level 4. / Corrected to: *"Concomitant use of Biologics by ATC Level 4 and Preferred Term"*
Section 14.3 –	Figures 14.2.6, 14.2.7, 14.2.8, described as	Per section 8.1, "The efficacy

Planned Figure Descriptions/ Update populations	Kaplan Meier curves, will be produced on the All Treated Population per the Population column.	analysis will be based on the All Treated Population. Efficacy analyses will be repeated for the EVAL Population."; figures should also be produced on the Evaluable Population / Corrected to: *"All Treated Population, All Evaluable Population"*
Section 15.2 – Figure 1: Patient Profile Shells/ Remove DOB from the Patient Profile	[redacted]	Date of birth (DOB) is protected information under the GDPR. The age in years is sufficient and there is no need to present the DOB. / Removal of Date of Birth in the header of Patient Profile as age in years is sufficient.

List of Abbreviations

Abbreviation	Definition
AE	adverse event
AOSD	adult onset Still's disease
ATC	anatomical therapeutic chemical
BSA	body surface area
CSR	clinical study report
DOB	date of birth
Eudra CT	European Union Drug Regulating Authorities Clinical Trials Database
GCP	Good Clinical Practice
GDPR	general data protection regulation
HLGT	high level group term
HLH	hemophagocytic lymphohistiocytosis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRR	infusion related reactions
LLOQ	lower limit of quantification
MAS	macrophage activation syndrome
MedDRA	medical dictionary for regulatory activities
SAP	statistical analysis plan
SD	study day

Abbreviation	Definition
SOC	system organ class
sJIA	systemic juvenile idiopathic arthritis
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
WHO-DD	world health organization drug dictionary

Sponsor	*Sobi AG*
Protocol Title:	*A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) or Adult-onset Still's Disease (AOSD) developing Macrophage Activation Syndrome/secondary HLH (MAS/sHLH)*
Protocol Number:	*NI-0501-06*
Premier Research PCN:	*NOVI 176557*
Document Version:	*Final Version 1.0*
Document Date:	*22-Apr-2021*

Approvals

Role	Signatures
Biostatistician	Print Name: [redacted] Senior Biostatistician, Premier Research
	Sign Name: [redacted]

Role	Signatures
Sobi AG Representative	Print Name: [redacted] Senior Statistical Scientist, Sobi
	Sign Name: [redacted]

Document History

The post-hoc analysis plan describes additional analyses to the signed Statistical Analysis Plan (SAP) version 2.0 (dated on 29-OCT-2020) considering the SAP Errata version 1.0 (dated on 19-Apr-2021) reported for Sobi AG protocol number NI-0501-06 (A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) or Adult-onset Still's Disease (AOSD) developing Macrophage Activation Syndrome/secondary HLH (MAS/sHLH)).

The post-hoc analyses identified in this document will be included in the clinical study report (CSR), in regulatory submissions, or future manuscripts. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR. In that regards, "Post-Hoc Analysis" will be added on the top right header of each additional outputs described in the current document.

Post-hoc analysis description

SAP Section	Description
Section 6.1.7 - Derived variables	The following variables will be added and derived: • Number of emapalumab doses = number of emapalumab doses received during the study regardless the dose was completed or interrupted. • Prescribed dose of emapalumab (mg/kg) = prescribed dose of emapalumab (mg) / weight (kg) • Cumulative prescribed dose of emapalumab (mg/kg) = sum of prescribed emapalumab doses (mg/kg) • Average prescribed dose of emapalumab (mg/kg) = (cumulative dose of emapalumab)/(number of doses)
Section 7.4 – Exposure and drug administration	The following text will be added for creation of a new variables and listing: *Study drug exposure data (date of first dosing, date of last dosing, the number of doses received, prescribed dose (mg/kg), average prescribed dose (mg/kg), cumulative prescribed dose (mg/kg), average administered dose (mg/kg), cumulative administered dose (mg/kg), and duration of exposure (days)), will be listed for patients in the All Treated Population.*
Section 8.1 – Efficacy analysis	The following text will be added for creation of new listing: *Assessments to MAS remission data will be presented in data listing using the All Treated Population.*
Section 9.1 – Adverse events	The following text will be added for creation of new table: *Summary of the incidence of non-serious TEAEs will be displayed by SOC and PT.*
Section 12 – Other Planned Analysis	New narrative figure per patient: • Overview of sJIA and/or MAS therapies prior to emapalumab initiation Presentation of MAS episodes and treatments from Study day -180 to Study day 0. The following medications will be presented separately: anakinra, canakinumab, ciclosporin, etoposide, and tocilizumab

SAP Section	Description
	Medications under ATC level 4 'H02AB' will be presented under 'Equivalent dose of Prednisone'. Pulses (i.e. equivalent dose of prednisone ≥ 20 mg/kg/day) will be presented using symbol. Anakinra daily dose (mg/kg/day) will be displayed from Study day -180 to Study day 0. 
Section 14.1 - Planned Table Descriptions	New table: • Table 14.3.1.7- Non Serious Treatment-Emergent Adverse Events by SOC and Preferred Term
Section 14.2 - Planned Listing Descriptions	New listings: • Data Listing 16.2.4.9 – MAS History Comments • Data Listing 16.2.5.3 – Study Drug Exposure, All Treated Population • Data Listing 16.2.6.2 – Assessment of MAS Remission, All Treated Population • Data Listing 16.2.9.17 - Search for Infection, All Treated Population

SAP Section	Description
	• Data Listing 16.2.9.18 – BCG Vaccine, All Treated Population

List of Abbreviations

Abbreviation	Definition
AOSD	Adult-onset Still's disease
ATC	anatomical therapeutic chemical
BCG	bacille Calmette Guerin
CSR	clinical study report
HLH	hemophagocytic lymphohistiocytosis
MAS	macrophage activation syndrome
PT	preferred term
SAP	statistical analysis plan
SD	study day
SOC	system organ class
sJIA	systemic juvenile idiopathic arthritis
TEAE	treatment-emergent adverse event